Weight Loss Studies in Obese Patients
Aspects of very-low-energy diet treatment and effects of obesity surgery on disability pension

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ABSTRACT

Obesity is associated with increased risk of serious medical conditions, impaired quality of life, reduced working capacity, and shortened life expectancy. Obesity surgery is the most effective weight loss treatment with large health benefits, including reduced mortality. However, the long-term effects on productivity loss are not known. Surgical treatment is not an option for all obese patients and effective dietary treatments are much needed. Very-low-energy diets (VLED) induce rapid and substantial weight loss. After the VLED period, patients switch back to ordinary food. The refeeding period may be crucial in adjusting eating habits to maintain weight loss. The effect of different refeeding strategies on weight development has so far not been examined. VLED does not work for all patients and it is therefore important to understand who will benefit the most from VLED treatment and identify those who need extra support. The aim of this thesis was to test if a prolonged refeeding duration after VLED-induced weight loss improves weight development, to explore factors predicting VLED weight loss and drop out, and to study the effect of obesity surgery on disability pension.

Obese patients were recruited to a 1-year, randomised weight management intervention with 12 weeks of initial VLED. Those who lost at least 10 percent of their weight on the VLED were randomised to either 1 or 6 weeks of refeeding to an ordinary, energy-reduced diet. Patients with longer refeeding regained significantly less weight up to 1 year and maintained higher levels of dietary restraint, reflecting an improved ability to restrict food intake and follow dietary prescriptions.

VLED treatment resulted in similar outcomes in women and men. However, the predictors differed by gender. Variables related to perceived physical health, social interaction, socioeconomic factors and obesity-related psychosocial problems predicted VLED outcome. Furthermore, the results suggest that social support and walking capacity are important determinants of successful weight loss in men whereas psychosocial function may influence VLED outcome in women.

The Swedish Obese Subjects (SOS) study involves 2010 surgically treated patients and 2037 obese, contemporaneously, matched control patients followed for up to 20 years. The surgically treated patients achieved sustained weight loss whereas the conventionally treated controls were on average weight stable. Information on granted disability pension was obtained for all participants from the Swedish Social Insurance Agency. The risk of disability pension was lower in the surgically treated men than in the control men when adjusting for confounders (HR=0.79; 95% CI: 0.62–1.00, P=0.05). Number of disability pension days was also lower in men (609 versus 734 days, P=0.01) in a subgroup followed over 10 years (903 men/1994 women). In women, the risk of disability pension or adjusted number of days over 10 years (889 versus 888 days) did not differ between the treatment groups (P=0.97).

The main findings of this work suggest that weight loss after VLED treatment can be improved by prolonged refeeding, that different factors influence VLED outcome in women and men, and that bariatric surgery is associated with reduced disability pension in men.
ORIGINAL PAPERS

This thesis for the doctoral degree is based on the following papers referred to in the text by their Roman numerals:

I  Lena Gripeteg, Jarl Torgerson, Jan Karlsson, and Anna Karin Lindroos. 
Prolonged refeeding improves weight maintenance after weight loss with very-low-energy diets. 

II Lena Gripeteg, Jan Karlsson, Jarl Torgerson, and Anna Karin Lindroos. 
Predictors of Very-Low-Energy Diet (VLED) outcome in obese women and men. 
Obesity Facts 2010, in press.

Effects of Bariatric Surgery on Disability Pension in Swedish Obese Subjects. 
Submitted for publication.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COI</td>
<td>Cost-of-illness</td>
</tr>
<tr>
<td>DPP</td>
<td>Diabetes Prevention Program</td>
</tr>
<tr>
<td>DPS</td>
<td>Diabetes Prevention Study</td>
</tr>
<tr>
<td>EI</td>
<td>Eating Inventory</td>
</tr>
<tr>
<td>FTO</td>
<td>Fat mass- and obesity-associated</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HR</td>
<td>Hazards ratio</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LED</td>
<td>Low-energy diet</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
</tr>
<tr>
<td>MACL</td>
<td>Mood Adjective Check List</td>
</tr>
<tr>
<td>OF</td>
<td>Obesity Functional health scale</td>
</tr>
<tr>
<td>OP</td>
<td>Obesity-related Problems scale</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life-years</td>
</tr>
<tr>
<td>RSE</td>
<td>Rosenberg Self-Esteem scale</td>
</tr>
<tr>
<td>SF-36</td>
<td>Medical Outcomes Study 36-Item Short Form Survey</td>
</tr>
<tr>
<td>SOS</td>
<td>Swedish Obese Subjects</td>
</tr>
<tr>
<td>TFEQ</td>
<td>Three-Factor Eating Questionnaire</td>
</tr>
<tr>
<td>TFEQ-R21</td>
<td>Revised 21-item Three-Factor Eating Questionnaire</td>
</tr>
<tr>
<td>TG</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>VBG</td>
<td>Vertical banded gastroplasty</td>
</tr>
<tr>
<td>VLED</td>
<td>Very-low-energy diet</td>
</tr>
</tbody>
</table>
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BACKGROUND

OBESITY

Definition and prevalence

Obesity is a condition of potentially health-impairing excess weight, defined by the World Health Organization (WHO) as a body mass index (BMI) equal to, or greater than 30 kg/m$^2$ [1] (Table 1). The reported prevalence of adult obesity in the European Union ranges between 9–26 percent in women and 8–26 percent in men, as compared to 33 and 31 percent in women and men in the United States (U.S.) [2]. In Sweden, 11 and 12 percent of the adult women and men are currently obese, whereas 28 percent of the women and 42 percent of the men are overweight [3].

<table>
<thead>
<tr>
<th>Weight status</th>
<th>BMI kg/m$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>≥30</td>
</tr>
<tr>
<td>Obesity class I</td>
<td>30–34.9</td>
</tr>
<tr>
<td>Obesity class II</td>
<td>35–39.9</td>
</tr>
<tr>
<td>Obesity class III</td>
<td>≥40</td>
</tr>
</tbody>
</table>

The rapid obesity increase during the last decades has caused great concern globally. During the years 1976 to 2004, the fraction of obese adults in the U.S. increased from 15 to 32 percent and in 2008 only one state had obesity prevalence below 20 percent. Throughout the same period, however, the overweight prevalence has been relatively stable, slightly above 30 percent [4]. In Sweden, the obesity prevalence rose from 5 to 10 percent in women and men between 1980 and 2005, although the most rapid change occurred in the early 1990’s [5].

Increases in body weight have also affected children and adolescents. The prevalence of overweight children in the U.S. has more than doubled the past three decades to 12 percent in children aged 2–5 years and 17 percent in children 6-11 years old. For those aged 12–19 years the prevalence has increased from 5 to 18 percent [4, 6]. In Sweden, the fraction of obese 10-year old children has fourfolded from 1984 to 2005 and reached 3 percent [7, 8], whereas the prevalence of overweight has doubled to 20 percent in girls.
and 17 percent in boys. Overweight children are not only at risk of obesity-related health problems during childhood [9], but are also more prone to become obese as adults. Studies have shown that 80 percent of children who were obese at age 10–15 years still were obese at age 25 [10], and that 25 percent of obese adults suffered from overweight in childhood [11].

The health risks with excess body weight are due in large part to the location of the adipose tissue. Fat tissue accumulated inside the abdomen, visceral adipose tissue, is considered more dangerous than peripheral fat tissue, due to higher metabolic activity [12] and strong links to obesity-related comorbidities [13-15]. A waist circumference above 88 cm in women and 102 cm in men indicates central obesity [16].

Aetiology

Weight gain is a result of long standing positive energy balance, i.e. energy intake exceeding energy expenditure. Weight loss on the other hand requires negative energy balance over time. In theory, energy balance and the relation between intake and expenditure is quite easy to understand. In real life, however, the process of weight gain is often unintentional and passive, while losing weight requires extensive, long-term efforts.

There is an ongoing debate around the causes for the present obesity epidemic, and the relative impact of the various components. Obesity is the consequence of a complex interaction between genetic, social and lifestyle factors and is hence very difficult to understand and prevent [17]. With the discovery of leptin [18] – a protein synthesized in adipocytes, lacking in the obese, overeating ob/ob mouse – there was hope for a better genetic understanding and treatment of obesity. Today, it is however known, that monogenic obesity is very rare and unlike monogenic obesity, many genes and chromosomal regions contribute to defining the common obese phenotype [19, 20]. The strongest predictor of polygenic obesity identified so far is the FTO (fat mass- and obesity-associated) gene explaining about one percent of the total heritability [21]. Using twin and family studies the overall genetic influence on the inter-individual variation in BMI has been estimated to 45–75 percent [22-25], thus leaving 25–55 percent to be explained by environmental causes, e.g. a sedentary lifestyle and constant access to palatable, energy-dense foods. Societal development certainly challenges the individual ability to balance food intake and physical exercise. For example, between 1965 and 2002, the percentage of energy intake from beverages increased from 12 to 21 percent in the U.S., representing a 222 kcal daily increase per person [26]. Whether an individual develops obesity or not mainly depends on genetic vulnerability for an “obesogenic” environment, whereas on the population level, obesity is primarily increasing as a result of changes in lifestyle and environment [20].
Comorbidity

Obese individuals have an elevated risk for psychiatric illnesses as depression and anxiety [27]. Other negative consequences are social stigmatization, poor mental well-being, poor mood, and impaired psychosocial and physical functioning due to the high body weight [27, 28]. Furthermore, there is an increased risk of a wide range of medical conditions that may cause further health impairment. Obesity increases the risk of developing type 2 diabetes, coronary artery disease, hypertension, stroke, asthma, gall bladder disease, osteoarthritis, chronic back pain, and some cancers [29]. Table 2 summarizes some of the relative comorbidity risks for obese women and men, as compared to normal weight individuals.

Table 2. Relative comorbidity risk attributable to obesity [29].

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>12.41</td>
<td>6.74</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.10</td>
<td>1.72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.42</td>
<td>1.84</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.49</td>
<td>1.51</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.78</td>
<td>1.43</td>
</tr>
<tr>
<td>Gall bladder disease</td>
<td>2.32</td>
<td>1.43</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.96</td>
<td>4.20</td>
</tr>
<tr>
<td>Chronic back pain</td>
<td>2.81</td>
<td>2.81</td>
</tr>
<tr>
<td>Various cancers(^1)</td>
<td>1.13–3.22</td>
<td>1.05–2.29</td>
</tr>
</tbody>
</table>


About 40 percent of adults over the age of 40 years have the metabolic syndrome, a cluster of risk factors for diabetes type 2 and cardiovascular disease [30]. Different definitions of the metabolic syndrome have been proposed, but the core aspects are hypertension, lipid disturbances (hypertriglyceridaemia, low HDL cholesterol), central obesity and hyperglycaemia/impaired glucose tolerance/type 2 diabetes [16]. The risk factors included in the metabolic syndrome are estimated to cause approximately 70 percent of first time myocardial infarctions in women and men [31].

Several large epidemiological studies have also shown that obesity is associated with increased mortality [32–35]. The risk of premature death increases gradually above BMI 25 kg/m\(^2\) [34], although the impact of overweight (BMI 25–30 kg/m\(^2\)) on mortality is somewhat ambiguous [36]. Obesity-related deaths are mainly due to cardiovascular...
disease, type 2 diabetes and some cancers [37]. The life-shortening effect of being obese has been estimated to 2–4 years at BMI 30–35 kg/m², and 8–10 years at BMI 40–45 kg/m² [34]. In the U.S., obesity is causing nearly one of ten deaths and is together with smoking and hypertension among the leading reasons for preventable death [38].

