

FROM THE DEPARTMENT OF MEDICINE  
Karolinska Institutet, Stockholm, Sweden

# **VERY LOW ENERGY DIETS IN THE TREATMENT OF OBESITY**

Studies of Obstructive Sleep Apnoea, Side-Effects,  
and Treatment Discontinuation

Kari Johansson



**Karolinska  
Institutet**

Stockholm 2012

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

Published by Karolinska Institutet. Printed by E-print AB.

© Kari Johansson, 2012  
ISBN 978-91-7457-736-5

*Choose a job you love  
and you will never have to work  
a day in your life.*

Confucius

## ABSTRACT

**Background** The prevalence of obesity has increased dramatically during the last decades worldwide. Obesity is associated with increased risk of morbidity and mortality, leading to an increased suffering for the individual patient and an increased burden on the health care system. Currently, the most effective treatment is bariatric surgery. Since bariatric surgery cannot be provided to all obese patients, other non-surgical obesity treatment methods are needed.

**Aim** The overall objective of this thesis was to evaluate effects and side-effects of very low energy diets (VLEDs), as well as to characterise treatment discontinuation. Specific objectives were to evaluate weight loss as treatment option for patients with obstructive sleep apnoea (OSA; *Study I&II*); to assess the risk of gallstones requiring hospital care, and cholecystectomy, in a commercial weight loss programme using VLED or low energy diet (LED; *Study III*); and to characterise discontinuation patterns in obesity treatment programmes by analysing data from anti-obesity drug trials (*Study IV*).

**Methods** The study on OSA and weight loss (*Study I&II*) consisted of a randomised controlled trial (RCT) followed by an observational follow-up for a total duration of one year. Included were obese men (n=63, BMI 30-40, aged 30-65 years) with moderate to severe OSA (apnoea-hypopnoea index (AHI)  $\geq 15$ ) treated with CPAP. The intervention consisted of a hospital-based weight loss programme, using VLED (554 kcal/day) to promote weight loss for nine weeks. After the RCT was finished the controls also received VLED. The VLED, in both groups, was followed by a 43-week weight loss maintenance phase. *Study III* was a one-year matched cohort study of consecutively enrolled adults in a commercial weight loss programme in Sweden between 2006 and 2009 (n=6,640; mean age 46y; 83% women; mean BMI 33). The intervention included a three-month weight loss phase, consisting of either VLED (500 kcal/day) or LED (1,200-1,500 kcal/day), followed by a nine-month weight loss maintenance phase. Gallstones requiring hospital care and cholecystectomies during the one-year programme were collected from the National Patient Register. *Study IV* was a systematic review and meta-analysis including published placebo-controlled anti-obesity trials of orlistat, sibutramine and rimonabant (n=13,457).

**Results** *Study I&II*: After the nine-week RCT the intervention group's mean body weight was 20 kg lower than that of the control group, and its mean AHI was 23 events/h lower. In total 70% (44/63) completed the one-year pooled observational follow-up. The AHI changes after nine weeks of VLED (-58%) were largely maintained at one-year (-47%) following the initial weight loss of 18 kg, and 12 kg at one year. *Study III*: The absolute risks of gallstones requiring hospital care and cholecystectomy were found to be low, but three times higher in the VLED than the LED programme (hazard ratio 3.4 and 3.1, respectively; both  $P < 0.001$ ). While the risks were greater in the VLED compared to LED group, the benefits in terms of one-year weight loss was also greater (11 vs 8 kg;  $P < 0.001$ ), and the proportion remaining in the programme (82% vs 78%;  $P < 0.001$ ). *Study IV*: The overall combined one-year dropout rates were high in both the drug (30-39%) and placebo arms (37%) of placebo-controlled anti-obesity drug trials, but marginally lower in the drug arms (pooled risk ratio 0.9;  $P = 0.001$ ).

**Conclusion** VLED-induced weight loss resulted in a significant reduction of moderate to severe OSA, with the majority of the initial improvement maintained at one year. Albeit low, the risks of gallstones and cholecystectomy were greater with VLED than LED treatment, as was weight loss. Treatment discontinuation was lower both in the hospital-based weight loss programme and in the commercial weight loss programme, as compared to pooled data from the placebo arms in anti-obesity drug trials.

## LIST OF PUBLICATIONS

- I **Johansson K**, Neovius M, Trolle Lagerros Y, Harlid R, Rössner S, Granath F, Hemmingsson E. Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *BMJ* 2009 Dec 3;339:b4609.
- II **Johansson K**, Hemmingsson E, Harlid R, Trolle Lagerros Y, Granath F, Rössner S, Neovius M. Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. *BMJ* 2011 Jun 1;342:d3017.
- III **Johansson K**, Sundström J, Marcus C, Hemmingsson E, Neovius M. Risk of gallstones in a commercial weight loss program using very low energy diet or low energy diet: matched cohort study. *Manuscript*.
- IV **Johansson K**, Neovius K, DeSantis SM, Rössner S, Neovius M. Discontinuation due to adverse events in randomized trials of orlistat, sibutramine and rimonabant: a meta-analysis. *Obes Rev.* 2009 Sep;10(5):564-75.