**OBESITY TREATMENT**

**Diet and lifestyle changes**

A majority of weight loss programs are based on changing diet and lifestyle behaviour. Several hypotheses on diet composition have been proposed, and among those are the potential benefits of high-protein diets, low-carbohydrate diets, high-fat diets, and low glycemic index. However, weight loss can be achieved with any energy reduced diet [39], and the choice of diet for short term weight loss is therefore mainly a matter of individual preference. In contrast, the effects of weight maintenance diets are more complex to evaluate [40] and do not only include likelihood of diet adherence and weight stability, but also long term consequences on health and obesity-related comorbidity. Although there are different opinions on the optimal macronutrient composition of weight reducing diets, recent randomized trials have reported similar effects on weight loss [40-42], body composition [41] and risk factors for cardiovascular disease and diabetes [40] during isoenergetic conditions. These findings suggest that weight reduction is primarily an effect of diet compliance, not diet composition [42, 43].

Dietary obesity interventions generally include strategies such as energy restriction based on either estimated energy requirements or standardized energy levels, meal pattern and composition, food choice, portion size, dietary counselling, and self-monitoring tasks such as diet records. A negative energy balance can be achieved by reduced energy intake or increased energy expenditure. In general, however, obesity interventions focus on the energy intake. In theory, physical exercise can produce negative energy balance if no compensatory increase of food intake occurs. However, a daily energy deficit equal to an energy reduced diet requires large amounts of physical activity. As pointed out by Catenacci and Wyatt [44], interventions based on exercise often intend to induce an energy deficit of 1000–1500 kcal per week, which should be compared with daily energy reductions of 500–1000 kcal in dietary interventions [44].

Psychological treatments for obesity include behaviour therapy, cognitive behaviour therapy, relaxation therapy and hypnotherapy [45]. The weight reducing effect of some of these treatments have not been established [45]. However, behaviour therapy or cognitive behaviour therapy alone may induce significant weight loss and enhances weight loss when incorporated in dietary and exercise interventions [45].
Exercise and dietary interventions share the same problems with insufficient adherence and prevalent drop out, although the problems are even more pronounced for exercise programmes [44]. However, most evidence suggests that physical activity do play an important role in weight maintenance [44]. Results from the American Nurses’ Health Study II suggest that 30 minutes or more of daily physical exercise prevents weight regain in women who previously lost at least 5% in weight [46]. On the other hand, data from energy expenditure measurements with the doubly-labelled water method indicates that approximately 80 minutes of moderately intensive exercise is required to prevent weight regain after weigh loss [47]. The National Weight Control Registry (NWCR) in the U.S. has collected information from over 4800 individuals who have succeeded to maintain a minimum of 13.6 kg weight loss for at least one year [48]. Reports from this registry suggest that important strategies for weight maintenance were consuming a low-fat diet of restricted diversity, eating breakfast most days and exercising about one hour daily [48]. Moreover, daily weighing seemed beneficial for weight control [48], a finding that has also been confirmed in a randomized trial [49].

In a recent systematic review and meta-analysis of weight-loss in clinical trials Franz et al reported that the mean weight loss after 6 months of dietary counselling alone was 4.9 kg (5%), with a maintained weight loss of 4.6 kg (4.6%) at 12 months, 4.4 kg (4.4%) at 24 months, and 3.0 kg (3.0%) at 48 months [50]. The mean 6-months effect of exercise as only intervention was 2.4 kg (2.7%), as compared to 7.9 kg (8.5%) for dietary counselling combined with exercise, and 8.6 kg (9.6%) for structured dietary interventions (i.e. meal replacements) [50]. Obesity treatment with energy reduced (-600 kcal), low-fat diets and lifestyle changes can be expected to induce a one-year weigh loss of 5.3 kg [51], whereas treatment programs that include VLED have reported weight losses of 10.9 kg (10%) after 1 year [50].

In general, the weight loss effect of diet and lifestyle modification is relatively modest [52]. It is, however, often argued that a weight reduction of 5–10 percent in obese patients with comorbidity could be expected to have positive effects on health [53]. Accordingly, dietary treatment, combined with exercise, or with exercise and behaviour therapy, is associated with beneficial changes in blood pressure and HDL-cholesterol and triglyceride levels [54]. The US Diabetes Prevention Program (DPP) [55] and the Finnish Diabetes Prevention Study (DPS) [56] both found that three years of intensive lifestyle intervention, that included an energy-reduced, low-fat diet and increased physical activity, reduced the incidence of type 2 diabetes with 58 percent. The weight losses were modest, 5–7% of initial body weight. A post-intervention follow-up after seven years in the DPS-study showed a 36 percent risk reduction for diabetes [57]. So far, however, the DPS-study has not been able to demonstrate any effect of lifestyle intervention on the incidence of cardiovascular mortality [58]. The authors discuss that this may be due to low total mortality rates and small differences between the intervention and control groups [58].
Very-low-energy diets

The use of very-low-energy diets (VLED) in clinical obesity treatment commenced during the 1920’s [59]. At this time, the VLED consisted of conventional food. During the 1970’s, Cambridge professor Allan Howard developed the type of nutrient complete VLED used today; powder formulas, based on high quality proteins [60].

Very-low-energy diets are defined as total diet replacements with an energy content of 450–800 kcal per day [61]. A VLED should be composed of a minimum of 50 grams protein, 55 grams of carbohydrate, 7 grams of fat including essential fatty acids, 10 grams of fiber, and the recommended daily allowances of vitamins and minerals [61]. Very-low-energy diets are not defined as pharmaceutical agents and are on the market as over-the-counter products. In Sweden, the daily cost was approximately 50–65 SEK (5–7 EUR) in 2008.

Table 3. Contraindications for VLED treatment [62].

<table>
<thead>
<tr>
<th>Contraindication</th>
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<tbody>
<tr>
<td>BMI &lt;25 kg/m$^2$</td>
</tr>
<tr>
<td>Age &lt;18 years</td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
</tr>
<tr>
<td>Severe catabolic disease</td>
</tr>
<tr>
<td>Unstable diabetes type 1</td>
</tr>
<tr>
<td>Unstable cardiovascular disease</td>
</tr>
<tr>
<td>Recent cerebrovascular disease</td>
</tr>
<tr>
<td>History of eating disorder</td>
</tr>
<tr>
<td>Severe psychiatric disorder</td>
</tr>
</tbody>
</table>

Treatment with VLED is indicated in obese patients and patients with overweight and comorbidity that could improve by rapid and substantial weight loss [61, 62]. In addition, VLED is often used before obesity surgery to reduce surgical risk and complexity [63]. Although no prescription is required, a strict VLED should be followed for no longer than three weeks without medical supervision [61]. Before VLED start, a medical and dietary examination should be performed to assess cardiovascular risk factors, identify possible contraindications and thoroughly discuss the treatment. Some patients require extra monitoring and adjustment of medication; those with medically treated type 2 diabetes or hypertension and patients on oral anti-coagulants [61]. Patients with gout need monitoring due to elevated levels of serum uric acid during VLED [64]. There is no total agreement about VLED contraindications, but the most important are listed in Table 3 [62].

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Although young age is a general contraindication, VLED can be safely used under careful medical supervision in severely obese adolescents with comorbidity [65]. In children, VLED should only be used during exceptional circumstances at specialist paediatric departments [65]. Age below 10–12 years is considered an absolute contraindication [61]. Furthermore, VLED should only be considered if other dietary treatments have failed, and should always be incorporated in a lifestyle intervention with parental involvement [65].

In obesity treatment programs, VLED is often used for 12–16 weeks with an expected weight reduction of 1.5–2.5 kg per week [62]. Depending on product, three to five VLED portions are consumed per day together with around 2 litres of non-energy beverages. The powder is dissolved in water and consumed cold, as a milkshake, or as a heated soup meal. To obtain a satisfying nutrient intake it is important that no VLED portions are omitted. The energy intake from a VLED is fixed. Hence, the individual weight loss depends on the energy deficit in relation to energy requirement, and the treatment time. Studies have shown that strict adherence to VLED is better than a liberal approach that allows limited consumption of other foods, and that an initial week on a metabolic ward does not generate greater weight reduction [66]. There has been some concern about lean tissue mass depletion and negative nitrogen balance during rapid weight loss. The low energy intake from VLED, however, results in increased fat oxidation and ketogenesis, which may have a protein sparing effect [61].

The major advantage with VLED is the simplicity of food choice. If the diet is strictly followed weight loss will occur and hence increase patient’s motivation to stay on the diet. In contrast, low-energy diets (LED) based on ordinary foods often results in lower than expected weight reduction due to poor compliance [67]. Differences in diet adherence may partly be explained by a greater reduction of food cravings during VLED than during LED [68]. Certainly, all patients do not find VLED a convenient treatment. The monotonous liquid formula and sensory properties of the diet may lead to diet aversion. Also, a number of minor side effects have been reported from VLED programs. In short term, postural dizziness and tiredness is common, whereas transient hair loss is the most frequent complaint during prolonged VLED use [69]. Other adverse effects are dry mouth, constipation, diarrhoea, headache, nausea, cramps, fatigue, hunger, cold intolerance, dry skin and menstrual irregularities [70]. Although uncomfortable, the majority of those side effects are easy to manage and are due to the negative energy balance or too little fluid intake [70]. More occasional and severe complications are gout and cholelithiasis. However, if the VLED fat content is at minimum 7 grams, the risk for cholelithiasis is not believed to be increased [70].

Treatment programs that include VLED have reported mean weight losses of 10.9 kg (10%) after 1 year and 5.6 kg (5%) after 36 months [50]. However, to achieve a beneficial weight development long term, VLED must be combined with other treatment strategies,
such as dietary counselling, physical exercise and behaviour therapy [62]. After the VLED weight loss phase, ordinary foods are gradually reintroduced. Refeeding periods of one to six weeks have been reported from different VLED studies [66, 68, 71-78]. Little is known about the effect of different approaches to reintroduce foods after VLED. Hence, refeeding method mainly depend on local traditions. A gradual weight rebound is generally seen after VLED [71, 79, 80]. Various strategies have been suggested to prevent or limit post VLED weight regain. Improved weight development has been observed with pharmacological treatment [72, 81], exercise [82], continuous use of VLED as part of the dietary allowance [73] and protein supplementation [83].

**Drug treatment**

Pharmacotherapy is indicated in obese individuals and those with cardiovascular risk factors and a BMI ≥27 kg/m² [84]. Until recently two weight loss drugs have been available in Sweden – orlistat, which is a lipase inhibitor, and sibutramine, an anorexiant which suppresses appetite. Sibutramine was however recently withdrawn from the European market (January 2010).

Orlistat inhibits about 30 percent of the dietary fat from enzymatic splitting in the small intestine. The recommended dose is 120 mg three times daily [85]. Because of the fat-specific and local effect the capsules should be ingested together with main meals containing no more than 30 percent of energy from fat. The unabsorbed fat passes through the intestine and is eliminated with faeces. Common side effects are diarrhoea, flatulence and bloating, all related to the expected fat malabsorption [84]. Sibutramine, on the other hand, enhances satiety by acting on the central nervous system as a combined noradrenaline and serotonin reuptake inhibitor. Sibutramine is administered as a single 10–15 mg daily dose [85]. Increased blood pressure and pulse rate are reported complications and should be regularly monitored [84].

Both should be combined with lifestyle changes and are in Sweden restricted for patients with a BMI >35 kg/m², or BMI >28 kg/m² with concurrent diabetes type 2 (orlistat, sibutramine) or dyslipidemia (sibutramine) [85]. In addition, a minimum of 5 percent weight loss the first 12 weeks is recommended for continued prescription [85].

In the four-year XENDOS study, 3305 obese patients were randomised to intensive lifestyle treatment plus orlistat therapy or placebo [86]. The mean weight loss after four years of treatment was significantly greater in the orlistat group than in the placebo group, 5.8 kg versus 3.0 kg [86]. The two-year STORM study included 605 obese participants, of which 467 were subsequently randomised to intensive lifestyle treatment plus sibutramine therapy or placebo [87]. After two years of treatment was the mean weight loss
significantly greater in the sibutramine group, as compared to the placebo group, 10.2 kg and 4.7 kg, respectively [87]. In general, the mean weight loss after 6 months of orlistat therapy is 8.3 kg (8%), and 8.2 kg (8%), and 7.7 kg (7%), 7.8 kg (7%), and 5.8 kg (5.3%) after 12, 24, 36, and 48 months, respectively [50]. Sibutramine therapy, on the other hand, induces a mean weight loss of 8.2 kg (8.4%) after 6 months, and 8.2 kg (8.4%) and 10.8 kg (11%) after 12 and 24 months, respectively [50]. There is, however, some evidence for better weight loss with sibutramine (2.2 kg more effective) than orlistat therapy short-term (up to 1 year), while the combination of both drugs do not induce greater weight loss than sibutramine alone [88].

Weight loss medication may be helpful to prevent weight regain after VLED induced weight loss [75, 81, 89]. Furthermore, life style intervention combined with orlistat therapy improves the glycemic control, blood pressure and total- and LDL-cholesterol levels [54, 86]. In addition, the XENDOS study showed that intensive lifestyle treatment combined with orlistat therapy reduced the incidence of diabetes with 37% [86]. Sibutramine therapy, combined with life style changes, have shown positive effects on HDL-cholesterol and triglycerides, but adverse effects on blood pressure [54, 87]. Recently, an increased risk of cardiovascular events has also been confirmed and the drug therefore withdrawn [90].

**Obesity surgery**

Bariatric (weight loss) surgery is a treatment alternative for patients with severe obesity when other treatments have failed [91]. Eligible patients are, in general, those with a BMI greater than 40 kg/m² or greater than 35 kg/m² with serious comorbidity [91]. Bariatric surgery may cause considerable complications and is contraindicated in patients with poor myocardial reserve, severe chronic obstructive airway disease or respiratory dysfunction, severe psychological disorder and poor compliance [91]. A number of surgical procedures are available, but the main types are restrictive surgery that limits food intake, malabsorptive surgery, and a combination of these.

Gastric banding (Figure 1) is an entirely restrictive method. A constricting band is placed around the upper part of the stomach [91]. Earlier, nonadjustable bands were used. Modern bands, however, have an inner balloon that can be adjusted from a subcutaneous access port. Gastric banding is the less invasive bariatric procedure, it cause no malabsorption or dumping, and is also reversible [91]. Complications of gastric banding are those related to the surgical procedure, as splenic and oesophageal injury, wound infection, band slipping, band erosion or migration, reservoir leak, frequent vomiting, acid reflux and poor weight loss [91]. Reoperation may be required in 20–30% of patients due to complications [92].
Vertical banded gastroplasty (VBG) (Figure 2) is sporadically used today. It is a restrictive procedure which partitions the stomach by use of staples, creating a small pouch [91]. In addition, a band around the exit part of the pouch reduces stretching. Advantages with VBG are absence of malabsorption and dumping. Drawbacks, however, are prevalent weight regain and need of surgical revision in about 30 percent of the patients [92]. Complications after VBG include leakage, stenosis, ulcer, incisional hernia, wound infection, staple disruption, pouch dilatation and band erosion [91]. Specific adverse effects are bolus obstruction and infrequent cases of calcium and vitamin deficiencies and anaemia [91].

Gastric bypass (Figure 3) has both restrictive and malabsorptive properties. A small pouch is created using staples, and the first part of the intestine is bypassed, by connecting the intestine to an outlet on the gastric pouch [91]. The method can be adjusted to produce greater malabsorption and weight loss, and is reversible. It has been suggested that part of the weight loss effect is mediated through increased levels of the satiety gut hormones peptide YY (PYY) and glucagon-like peptide 1 (GLP-1), which reduces appetite [93]. Following a gastric bypass, patients seem to be able to consume all types of foods [94], although energy-dense, high-carbohydrate foods may cause dumping syndrome, a side effect that comprises increased heart rate, nausea, tremor, faint feeling and diarrhoea [91].

Patients who lose more weight after restrictive surgery with gastric banding or VBG appear to be those who consume a low quality diet with high amounts of sweet foods and avoid whole meat and vegetables [94, 95]. However, long term nutritional complications

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**Figures 1–3.** Examples of surgical procedures.
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are in general more frequent after malabsorptive surgery than restrictive surgery [96]. Iron, folate and vitamin B₁₂ are prevalent deficiencies. In addition, deficiency of fat-soluble vitamins has been reported after malabsorptive surgery [97], and thiamin deficiency has been described in patients with particularly poor food intake and/or nausea and vomiting. Although supplementation practices varies, a minimum is a multivitamin with minerals [96].

Gastric banding, VBG and gastric bypass can be performed laparoscopically, which reduces the time for hospital care and recovery [91]. In the U.S., laparoscopic gastric bypass and laparoscopic adjustable gastric banding are the most common operations [98]. In Sweden, 2486 bariatric operations were carried out in 2008 (Ingmar Näslund, personal communication, 31 August 2009). The majority of the procedures, 2381 (96%), were gastric bypass whereas only 38 were gastric banding and two were VBG. Laparoscopic procedure was utilized in 79 percent of the operations. The mortality rate was 0.14 percent (Ingmar Näslund, personal communication, 31 August 2009).

In the Swedish Obese Subjects (SOS) study, the effect on weight loss, one to two years after bariatric surgery, was 20 percent, 25 percent, and 32 percent for gastric banding, VBG, and gastric bypass, respectively [99]. The corresponding weight losses after ten years were 14 percent, 16 percent and 25 percent, respectively [99]. Several reports from the SOS study have described the long-term effects of intentional weight loss by means of bariatric surgery. The health-related quality of life was significantly improved in surgically treated patients [100]. After ten years, the outcome was better in the surgery group than in the control group on current health perception, social interaction, psychosocial functioning and depression [100]. Ten years after surgery, the incidence of diabetes was significantly lower in the surgery group compared to the control group [101]. Furthermore, obesity surgery is associated with a reduced incidence of cancer in women, whereas there is no effect in men [102]. The number of first-time cancers after inclusion in the study was lower in the surgically treated women than in the control women, but the cancer incidence was not associated to weight loss in any of the treatment groups [102]. The main end point in the Swedish Obese Subjects study is the effect of intentional weight loss (through obesity surgery) on mortality [103]. This outcome was reported in 2007 [99] and showed that the risk for early death was reduced by 24 percent in surgically treated obese patients [99].

**Obesity treatment – Summary**

In summary, significant short term weigh reductions can be achieved by several treatment approaches, whereas bariatric surgery so far is the only treatment that results in major
weight loss long term. A summary of mean weight losses after two years of treatment with exercise, diet, drugs and obesity surgery is depicted in Figure 4.

![Figure 4](image)

**Figure 4.** Two-year weight loss after treatment with exercise, dietary counselling, orlistat, sibutramine [50] and bariatric surgery [104].

Even quite a modest weight reduction improves cardiovascular risk factors. A weight loss in the order of 5–10 percent is associated with a reduction in LDL-cholesterol by 15 percent and triglycerides by 20–30 percent, and an increase in HDL-cholesterol by 8–10 percent [105]. An equivalent weight loss in obese individuals with type 2 diabetes is associated with a reduction of 1.1 percent in HbA1c, 1.6 mmol/l in fasting blood glucose, 0.5 mmol/l in triglycerides, and an increase by 0.1 mmol/l in HDL-cholesterol [106]. In addition, a 2–4 kg weight reduction is associated with a 3–81 mmHg decrease of systolic blood pressure, although this effect is generally transient [107].

**HEALTH-RELATED QUALITY OF LIFE**

The definition of health as “the absence of disease” was in 1947 extended by the WHO to also include quality aspects in terms of physical, mental, and social wellbeing [108]. Accordingly, “health” from the perspective of quality of life relates to almost all essential features of life [109] and comprises for example self-perceived health status, physical functioning, emotional status, happiness, pain, fatigue, life satisfaction, social relations, and economic status [110]. The concept of health-related quality of life (HRQL) refers to the components of quality of life that are linked specifically to health status [111], and is measured as self-perceived functioning and wellbeing in relation to health, disease and treatment [112]. In patients with chronic disease, quality of life measures may be
especially valuable as the existing treatments cannot cure the illness, only reduce symptoms and the burden of the disease. Furthermore, due to the influence of health expectations and ability to cope with functional limitations, two individuals with similar health status may assess their quality of life differently [113]. Hence, the purpose of quality of life measures is to find out what diseased individuals actually feel about their life, not what they are assumed to feel [109].

**Generic and disease-specific measures**

Generic (general) health-related quality of life measures are intended for use across various populations, patient groups and interventions [111]. Thus, the generic measures make it possible to evaluate the relative impact of different diseases compared with norm values in the general population [111] and to assess changes during treatment [114]. A well established generic health status measure is the Medical Outcomes Study 36-Item Short Form Survey (SF-36), which covers eight general health status domains: physical functioning, role-limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role-limitations due to emotional health problems, and mental health [114, 115]. The Mood Adjective Check List (MACL) is a measure of mood/mental well-being. The MACL contains 38 adjectives which covers three bipolar dimensions of mood: pleasantness/unpleasantness (for example, satisfied, optimistic/depressed, resigned), activation/deactivation (for example, alert, active/passive, apathetic) and calmness/tension (for example, relaxed/tensed, distressed) [116]. An overall mood score is also calculated. Self-esteem is the general perception an individual have of his or hers own value or worth [117]. The Rosenberg Self-Esteem scale (RSE) is a measure of global self-esteem [118]. RSE comprises 10 items and responses are aggregated to a total score.

Disease-specific health-related quality of life measures are designed to evaluate the effects of a particular disease on quality of life [109, 114] and to detect changes during treatment [111]. In general, disease-specific measures have high content validity, which means that the patients find the topics relevant [111]. In addition, disease-specific measures are often more sensitive to changes than generic measures [111]. Different measures have been developed to assess the impact of obesity on health-related quality of life. The Obesity Functional health scale (OF) is designed to assess obesity-specific functional limitations [119]. OF comprises 39 items which covers nine domains: mobility, ambulation, sleep and rest, home management, work, recreation, social interaction, sex life, and aches and pain. An overall functional health score is also calculated. The extended 14-item version of the Obesity-related Problems scale (OP) measures the impact of obesity on psychosocial functioning [28]. Subjects indicate how bothered they are by their obesity in a broad range of social activities. Responses are aggregated to a total score, where 0 represents no impairment and 100 represents maximal impairment. A mild
impairment in psychosocial functioning is indicated by score <40, a moderate impairment by score 40–59, and severe to extreme impairment by score ≥60 [28].

**Obesity and health-related quality of life**

Obesity is a condition that cannot be concealed when meeting with others. Studies have confirmed that health care staff attribute obese individuals negative attitudes and stereotypes, that obese characters in the media (television and movies) are stigmatized, and that obese individuals perceive weight-based discrimination in employment settings [120]. In a study of 94 patients seeking surgical obesity treatment, all individuals had experienced weight-based stigmatization (e.g. physical obstacles, nasty comments) during the past month [121]. Furthermore, the psychological distress from weight-based stigmatization may function as a mediating factor in binge eating and other maladaptive eating behaviours [120, 122].

An association between higher BMI and greater impairment in health-related quality of life have been reported from a large sample of U.S. adults [123]. In addition, the findings suggested joint pain and obesity-related comorbidities to be mediating factors [123]. As compared with healthy reference subjects, obese men and women have reported worse general health [27], lower mental wellbeing [27], more anxiety [27, 124], more depressive symptoms [27, 125], and greater impairment in social interaction [27] and sexual functioning [126]. Furthermore, obese patients have reported worse perceived wellbeing than patients with other severe chronic conditions, such as rheumatic disease, spinal-cord injury, and cancer survivors [27]. The negative effect of obesity on wellbeing [27] and psychosocial functioning [28] seems to be especially pronounced in women. Moreover, studies suggest that the higher rates of depression and greater negative impact on self-esteem, and physical and sexual functioning in obese women may contribute to the higher frequency of bariatric surgery in women than men [127].

After 2–4 years of follow up, weight loss by means of VLED and behaviour modification improves physical and psychosocial functioning [71], whereas large weight loss after bariatric surgery improves generic and weight-related functional status [128, 129], current health perception [130], psychosocial functioning[28, 130], social interaction [130], overall mood [28, 130], anxiety [28, 130], and depression [28, 130]. Ten years after weight loss surgery, there are still significant improvements in current health perception, psychosocial functioning, social interaction, and depression [100]. Patients with greater weight loss perceive greater improvements in health-related quality of life [28, 130].
EATING BEHAVIOUR

Human eating behaviour is influenced by various factors such as food likes and dislikes, health beliefs, social aspects [131] and emotions [132]. A satisfactory control of eating behaviour and food intake is essential for weight maintenance. Both lean and obese individuals may consciously restrict their food intake in order to lose weight or prevent weight gain. Binge eating, on the other hand, is an overeating behaviour characterized by consumption of large amounts of food during a short period of time, and a concurrent sense of lack of control [133, 134]. The reported prevalence of binge eating disorder in community samples is 2–5%, as compared to 16–30% of individuals seeking weight loss treatment [133]. These contradictory types of eating behaviour may also interact and contribute to weight gain. The “dietary restraint hypothesis” suggests a causal relationship between high levels of dietary restraint and overeating after a pre-load that interrupts dietary restraint [132, 135, 136].

The Three-Factor Eating Questionnaire

The Three-Factor Eating Questionnaire (TFEQ), also called Eating Inventory, was developed to measure three distinct dimensions of eating behaviour in obese subjects: cognitive restraint of eating, disinhibition and hunger [137]. The construct validity of the 51-item TFEQ was evaluated in 4377 Swedish obese women and men [138]. However, the original TFEQ factor structure could not be replicated. The cognitive restraint factor was reproduced while most disinhibition and hunger items grouped in one global factor labelled uncontrolled eating. A third cluster containing items on emotional eating was also identified. In the original TFEQ, emotional eating items are included in the disinhibition scale. A short, revised, 18-item instrument representing the three derived factors was developed, and subsequently further refined to a 21-item version of the instrument (TFEQ-R21) which include three additional items on emotional eating. In the present study, self-assessed eating behaviour was measured by the TFEQ-R21 which covers the domains cognitive restraint, uncontrolled eating, and emotional eating [138, 139]. The cognitive restraint scale assesses control of food intake in order to influence body weight and body shape. The uncontrolled eating scale assesses the tendency to lose control over eating when feeling hungry or when exposed to external stimuli. The emotional eating scale measures the propensity to overeat in relation to negative mood states, e.g., when feeling lonely, anxious, or depressed. The constructs of cognitive restraint, uncontrolled eating, and emotional eating have been replicated in other studies [140]. Correlations between the original TFEQ scales and the revised, short-form scales have been presented elsewhere [138, 139].
The association between eating behaviour and BMI (range, 15 to 87 kg/m²) was studied in 2509 women and men. In both women and men, disinhibition scores were positively correlated with BMI, whereas restraint scores were positively associated with BMI only in men [141]. Hunger scores did not vary with weight status. Similarly, a positive association between uncontrolled eating and BMI was reported from a study of normal weight and overweight adults [142]. In the later study, emotional eating was also positively associated with BMI [142]. However, restrained eating was not associated with weight status in overweight individuals, although there was a positive association in normal-weight individuals [142]. In a study of non-obese and obese women, disinhibition scores differentiated the groups better than did restraint and hunger scores [143]. Restraint scores did not differ between the groups. Furthermore, in the obese women, restraint and disinhibition were negatively correlated, whereas there was a weak positive correlation in the non-obese women [143]. Another study of women enrolled in weight loss trials reported high pre-treatment restraint in women with lower weights [144].

The restraint scale of TFEQ is considered a reliable measure of the intent to diet [145]. Moreover, changes in dietary restraint scores have been associated with actual caloric restriction [145]. In obese women, higher energy intakes have been associated with lower restraint scores, and higher disinhibition and hunger scores [143]. In addition, high scores in disinhibition have been associated with binge eating behaviour [144]. During weight loss, characteristic changes in eating behaviour are increased dietary restraint scores [82, 130, 144, 146-148] and decreased scores of uncontrolled and emotional eating [82, 130, 144, 146, 148]. This pattern of eating behaviour changes has been associated with beneficial changes in dietary intake [146]. In addition, high scores in cognitive restraint have been associated with weight loss and engagement in weight-controlling behaviour [147].

HEALTH ECONOMICS

The financial burden of chronic disease is considerable for the individual and the society, and the cost increases with number of comorbidities [149, 150]. New technology, more effective and expensive treatments, and an increasing demand for health care increases health expenditures [151] and raises the importance of health economic studies. Health economics topics include estimation of costs associated with disease, evaluation of the consequences of different resource allocation, and evaluation of costs in relation to different outcomes [152].

Health economic studies are in general carried out from a societal perspective, when all identified costs can be included irrespective of to whom they incur, or a third party payer perspective (e.g. government, insurance company), when only the costs for the specific
third party are considered [152]. Furthermore, economic evaluations that comprise longer time periods must deal with costs and consequences of treatment that occur over time [152].

Three categories of costs are distinguished in health economics: direct costs, indirect or productivity costs, and intangible costs [152]. Direct medical costs are recourses related to providing health care, for example costs for hospitalization, blood chemistry, medication, surgical procedures, and staff time [152, 153]. Direct non-medical costs are e.g. the patients’ costs for receiving care, such as charges and time for travelling, and time for informal care provided by family and others [152, 153]. Indirect or productivity costs are the productivity losses related to ill health, treatment, and death [153] and include aspects such as working time (paid and non-paid), sick leave, disability pension, working capacity, and leisure time [152]. Intangible costs are related to the pain and suffering due to ill health and treatment. The intangible costs are especially difficult to quantify and are rarely included in analyses [153].

The first economic analysis to be used in the health care field was the cost-of-illness analysis [153]. The method is primarily used to measure the financial burden of disease on the society [153-155]. Cost-of-illness studies are prevalence based or incidence based, depending on time frame. In a prevalence based approach the costs during a specified time period are estimated for a patient population [156], whereas the costs until cure, or for chronic diseases the lifetime costs for individuals diagnosed at a specific year are estimated in an incidence based approach [156]. The latter procedure account for disease progression over time and may therefore be more useful in cost evaluation of chronic conditions [156]. Outcome estimates are not included in cost-of-illness analysis and it may therefore not be regarded as an actual economic evaluation [152]. However, cost analyses provide valuable information on the potential savings with effective treatment [152, 154, 155, 157].

There are five forms of economic evaluations where the costs are compared for two or more options: cost-consequence analysis, cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis [152]. Common for these methods are that they all assess treatment costs. The outcome measures may, however, differ. The outcome of treatment is measured for example as increased life expectancy/survival, quality-adjusted life-years (QALYs), improvement in measures of health status (e.g. disease measures), monetary value, or as patient reported outcome (HRQL) [152]. A cost-consequence analysis can be used to describe the costs and outcomes of a specific treatment [158], whereas a cost-minimization analysis is undertaken to find the treatment with the lowest cost among equally effective interventions for a disease [152]. In a cost-utility analysis, treatment consequences are compared for different diseases using a combined measure of survival and quality of life (e.g. QALYs) [152]. In a cost-benefit
analysis, costs and benefits of different resource allocation (the health care sector compared with other sectors) are measured in monetary value, and the gains or losses calculated [152]. In a cost-effectiveness analysis, the costs and effects of different treatments for a specific disease are compared [152]. If one treatment is less expensive and more effective, no more calculations are needed. However, if one treatment is more expensive and more effective, the incremental cost-effectiveness ratio (ICER) can be calculated as the extra or incremental cost divided by the extra effect [152].

**Obesity and health economics**

Obese individuals have an increased risk for comorbidities [29] and functional limitations [159]. In addition, the frequency of sick leave [160-162] and disability pension [163, 164] is higher in obese than in normal weight individuals. Consequently, obesity is associated with substantial costs for the society in terms of health care costs [150, 154, 155, 165, 166] and costs for productivity losses due to early death [167], work absenteeism [164, 168], and disability pension [164, 169]. Recent data from the U.S. estimates that about 10% of the costs for health care in adults are attributable to obesity [165]. The annual health care cost was 1,429 dollar (about 11,000 SEK) higher for an obese adult compared to a normal weight individual, mainly due to the comorbidities diabetes, cardiovascular disease and rheumatic disease [165]. Recent cost-effectiveness studies suggest that pharmacological obesity treatment is cost-effective as compared to treatment with diet and exercise [170] and that surgical treatment is cost-effective as compared with non-surgical treatment [92, 171].

**PREDICTORS OF OUTCOME**

The treatment options for obesity are diverse and there is an overall high risk of poor treatment effect. However, the outcomes of obesity interventions are mainly reported as mean weight losses and do not describe the fraction of participants that are in fact successful. One possible approach to improve the management of obesity is to identify predictors of successful/non-successful outcome [172]. This subject has accordingly been addressed in several studies. However, the complexity of treatment strategies, definitions of outcome (e.g. weight loss, weight regain, weight maintenance, drop-out), choice of predictors (e.g. metabolic, anthropometric, demographic, psychosocial, behavioural), and time periods and patient groups studied makes it very difficult to compare studies and get an overall picture.

Attrition from treatment is a major concern in obesity programs. Young age has been identified as a predictor of drop-out both short [66, 173, 174] and long term [175]. Other
reported predictors of attrition are the number of previous dieting attempts [176], high weight loss expectations [173], absence of depressive syndrome and other obesity-related diseases [177], high scores on pre-treatment hunger [80], and working full-time [177].

Studies including both women and men have reported male sex [174, 178, 179], and pre-treatment body weight or BMI to predict better weight loss outcome [180-182]. Poor weight loss has been associated with previous participation in an obesity intervention [183], high numbers of previous dieting attempts [176, 184, 185] and low treatment attendance, both short [182, 183, 186], interim [183], and long term [175]. Greater weight reduction has been associated with high self-efficacy expectations [183]. Furthermore, better weight loss has been reported in patients who perceive greater social support, whereas attendance of a spouse during consultation [183] and earning a lower income has been associated with lower weight loss [187]. The presence of a medical trigger has been associated with better outcome [188], whereas the impact of self-rated pre-treatment physical health on weight loss outcome is inconclusive [176, 182].

Different aspects of eating behaviour have been associated with weight loss in several obesity programs. Higher disinhibition and hunger scores and lower dietary restraint scores predicted poor outcome in a 10 week VLED treatment with behaviour modification [189]. High dietary restraint and depression scores predicted lower 1-year weight loss in an intervention with lifestyle changes and sibutramine therapy [181], whereas lower disinhibition scores, indicating better control of overeating, predicted better weight maintenance in a 1-year treatment with 8 initial weeks of VLED [82]. Furthermore, better self-efficacy regarding control of eating behaviour predicted greater weight loss after 8 weeks of a low-energy diet with meal replacements [190]. Similarly, less problems with binge eating predicted greater weight loss after 55 weeks of follow-up in an cognitive-behavioural intervention, in some subjects combined with a VLED [187].

Larger initial weight reduction has been associated with better weight loss short [82, 191], interim [192, 193] and long term [194, 195]. Contradictory to what is commonly believed, a greater initial weight loss achieved without lifestyle changes (for example by use of VLED or anorectic drugs) is associated with a better long term result, given that the weight loss phase is followed by a comprehensive lifestyle intervention [195]. In a meta-analysis of 29 U.S. studies, weight maintenance at 5-year follow-up was significantly better after VLED treatment or initial weight losses of 20 kg or more, than after treatment with food-based energy reduced diets or initial weight losses of less than 10 kg [194]. Although studies have reported associations between poor outcome and greater expectations for weigh loss success [182], others have reported better weight loss in patients with “unrealistic” weight loss expectations [196]. The authors conclude that even though high expectations may be somewhat problematic it does not necessitate reformulation of weight loss goals [196].
AIMS OF THE THESIS

The overall aim of this thesis was to improve outcomes of VLED treatment and to evaluate effects of surgical treatment on disability pension in obese patients.

The specific aims were:

Paper I
• To test the hypothesis that prolonged refeeding duration after successful VLED-induced weight loss beneficially affects weight development in a 1-year perspective
• To test the hypothesis that prolonged refeeding duration beneficially affects eating behaviour

Paper II
• To explore baseline outcome predictors of a 12-week VLED treatment

The telephone interview
• To examine reasons for VLED failure

Paper III
• To prospectively compare disability pension incidence in surgically and conventionally treated obese men and women
• To compare disability pension days over 10 years in surgically and conventionally treated obese men and women
STUDY POPULATIONS AND METHODS

This thesis is based on studies from two different obesity interventions; the 1-year Refeeding study, and the 20-year Swedish Obese Subjects (SOS) study. The subjects in Papers I, II, and the Telephone interview were participants in the Refeeding study, whereas subjects in Paper III were participants in the Swedish Obese Subjects study. An overview of the studies is given in Table 4.

Table 4. Study description and number of participants.

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Study</th>
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<tbody>
<tr>
<td>Paper I</td>
<td>Randomised intervention</td>
<td>169</td>
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<tr>
<td>Paper II</td>
<td>Explorative prediction analysis</td>
<td>267</td>
</tr>
<tr>
<td>Telephone interview</td>
<td>Semi-structured interview</td>
<td>118</td>
</tr>
<tr>
<td>Paper III</td>
<td>Controlled intervention</td>
<td>4047</td>
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Refeeding study

The Refeeding study is a randomised, 1-year clinical trial initiated with 12 weeks of VLED treatment, that was conducted to examine the effect of prolonged refeeding on weight maintenance and eating behaviour in obese patients after a VLED-induced weight loss. The study was carried out between August 2004 and January 2008. Participants were patients referred to the Obesity Unit at Sahlgrenska University Hospital, and were eligible for the trial if aged 18–60 years with BMI ≥30.0 kg/m² and meeting the criteria for VLED treatment based on current guidance [61]. All participants had to pass an initial medical and dietary examination to identify possible contraindications for VLED treatment including pregnancy and lactation, unstable type 1 diabetes or cardiac disease, recent cerebrovascular disease, history of eating disorder, severe psychiatric disorder or other severe disease. Concomitant weight loss medication was not allowed.

Patients with a weight loss equal to, or greater, than 10 percent after 12 weeks of VLED were randomized to 1 or 6 weeks of refeeding, and followed and actively treated for an additional 40 weeks. Non-randomised patients were offered routine treatment at the obesity unit. The study was approved by the regional ethical review board and all participants gave written informed consent.

Swedish obese subjects (SOS) study

The Swedish Obese Subjects (SOS) study is an ongoing, prospective, non-randomized, controlled intervention study that investigates the effect of intentional long-term weight
loss on morbidity and mortality [99, 101, 103]. Between September 1987 and January 2001 obese individuals were recruited to the SOS study through advertisement campaigns in mass media and within the Swedish primary health care system. A matching examination was completed by 6905 individuals. Inclusion criteria for the subsequent intervention study were age 37 to 60 years and a body mass index (BMI) of \( \geq 34 \text{ kg/m}^2 \) for men and \( \geq 38 \text{ kg/m}^2 \) for women. Exclusion criteria, described elsewhere [103], where minimal and aimed at ensuring that the subjects in the surgery group could tolerate the operation. Identical inclusion and exclusion criteria applied to both groups.

Among eligible subjects (N=5335), 2010 selected surgical treatment and constituted the surgery group and a concurrently matched control group of 2037 individuals was created using sex and 18 variables from the matching examination [103]. The remaining 1288 eligible patients offered less optimal matching and were thus not selected by the automatic matching system [103]. In the matching procedure, each control subject was selected from the pool of potential controls to make the current mean values of the matching variables as similar as possible in control and surgical groups. Both the operated patient and the conventionally treated control patient started the intervention study on the day of surgery. All the regional ethics review boards involved approved the study protocol and informed consent was obtained from all subjects.

Approximately 4 weeks before operation, the surgery and control patients underwent baseline examinations. Follow-up examinations were performed after 6 months, 1, 2, 3, 4, 6, 8, 10, 15 and 20 years. Blood chemistry was centrally analyzed at the matching and baseline examinations and after 2, 10, and 15 years. The participants also completed questionnaires on health status, dietary intake and health-related quality of life at each time point.

Surgical treatments were non-adjustable or adjustable gastric banding (18.7%), vertical banded gastroplasty (VBG) (68.1%), or gastric bypass (13.2%) [91] depending on local practice at the surgical departments. Conventional treatments ranged from no treatment at all to dietary advice, behavior modification, very-low-energy diet, physical exercise or pharmaceutical treatment.

**Study participants**

Paper I is based on 169 obese patients who had lost \( \geq 10\% \) of weight after a 12-week VLED. Initially, 300 patients were enrolled to the Refeeding study between August 2004 and January 2007 (Figure 5). Of these, 20 subjects never completed the baseline questionnaires and 11 never started treatment. Thus, 269 patients started the VLED phase of the study and 169 were subsequently randomised to one or six weeks of refeeding.
Figure 5. Flow chart of the Refeeding study. LOCF, last observation carried forward.

Paper II includes 267 participants recruited to the Refeeding study (Paper I). Of the 300 patients, 22 subjects never completed the baseline questionnaires and 11 never started treatment, thus leaving 267 patients to be evaluated for predictors of VLED outcome.

A Telephone interview was conducted with patients who had a non-successful outcome (drop-out or ≤10% weight loss) to explore reasons for VLED failure. Of the 96 non-successful patients, 87 patients (91%) were interviewed whereas 9 patients could not be reached. For comparison, interviews were also carried out with a subsample of 31 (18%) successful patients.

Paper III is based on the 4047 participants in the Swedish Obese Subjects intervention study [101, 103]. In total, 673 individuals had disability pension at study inclusion and were excluded from the incidence calculations. Thus, the incidence of disability pension was analysed in 3374 individuals (1022 men and 2352 women) from the date of their inclusion into the study to December 31, 2006. Number of disability pension days over 10 years was calculated in a subgroup of 2901 individuals included in the SOS study 31 December 1996 or earlier and followed for at least 10 years at 31 December 2006.
Design of Paper I

VLED program (Papers I, II)
During 12 weeks patients were encouraged to follow a strict liquid very-low-energy diet (2.0-3.4 MJ/day). Patients selected and paid themselves for one of the following, commercially available diets; Modifast® (3.4 MJ/day), Nutrilett® (2.3 MJ/day) or Cambridgekuren® (2.0 MJ/day). Free consumption of non-caloric beverages (< 25 kJ/100 g) was allowed. All patients had scheduled nurse visits at weeks 0 (baseline), 2, 5, 8, and 12. During the clinic visits, patients were given support and counselling to enhance VLED compliance. Side effects were monitored and more frequent contacts were offered if needed. All patients were encouraged to be physically active.

Randomisation
At week 12, patients with ≥10% weight loss were randomised to one or six weeks of refeeding to an ordinary, energy reduced diet. The randomisation was stratified by sex and degree of weight loss (strictly greater than or less than 17.1%). Eligible patients were randomly assigned within each of the four strata to one of the two treatments (1 or 6 weeks refeeding) in blocks of size two, with equal allocation of treatments within each block. The randomisation list was generated with a pseudo-random number generator. The treatment allocation order was arranged in numbered, sealed envelopes and kept in separate boxes for each stratum. At patient assignment, the next envelope in order was drawn from the appropriate box.

Refeeding and dietary treatment
Following VLED, dietary treatment advice was given during nine individual sessions with a dietician (week 12, 15, 18, 21, 26, 32, 38, 44, and 52). Standardized written and oral instructions for one or six weeks of refeeding were provided. During refeeding, ordinary meals were gradually re-introduced and VLED portions removed. Recommended energy intake was based on estimated energy requirement minus 30% to achieve an energy-reduced level. Energy requirement was calculated from the equation of Harris-Benedict [197] for estimation of basal metabolic rate, and multiplied by a factor of 1.3 for total energy expenditure (moderate physical activity level). All patients received written dietary advice based on three main meals with portion sizes in grams of different meal components. Recommended energy distribution was for breakfast 20%, lunch 35%, and dinner 35% of daily energy intake, and 10% from snacks. The specific dietary advice covered meal pattern and composition, food choice, portion size, eating behaviour and physical activity. Dietary prescriptions followed Swedish Nutrition Recommendations [198].
Measurements

Anthropometric measures and blood pressure
Body weight was measured on calibrated, electronic scales in underwear and without shoes to the nearest 0.1 kg. Height was measured in standing position to the nearest 0.5 cm. Body mass index (BMI) was calculated (kg/m$^2$). Waist circumference was measured midway between the costal arch and the iliac crest and hip circumference at the symphysis-trochanter femoris level to nearest 1.0 cm. Baseline systolic and diastolic blood pressure were measured once in both arms, whereafter the arm with highest pressure was used throughout the study. At week 26 and 52, systolic and diastolic blood pressure were measured twice in sitting position after 5 minutes rest, registering the mean value.

Biochemical analyses
At baseline, week 26 and 52, blood samples for biochemical analyses were drawn after overnight fasting. The analyses included fasting plasma (P)-Glucose, serum (S)-High density lipoprotein cholesterol (S-HDL), and S-Triglycerides (S-TG), and S-Insulin (only at baseline).

Three-Factor Eating Questionnaire
The revised Three-Factor Eating Questionnaire (TFEQ-R21) was used to measure self-assessed eating behaviour at baseline and follow-up assessments were performed at weeks 15, 21, 26, and 52. TFEQ-R21 covers three eating behaviour domains: cognitive restraint, emotional eating, and uncontrolled eating [138, 139]. Additional questions on eating behaviour, dietary habits and attitudes toward dieting were also constructed for this study. Additional questions on eating behaviour included: a) perceived hunger during different times of the day; b) degree of cravings for specific snack foods; c) frequency of snacking; and d) binge eating. A 9-item module on attitudes toward dieting comprised questions on motivation to diet, self-prognostication, social orientation, and social support.

Design of Paper II

VLED program
All participants initiated the 12-week VLED treatment described for Paper I.

Outcome variables
Three different outcome measures of VLED treatment were evaluated: percent weight change at week 12 (I), successful versus non-successful outcome at week 12 (II) and attrition during the 12-week VLED (III). The treatment was classified as successful if
weight reduction after 12 weeks was ≥10% of initial body weight. Smaller weight loss or attrition was classified as non-successful treatment outcome.

**Measurements**

**Short Form-36**
Generic Health-related quality of life (HRQL) was assessed by the established Short Form-36 (SF-36) questionnaire that covers eight general health status domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health [115]. In addition, a physical and mental component summary score is calculated.

**Mood Adjective Check List**
Mood/mental well-being was measured by the Mood Adjective Check List (MACL). MACL contains 38 adjectives which covers three bipolar mood dimensions: pleasantness/unpleasantness (for example, satisfied, optimistic/depressed, resigned), activation/deactivation (for example, alert, active/passive, apathetic) and calmness/tension (for example, relaxed/tensed, distressed) [116]. An overall mood score is also calculated.

**Rosenberg Self-Esteem scale**
The Rosenberg Self-Esteem scale (RSE) was used to assess global self-esteem [118]. RSE comprises 10 items and responses are aggregated to a total score.

**Obesity-related Problems scale**
An extended 14-item version of the Obesity-related Problems scale (OP) was used to measure the impact of obesity on psychosocial functioning [28]. Subjects indicate how bothered they are by their obesity in a broad range of social activities. Responses are aggregated to a total score.

**Obesity Functional health scale**
The Obesity Functional health scale (OF) was used to assess condition-specific functional limitations [119]. OF comprises 39 items which covers nine domains: mobility, ambulation, sleep and rest, home management, work, recreation, social interaction, sex life, and aches and pain. An overall functional health score is also calculated.

**Socio-economic data**
The participants completed questions on marital status, family structure, education, income, employment, sick leave and disability pension.
Other variables
Information on comorbidity and prescribed medication was collected from the patients’ medical records.

Design of the Telephone interview

A qualitative approach was used to explore reasons for VLED failure. Patients with a non-successful treatment outcome (Paper II) were contacted for a telephone interview one month or later after known outcome (drop-out or ≤10% weight loss). For comparison, interviews after VLED completion were conducted with a subsample of consecutively successful patients. Open, indirect questions were asked concerning diet convenience, perceived difficulties related to the diet, and perceived wellbeing during treatment. The patients’ reflections were written down by the interviewer. In every text, one main VLED failure description was identified and similar problems were grouped in categories and counted. All interviews were carried out by one researcher.

Design of Paper III

Measurements and questionnaires
The matching examination comprised anthropometric measures, blood pressure and blood chemistry.

All participants also completed questionnaires on health status, dietary intake and health-related quality of life. The general health questionnaire included questions on e.g. socioeconomic status, education, smoking, cohabitation, sleep habits, medical conditions, medication and self-rated health status. The health-related quality of life questionnaires included six scales that were used in the matching program, comprising personality traits (monotony avoidance and psychastenia) [199], self-rated current health [130], two scales on perceived social support [130], and one scale on stressful life events [130].

Disability pension register
Complete information on disability pension was obtained from the Swedish Social Insurance Agency on for each subject for the year before their inclusion into the SOS study and until 31 December 2006.
Statistical analyses

**Paper I**

The primary outcome measure was the difference in weight change (%) from week 12 to week 52 between the two treatment groups. Secondary outcome measures were changes in eating behaviour scores (Three-Factor Eating Questionnaire) and cardiovascular risk factors at week 52 as compared with baseline.

As the refeeding periods differed between the groups (1 week in group 1 and 6 weeks in group 6), a post hoc analysis was also carried out to test whether weight change differed between the two groups after the refeeding periods were completed. In this analysis time-points for baseline and endpoint thus differed between the groups with baseline and endpoint at weeks 13 and 47 in group 1, and at weeks 18 and 52 in group 6. The weight values at week 13 and at week 47 were imputed from the weights measured at the closest time points before and after weeks 13 and 47, respectively.

Differences between groups were tested by the two-sample t test (parametric variables) or the Wilcoxon two-sample test (non-parametric variables). Changes within groups were tested by the paired t test. The chi-square test was used to compare dichotomous data. Baseline to week 52 weight changes in the two treatment groups were tested by repeated-measures analysis in completers, and on an intention-to-treat basis with the last weight observation carried forward. In the post hoc analysis, analysis of covariance was used to test the difference in weight change from the new baselines (weeks 13 and 18) to the new endpoints (weeks 47 and 52), with weight loss (%) from study start (before the VLED) to the new baselines as a covariate.

**Paper II**

All analyses were stratified by sex. Differences between men and women, and between successful and non-successful patients, and between those who dropped-out or not were tested by two-sample t-test (parametric variables) or Wilcoxon two sample test (nonparametric variables). Fisher's exact test was used to compare dichotomous data.

Stepwise multivariate regression analyses were used to identify pre-treatment predictors of the three outcome variables. Based on initial Pearson correlations (I) or Wilcoxon two sample tests (II and III) independent variables with a $P$-value $\leq 0.1$ were considered as potential predictors in the models and allowed to stay if $P \leq 0.05$. In addition the identified predictors and percent weight change at week two were tested in multivariate regression models to evaluate the impact of early weight loss on treatment outcome.
Predictors of percent weight change (I)
Multivariate linear regression was used to identify pre-treatment predictors of weight change in patients who completed 12 VLED-weeks. Nineteen and 21 independent variables were entered in the models for women and men, respectively.

Predictors of successful outcome (II) and attrition (III)
Logistic regression analyses were used to identify variables associated with successful outcome (II) or attrition (III). For VLED success (II), ten independent variables were entered into the model for women and 19 for men. Four effect parameters were generated in women and five in men. One variable from each sub final model was removed due to the high correlation with the other identified predictors. For attrition (III), 13 variables were entered into the models for both sexes. The logistic analysis output was expressed as an odds ratio with a 95% confidence interval.

Paper III
Differences between study groups were tested by the two-sample t-test (continuous and ordinal variables) and the chi-square test (dichotomous variables). Because significantly fewer men than women had disability pension at inclusion (13.4% versus 18.0%; P<0.001) all analyses were stratified by sex.

Confounders
Despite the matching procedure, a number of factors that could be related to disability pension outcome differed between study groups. Therefore, the 18 matching variables and 11 other variables that we hypothesised could be associated with disability pension were tested for significant differences between treatment groups and for significant associations between the variable and the presence of disability pension at inclusion in the study. Confounders were tested separately for men and women. The following variables were chosen as confounders as they both differed between the treatment groups and were related to disability pension at inclusion; in men: age, BMI, diabetes (yes/no), self-rated health status (score 1-7 where 1 represents excellent health and 7 very poor), psychastenia score [199], back pain and hip, knee or foot pain restricting work capacity the last 12 months (yes/no), university education (yes/no), and in women: age, waist circumference, total cholesterol, triglycerides, daily smoking (yes/no), self-rated health status (score 1-7), psychastenia score [199], and three variables on pain (neck, back, and hip, knee, foot) restricting work capacity the last 12 months (yes/no), and university education (yes/no).

Incidence of disability pension
The time until partial or full disability pension after inclusion was compared between treatment groups using Kaplan-Meier estimates of cumulative incidence rates. Additionally, a hazard ratio was calculated using a Cox proportional-hazards model, adjusting for type of treatment only or for treatment and the defined confounders. The
observation period was censored at the date of old age pension (65 yrs), emigration or death.

**Number of disability pension days over 10 years**
Partial days of disability pension were converted into full days per year and the analysis separately comprised the year before inclusion and the following ten years. Number of days on disability pension was counted from the date of inclusion for each individual to the date that he or she had been followed for ten years. In addition, total number of potentially possible disability pension days that each subject theoretically could have experienced was calculated as the time from the date of inclusion to ten years later, or to the date of a censoring event [old age pension (65 yrs), emigration or death], whichever came first. The sum of disability pension days was compared between study groups, using a multiple regression model, adjusting for confounders, disability pension days the year prior to inclusion, and the number of potential disability pension days.
MAIN RESULTS

Paper I

Six patients allocated to group 1 dropped out at randomisation and twenty subjects from each group dropped out during the post-VLED dietary intervention (Figure 5). Drop-out rate did not differ by sex or by treatment arm. In total, 58 (69%) and 65 (76%) of participants in group 1 and group 6 completed the entire study (P=0.28).

Figure 6 shows relative weight change over 1-year for the 123 completers by treatment group. At randomisation, mean VLED weight loss was -16.5±3.7% in group 1 and -16.7±4.3% in group 6 (P=0.73). Between weeks 12 and 52, weight increased by 8.2±8.3% in group 1 and 3.9±9.1% in group 6. Group 6 regained significantly less weight over time, both in a completers’ analysis (P=0.006) and in an intention-to-treat analysis with last observation carried forward (P=0.05). Furthermore, the overall weight loss at week 52 compared with baseline was significantly greater in group 6 (-13.4±8.4) than in group 1 (-10.3±7.5%) (P=0.03).

**Figure 6.** Changes (%) in weight (mean±SEM) among completers during one treatment year with 12 initial weeks VLED followed by one (Group 1) or six weeks (Group 6) of refeeding to an ordinary, energy-reduced diet. *** Significant difference between groups over time in completers’ analysis (P=0.006) and in intention-to-treat analysis (P=0.05; repeated-measures analysis).
Of patients allocated to group 1 and group 6, 31 (37%) and 41 (48%), respectively, had achieved a weight reduction of ≥10% at week 52 (P=0.13). Eight (10%) and 20 (24%) patients in group 1 and group 6, respectively, continued to lose weight after ordinary foods were reintroduced and had a lower weight at week 52 than at week 12 (P=0.01).

Baseline eating behaviour did not differ between the two treatment groups. Substantial changes were observed in both groups after the VLED period, i.e. cognitive restraint increased, while uncontrolled and emotional eating decreased. All changes were statistically significant, except for emotional eating at week 52. At weeks 21 (P=0.01) and 26 (P=0.02), dietary restraint was significantly higher in group 6 than in group 1. After 1 year, cognitive restraint and uncontrolled eating had significantly improved in both groups as compared with baseline, while emotional eating did not differ from baseline values. The changes in eating behaviour at week 52 as compared with baseline did not differ significantly between treatment groups.

At week 52, waist circumference, systolic and diastolic blood pressure, plasma glucose, serum HDL and serum TG were significantly improved in both treatment groups as compared with baseline, with the exception of diastolic blood pressure in group 1. However, there were no significant differences between groups at week 52.

Paper II

*Predictors of weight change (I)*

A total of 148 (84%) women and 73 (81%) men completed treatment. Mean weight loss after 12 weeks was 13.5±5.6% and 15.1±6.1% in women and men, respectively (P=0.054). In women, greater relative weight loss was predicted by having more children, lower educational level and better perceived physical health (SF-36 Physical health, sum. score), \( R^2=12.7\% \). Greater weight loss in men was predicted by better self-assessed ambulatory capacity (OF Ambulation), living with a partner or child and snacking on ice cream more often, \( R^2=39.4\% \).

When entering early weight change (percent weight change at week two) into the above models it was independently associated with 12 week weight loss in both women (\( \beta \)-coeff.=1.72, SE=0.25, P<0.0001) and men (\( \beta \)-coeff.=1.57, SE=0.34, P<0.0001), and \( R^2 \) increased to 32.4% and 50.3%, respectively. The initial predictors were still significant.
**Predictors of successful outcome (II)**

Success rates did not differ between women and men (63% versus 67%, P=0.59). At week 12, weight loss in the successful women was 16.1±3.5% and in men 17.1±4.7%, and in non-successful women and men 5.8±2.7% and 5.9±2.4%, respectively.

In women, successful outcome was predicted by less obesity-related psychosocial dysfunction (OP) (Odds Ratio (OR): 0.98, 95% CI: 0.97–0.999), and in men by better functioning in social interaction (OF Social Interaction) (OR: 1.02, 95% CI: 1.004–1.04) and ambulation capacity (OF Ambulation) (OR: 1.02, 95% CI: 1.003–1.04).

When early weight change was entered into the models, the initial predictors were still significant. Early weight change at week two predicted successful outcome in both women (OR: 1.59, 95% CI: 1.24–2.04) and men (OR: 2.15, 95% CI: 1.38–2.35).

**Predictors of attrition (III)**

Attrition rates did not differ between women and men (16% versus 19%, P=0.61). Dropout in women was predicted by lower age (OR: 0.92, 95% CI: 0.88–0.97) and larger hip circumference (OR: 1.03, 95% CI: 1.001–1.07). Attrition in men was predicted by lower perceived general health (SF-36 General health) (OR: 0.97, 95% CI: 0.94–0.99).

When early weight change was entered into the models, it did not predict attrition in women. In men, lower weight loss at week two predicted attrition (OR: 0.57, 95% CI: 0.35–0.92) and the original predictor remained significant in the model.

**The Telephone interview**

Telephone interviews were conducted with 87 (91%) of the 96 non-successful patients whereas 9 patients could not be reached. Six categories of failure reasons were identified (Table 5). The most common problems were illness (28%), hunger and VLED aversion (25%), and mood effects (17%).

Among the 31 (18%) successful patients, 18 women (16%) and 13 men (22%) were interviewed (data not shown). The VLED was described as uncomplicated by 15 (48%) successful patients. Eight (26%) patients reported critical life events. Four patients described negative psychological effects, two reported hunger, one had repeated infections and one experienced social problems.
Table 5. Reasons for VLED failure reported in telephone interviews by 87 of 96 patients with non-successful outcome.

<table>
<thead>
<tr>
<th>Category</th>
<th>Women (n=60)</th>
<th>Men (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness-related (e.g. nausea, repeated infections), n=24</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Hunger and diet aversion, n=22</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Adverse psychological effects (e.g. lowered mood, irritability), n=15</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>No cause given (e.g. VLED perceived as uncomplicated), n=10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous (e.g. surgical treatment, cost of VLED), n=9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Critical life events (e.g. death of family member, divorce, bankruptcy), n=7</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

1. Non-successful: attrition or <10% weight loss after 12 weeks of VLED.

Paper III

At the time of inclusion in the study, the number of men with any degree of disability pension (partial or full) did not differ between the treatment groups (12.7% versus 14.1%; P=0.49). In women, significantly more subjects in the surgery group than in the control group had a disability pension at inclusion (19.9% versus 16.1%; P=0.009).

The mean (s.d.) 10 year weight change in the 2901 participants who had been followed for at least 10 years was -15.8% (12.3) in the surgically treated men and +1.9% (12.8) in the control men (P<0.001). Corresponding weight changes for the women were -16.1% (12.1) and +1.4% (12.1), respectively (P<0.001).

Incidence of disability pension

The effect of bariatric surgery on the incidence of disability pension did not differ between men and women (P=0.50 for gender-treatment interaction) or between subjects below or above median age (P=0.80 for age-treatment interaction). Although the treatment effect was not different between genders we still choose to present the results by gender due to the higher baseline prevalence of disability pension in women.

During the follow-up period, 156 (30.3%) of the men in the surgery group and 156 (30.8%) of the men in the control group were granted a disability pension (unadjusted HR=0.95, 95% CI 0.76–1.18; P=0.62). When adjusting for confounders, a reduced risk of disability pension was suggested in the surgery group compared to the control group (adjusted HR=0.79, 95% CI 0.62–1.00; P=0.05).
The number of women granted a disability pension was 475 (41.7%) in the surgery group and 462 (38.1%) in the control group (unadjusted HR=1.03, 95% CI 0.90–1.17; P=0.67). In women, the risk for disability pension did not differ between treatment groups when adjusting for confounders (adjusted HR=0.95, 95% CI 0.83–1.09; P=0.44).

Disability pension days

The year before inclusion in the study, the average number of disability pension days was 39 (95% CI 29–49) in the surgically treated men and 41 (95% CI 31–51) in the conventionally treated men (P=0.79 for difference). The unadjusted mean number of disability pension days over ten years were 647 (95% CI 540–755) in the surgery group and 696 (95% CI 589–804) in the control group (P=0.53 for difference). When adjusting for the confounders the adjusted number of disability pension days over the 10 year period was significantly lower in the surgery group compared to the control group, 609 (95% CI 540–678) versus 734 days (95% CI 666–803) (P=0.01).

In women, the average number of disability pension days the year before inclusion was 59 (95% CI 51–66) in the surgically treated women and 48 (95% CI 40–55) in the conventionally treated women (P=0.04). The unadjusted mean number of disability pension days was higher in the surgery group compared to the control group, 968 (95% CI 892–1045) and 804 (95% CI 722–886) days respectively, over ten years (P=0.004). When adjusting for the confounders the total number of disability pension days over the 10 year period did not differ between the groups. The adjusted number of days was 889 (95% CI 842–937) in the surgically treated women and 888 (95% CI 837–939) in the conventionally treated women (P=0.97).
**GENERAL DISCUSSION**

Obese individuals are at considerable risk for serious obesity-related comorbidity, impaired health-related quality of life, reduced working capacity, and shortened life expectancy. Consequently, the individual suffering and burden and the societal costs attributable to obesity are substantial and effective treatments required. Although the short term results appear promising for most weight loss approaches, a weight regain over time is seen for all treatments. Cognitive behaviour therapy have minimal side effects and could therefore be considered a preferable treatment option. However, it is not realistic to provide psychological obesity interventions in large scale within the health care system. Even though bariatric surgery is effective, all patients are not obese enough for such an invasive treatment or cannot undergo obesity surgery for other reasons. The Swedish Obese Subjects (SOS) study has confirmed beneficial effects of obesity surgery on for instance diabetes [101], cardiovascular risk factors [101], cancer [102] and life expectancy [99]. Despite intensive research, pharmacological obesity therapies have not been very successful. The long term weight loss is rather modest and the frequency and nature of adverse effects is problematic. Several promising anti-obesity drugs have been established on the European market. However, in 2008 rimonabant was withdrawn due to adverse psychiatric effects (e.g. depression, anxiety) [200, 201], in 1997 dexfenfluramine and fenfluramine was withdrawn due to increased risk of pulmonary hypertension [202] and cardiac valvulopathy [203], and in 2010 the marketing authorisation was postponed for sibutramine due to increased risk of cardiovascular events such as myocardial infarction and stroke [90]. The increased risk of severe adverse effects associated with pharmacological obesity treatment and the rather modest effects on weight loss emphasises the importance of continued efforts to improve treatment programs based on dietary and lifestyle changes.

**VLED in obesity treatment**

The benefit of very-low-energy diets in obesity treatment has been questioned. A common viewpoint, noted by Saris [70], is that weight lost at a slow rate should be easier to sustain and therefore preferable. However, a number of studies have shown that early large weight loss is associated with better treatment outcome long-term [192-195, 204]. The rapid and substantial weight loss, in combination with improvements of risk factors paralleling weight reduction [205], are the main advantages of VLED diets. This favours the use of VLED in patients with associated comorbidities[205]. Pre-operative VLED diets can also be used in patients who need to lose weight before elective surgery [206] or in patients before planned obesity surgery [63]. Moreover, replacing ordinary foods with VLED diets simplifies diet adherence by limiting the exposure of energy-dense foods and the risk of overeating. However, there are also arguments against VLED diets. These
include risks of side effects, difficulties for some patients to adhere to the diet, and problems with weight regain after the VLED period. Nevertheless, VLED diets are proven to be useful in the clinical management of obese patients [71, 73, 80, 207]. However, despite the numerous studies on VLED treatment little is known about which patients are most likely to benefit from VLED treatment and which patients need extra support. Another important issue is the effect of different refeeding strategies. Against this background, we planned the Refeeding study with the overall objective to improve the outcome of obesity treatment with an initial VLED weight loss phase. Three different approaches were used; (i) a randomized trial to study the effect of different refeeding periods on weight development and eating behaviour (Paper I), (ii) an explorative analysis to identify predictive factors for VLED outcome (Paper II), and (iii) a telephone interview to explore reasons for VLED failure (the Telephone interview).

Which patients should be offered VLED treatment?

Knowledge about predictors for weight loss can contribute to a better management of obesity [172]. A lot of work has been done on predictive factors in relation to weight loss and weight maintenance. However, most studies have examined predictors for long term outcome of energy reduced diets or treatments including VLED as one part of a more comprehensive weight loss programme [79, 80, 82, 172, 191, 204]. Although the long term maintenance of weight lost is crucial in obesity treatment, the actual weight loss phase also deserves attention. If the initial weight loss phase is successful, the probability for better weight loss long term is also increased. It is important to recognize that being on a VLED is very different from trying to lose weight on an energy reduced, ordinary diet. When the special characteristics of VLED are considered it is reasonable to believe that outcome predictors for VLED are probably different from other diets.

Some of the patients that initiate a VLED will find the diet hard to follow and others will drop out from treatment. In VLED programs over 10 to 12 weeks, attrition rates of 7–28% have been reported [63, 72, 73, 76, 189]. Moreover, although patients with comorbidity and poor health-related quality of life have a lot to gain from successful weight loss, those patients may also have a lower capacity to cope with additional stress if the VLED becomes complicated.

We explored a wide range of potential pre-treatment predictors for outcome of a 12-week VLED treatment in women and men separately (Paper II). Our findings clearly indicate that although women and men can achieve similar VLED outcomes, different factors may influence the outcome of VLED treatment in women and men. Variables related to perceived physical health, social interaction, socio-economic factors and obesity-related psychosocial problems predicted VLED outcome. Furthermore, the results suggest that
social support and walking capacity are important determinants of successful weight loss in men whereas psychosocial function is important for VLED success in women.

Several studies have investigated the predictive value of eating behavior aspects in obesity treatment and the results are contradictory [172, 204]. The lack of consistent results may partially be due to differences in patient selection, treatment approach, outcome measure, and follow up time. In our study, pre-treatment eating behaviour did not predict outcome (Paper II). One study that investigated predictors of weight loss after 10 weeks of VLED treatment found no association between weight loss and the Eating Inventory factors dietary restraint, disinhibition and hunger [189]. However, when LaPorte and Stunkard [189] categorised treatment compliance in four groups ranging from absolute diet adherence to attrition, participants in the two most compliant groups had significantly lower pre-treatment hunger scores and were also more likely to have a higher restraint score than hunger score. Long term, previous research have shown that higher hunger scores at baseline predicted attrition from a two-year treatment where one group initially received VLED for 12 weeks [80]. Contradictory to these findings, Fogelholm and coworkers [82] showed that higher pretreatment hunger and lower binging scores predicted greater weight reduction in a 12-week weight loss program including 8 weeks of VLED. The inconclusive results suggest that it may be difficult to predict treatment outcome of any dietary obesity intervention from pre-treatment eating behavior. Moreover, a VLED is a specific and well defined diet that differs from other dietary treatments in many essential aspects, e.g. diet monotony, consistency, energy level, restriction in food choice, and lack of ordinary foods. Therefore, it is not likely that factors that predict outcome of ordinary, energy-reduced diets also predict VLED outcome.

In accordance with previous studies [82, 186, 191], early weight loss was a strong predictor of final weight loss outcome in both women and men and attrition only in men (Paper II). Disappointment with treatment outcome has been reported as common reason for drop-out [208]. In the telephone interviews, focusing specifically on VLED treatment, no patient reported poor weight loss as a reason for drop-out. However, 70% of patients reported problems with illness, hunger and diet aversion, and depressed mood (the Telephone interview). An unexpected finding was that various comorbidities were as often reported as problems related to the large energy restriction and sensory properties of the diet. Adverse psychological effects were not uncommon reasons for non-successful outcome. Despite this, baseline mood did not predict outcome (Paper II), possibly due to the generally low values in the study group that indicate that we should have included a clinical measure of psychiatric morbidity, such as the Hospital Anxiety and Depression scale [209]. Seven non-successful patients specified critical life events, such as death of a family member or close friend, as a reason for VLED failure. Interestingly, 8 of the 31 interviewed successful patients also reported a critical life event during VLED. This
implies that differences in coping may influence VLED outcome. However, half of the successful patients found the treatment uncomplicated as compared to 12% of the non-successful patients (the Telephone interview).

There is only a limited range of non-surgical treatments that have capacity to induce substantial weight loss in severely obese subjects. Moreover, little is known about which patients are most likely to successfully lose weight on a specific treatment. Therefore, VLED treatment should be offered obese patients who meet the criteria for VLED based on current guidelines [61]. However, our findings (Paper II) suggest that patients with low perceived health and who lack a close social network may need extra support during treatment with VLED. Other factors that seem to influence VLED outcome and require more attention are ambulatory capacity in men and psychosocial functioning in women.

To our knowledge this is the first study that has evaluated possible predictors for outcome of the actual VLED period. Other studies on predictors for weight loss have included a limited number of variables [82, 189, 191] whereas we decided to include a wide range of independent variables in our analyses (Paper II). The rational for the generous number of variables was the scarce knowledge of which predictors to include in the models. An open-minded approach that comprised various potential predictors seemed as a logical first step. However, the large number of potential predictors used for three different outcomes, in both women and men, made it difficult to draw coherent and consistent conclusions from the analyses. It is possible that constructing separate predictive models for the different types of factors (e.g. socio-economy, obesity-specific HRQL, general HRQL) would have made interpretation easier. However the literature on prediction of weight loss and weight maintenance is diverse and Paper II is preliminary an exploratory study to identify which predictors to study further. More work is clearly needed to confirm the identified predictors.

**Improving weight maintenance after VLED**

In general, weight loss during VLED is large whereas the long term weight maintenance is poor [70, 210]. Therefore one of the most important issues to address in the management of VLED is how to prevent weight regain when the patient is switching back to a conventional diet after the weight loss phase. Throughout the refeeding, ordinary foods are reintroduced during stepwise substitution of VLED portions for energy reduced ordinary meals. Previous research has observed improved post-VLED weight maintenance with pharmacological therapy [72, 81], exercise [82], incorporation of VLED in the meal plan after the weight loss phase [73], and protein supplementation [83]. One aspect that could influence weight development after VLED is the time for which the refeeding phase is extended. After weight reduction with VLED, different studies have
practiced refeeding phases of one to six weeks [66, 68, 71-78, 211] and they do not provide any rational for the chosen refeeding periods. We hypothesized that a prolonged refeeding period may affect patients’ ability to adopt new eating behaviors and obtain long term weight control.

Consistent with our hypothesis, Paper I showed that after losing 10% or more in weight during VLED, patients with a prolonged, 6-week, refeeding period regained significantly less weight than patients with 1-week refeeding. Also in line with this hypothesis the group with the longer refeeding period maintained higher levels of dietary restraint after the refeeding was completed. Part of the greater weight loss after prolonged refeeding could be ascribed the lower recommended energy intake during the refeeding period. However, the essential aspect of any dietary obesity intervention is patient adherence [67]. We propose that the better weight development with prolonged refeeding is due to lower recommended refeeding energy intake, better control of eating behaviour and longer time to practise and adjust to each meal, resulting in improved ability to restrict food intake and follow dietary prescriptions.

We chose to randomise patients with weight losses greater than 10% after VLED. Equal amount of weight loss has also been required for randomisation in other studies with 12 weeks of initial VLED [72]. At randomisation, six patients dropped out from the group with one week of refeeding whereas no patient dropped out in the group with six weeks of refeeding. This implies that those who dropped out preferred a longer refeeding duration. Treatment preference is a recognized problem in clinical studies with a randomised design [212], and in dietary interventions like Paper I it is impossible to blind the study alternatives for the patients and the clinic staff. Although much effort was made when the patients were recruited to present both refeeding options as equally likely to be successful, and the clinic staff was aware of the necessity to deliver both treatments with comparable enthusiasm, it is possible that some patients regarded the shorter refeeding as less effective. However, it should be noted that the drop-out rates were not significantly different between treatment groups.

After the VLED period, 17% of the 169 randomised patients continued to lose weight and had a greater weight loss at week 52 than after the 12-week VLED (Paper I). Interestingly, after 1 year, a weight reduction of at least 10% was maintained in 43% of the randomised patients, corresponding to every fourth patient that initially started VLED treatment. This finding emphasize that even though overall weight loss development may be poor for obesity treatment with diet and lifestyle changes, a quite large proportion of obese patients can attain satisfactory treatment outcome. However it should also be noted that we only followed the patients for 1 year and this is a short time in obesity programmes. Thus the long term effect of the refeeding strategy is not clear. Due to lack of resources we were unable to extend the study for longer than 1 year. This is
unfortunate, but it should be pointed out that long-term follow up after obesity treatment is difficult to achieve as the drop-out from obesity programmes tend to be very high [213].

Research findings from treatment studies can be problematic to translate into clinical practice. This is for example the case if studies recruit healthier participants than obese patients seeking medical help for their obesity and comorbidities. Furthermore studies may use expensive and time-consuming procedures that are not applicable in ordinary health care settings [214]. However, the Refeeding study was carried out with participants from the actual target population: obese, referred patients with a variety of comorbidities. Overall, the treatment program was carried out with a quite modest resource use, in total 13 clinic visits to a nurse or a dietitian, and scheduled meetings with a physician every six months. Moreover, the refeeding after VLED weight loss is a behavioural technique utilized by the patient. In contrast to pharmacological therapy, a prolonged refeeding does not add to the costs for the health care or the patient. Furthermore, the longer refeeding does not require extra clinic visits for the patient.

**Obesity-related costs for disability pension**

Recently, it has been estimated that about 10% of the total costs for health care in adults are attributable to obesity [165]. Furthermore, obesity is associated with increased risk for disability pension [164, 215-217], and the related societal costs for productivity loss are considered substantial [164, 169]. In the early 1990’s, approximately 10% of the total cost of productivity loss due to sick leave and disability pension in Swedish women could be related to obesity and associated comorbidities [164].

Prior research has reported increased working capacity after surgical obesity treatment [218-222]. However, these studies were small, used self-reported information on working capacity, had short follow-up times or lacked control groups [219-221]. One small Swedish study found that surgically treated patients reported fewer disability pension days one to five years after surgery, as compared to an obese control group [218]. In addition, a previous report from the Swedish Obese Subjects (SOS) study showed reduced levels of sickness and disability pension three years after obesity surgery [222]. However, the difference compared to the control group attenuated over time, which indicated that an extended follow-up period was required to verify the results. Therefore, the objective of Paper III was to prospectively examine the effect of obesity surgery on disability pension incidence over a period of up to 19 years and number of disability pension days over a 10-year period.
We found a reduced risk of disability pension in surgically treated men when adjusting for confounders (Paper III). In line with this finding, the adjusted number of disability pension days was lower in surgically treated men as compared to conventionally treated, on average weight stable men. In obese women, however, disability pension did not differ between the surgery and control group.

The prevalence of disability pension is higher in women than in men in the general Swedish population [223] and approximately twice as high in obese Swedish women as compared to women in the general population [164]. In the present study, we also found a higher prevalence of disability pension at baseline in women than men (Paper III). Furthermore, women in the surgical group were more likely to have disability pension at baseline than women in the control group whereas this difference was not seen between male treatment groups (Paper III).

We did not examine the causes for granted disability pension in the present study (Paper III). This was not possible, since the Swedish Social Insurance Agency did not have complete information on the diagnose codes (according to the International Classification of Diseases, ICD). Thus, it is possible that some participants in our study have disability pension due to illness that is not weight related. Moreover, the range of diagnoses may also differ between female and male participants in the treatment groups. A Swedish prospective study has reported on the influence of diagnosis on risk for disability pension in individuals on long term (≥56 days) sick leave [224]. The findings suggested gender differences. The risk for disability pension was highest in men with mental disorders and women with musculoskeletal disorders [224]. A large number of severe medical conditions are prevalent in obese individuals [29] and numerous health-related factors may interact and affect an individual’s working capacity. Moreover, the causes of disability pension are complex and are affected by a number of external factors such as unemployment rates, former employment status and labour legislation. Disability pension may therefore be a problematic outcome measure in intervention studies.

Reduced levels of disability pension generate social productivity gains. In our study, bariatric surgery had beneficial effects on disability pension in men but no effect in women. However, it should be emphasised that bariatric surgery have positive effects on other outcomes, such as survival [99], cancer in women [102], and diabetes [101], all associated with substantial costs for health care [149, 150] and productivity loss [167]. In this study, we did not calculate the costs for disability pension in the study groups and hence we did not carry out any formal economic evaluation. However, the costs for disability pension cannot be estimated without knowledge about the number of disability pension days and the results of this study can therefore be used in future studies of societal costs for disability pension in obese patients who receive conventional and surgical treatment.
Summary and reflections

This thesis has focused on the use of VLED in obesity treatment. The Refeeding study suggests that the refeeding period is important for weight maintenance after one year. Although these studies do not address the challenge of long term weight maintenance this result has important practical implications for how VLED treatment should be administered. Successful VLED outcome is also a prerequisite for long term weight loss and studying the actual VLED period is therefore important in understanding longer term success. The exploratory prediction analyses identified factors such as physical health, social interaction, socioeconomic factors and obesity-related psychosocial problems that could be important for VLED outcome. Future studies are needed to confirm these results.

Few studies have explored the obese patients’ experience of their treatment. Qualitative studies may provide such important information. A qualitative interview study exploring the patients’ experience of the treatment during and after the VLED is currently being analysed and will provide new insights from the patients’ perspective and may also generate new hypotheses to be tested in randomised designs.

The exploratory prediction analyses suggested gender differences. Men and women may have different reasons for wanting to lose weight and may also encounter different problems when they attempt to lose weight. Future studies need to include both men and women and be statistically powered to study gender differences.

Gender differences were also suggested in the SOS study where obesity surgery was associated with reduced risk of disability pension in men but not in women. Causes for productivity loss are, however, complex and disability pension is only one aspect. Studies investigating sick leave and the causes for sick leave and disability pension, in both lean and obese men and women, will give us a more complete picture on how obesity is related to productivity loss.
CONCLUSIONS

The overall aim of this thesis was to improve outcomes of VLED treatment and to evaluate effects of surgical treatment on disability pension in obese patients.

From our findings, we conclude that:

• A prolonged refeeding duration after VLED-induced weight loss was associated with significantly improved weight maintenance in a 1-year perspective (Paper I)

• Patients with prolonged refeeding maintained higher levels of dietary restraint after the refeeding was completed, but eating behaviour did not differ between the refeeding groups after 1 year (Paper I)

• Obese women and men attained similar VLED outcomes, whereas the predictors of VLED outcome differed by gender (Paper II)

• Factors related to perceived physical health, social interaction, socio-economic factors and obesity-related psychosocial problems predicted VLED outcome (Paper II)

• The most frequently reported problems in patients with non-successful VLED outcome were illness, hunger and diet aversion, and depressed mood (The Telephone interview)

• In men, bariatric surgery was associated with a reduced incidence of disability pension for up to 19 years and reduced number of disability pension days over 10 years, whereas neither favourable nor unfavourable effects could be detected in women (Paper III)
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