## LIST OF ABBREVIATIONS

95%CI	95% confidence interval
AHEAD	Action for Health in Diabetes
AHI	Apnoea-hypopnoea index
ALAT	Alanine aminotransferase
ATC	Anatomical therapeutic chemical classification system
BMI	Body mass index
BOCF	Baseline observation carried forward
CBT	Cognitive behavioural treatment
CPAP	Continuous positive airway pressure
E%	Energy percent
FDA	Food and drug administration in the US
GBP	Gastric bypass
GCP	Good clinical practice
GLP-I	Glucagon-like peptide-I
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
ICD	International classification of diseases
ITT	Intention-to-treat
LCD	Low calorie diet
LDL	Low density lipoprotein
LED	Low energy diet
LOCF	Last observation carried forward
NHANES	National Health and Nutrition Examination Survey
NWCR	National Weight Control Registry
ODI <sub>4</sub>	Oxygen desaturation >4% per hour of sleep
OSA	Obstructive sleep apnoea
OSAS	Obstructive sleep apnoea syndrome
RCT	Randomised controlled trial
RDI	Respiratory disturbance index
SCOUT	Sibutramine Cardiovascular Outcomes Trial
SOS	Swedish Obese Subjects
TSH	Thyroid stimulating hormone
US	United States
VLCD	Very low calorie diet
VLED	Very low energy diet
WHO	World Health Organisation

# CONTENTS

<b>I</b>	<b>Introduction .....</b>	<b>6</b>
1.1	Obesity and Overweight .....	6
1.1.1	Definition.....	6
1.1.2	Prevalence .....	7
1.1.3	Health Consequences.....	7
1.1.4	Treatment .....	8
1.2	Very Low Energy Diets.....	12
1.2.1	History .....	12
1.2.2	Composition.....	12
1.2.3	Availability .....	13
1.2.4	Treatment .....	13
1.2.5	Side-Effects.....	15
1.3	Obesity and Obstructive Sleep Apnoea .....	17
1.3.1	Definition, Risk Factors, Symptoms and Treatment.....	17
1.3.2	Mechanisms.....	18
1.3.3	Previous Research regarding Weight Loss and Treatment.....	18
<b>2</b>	<b>Objectives.....</b>	<b>22</b>
2.1	Overall Objective .....	22
2.2	Specific Objectives .....	22
2.3	Rationale for Included Studies .....	23
2.3.1	Study I&II: Weight Loss and Obstructive Sleep Apnoea .....	23
2.3.2	Study III: Risk of Gallstones during VLED .....	23
2.3.3	Study IV: Treatment Discontinuation .....	23
<b>3</b>	<b>Methods .....</b>	<b>24</b>
3.1	Study Designs and Study Populations .....	24
3.2	Ethical Considerations .....	24
3.3	Study I&II: Weight Loss and Obstructive Sleep Apnoea.....	25
3.3.1	Participants and Design .....	25
3.3.2	Intervention .....	25
3.3.3	Outcomes .....	27
3.3.4	Side-Effects.....	27
3.4	Study III: Risk of Gallstones during VLED .....	28
3.4.1	Weight Loss Programme.....	28
3.4.2	National Health Register Data.....	29
3.4.3	Outcomes .....	30
3.5	Study IV: Treatment Discontinuation.....	31
3.6	Statistical Analysis.....	32
3.6.1	Student's T-Test – Continuous Data .....	32
3.6.2	Pearson's Chi-Squared Test – Categorical Data .....	32

3.6.3	Linear Regression.....	33
3.6.4	Logistic Regression.....	33
3.6.5	Analysis of Covariance .....	33
3.6.6	Cox Regression .....	33
3.6.7	Matching .....	34
3.6.8	Meta-Analysis .....	34
3.6.9	Missing Data .....	35
3.7	Role of the Funding Sources .....	35
<b>4</b>	<b>Results.....</b>	<b>36</b>
4.1	Study I: Weight Loss and Obstructive Sleep Apnoea.....	36
4.2	Study II: Maintenance and Obstructive Sleep Apnoea.....	37
4.3	Study III: Risk of Gallstones during VLED .....	38
4.4	Study IV: Treatment Discontinuation.....	39
<b>5</b>	<b>Discussion.....</b>	<b>40</b>
5.1	Main Findings.....	40
5.1.1	Weight Loss and Obstructive Sleep Apnoea.....	40
5.1.2	VLED and Risk of Gallstones.....	41
5.1.3	Dropout in Anti-Obesity Drug Trials.....	41
5.2	Comparison with Previous Research .....	41
5.2.1	Weight Loss and Obstructive Sleep Apnoea.....	41
5.2.2	VLED and Risk of Gallstones.....	42
5.2.3	Weight Loss Programme Discontinuation .....	43
5.3	Strengths and Limitations.....	43
5.4	Clinical Implications .....	45
5.5	Future Research.....	46
<b>6</b>	<b>Conclusion.....</b>	<b>47</b>
<b>7</b>	<b>Svensk sammanfattning .....</b>	<b>48</b>
<b>8</b>	<b>Acknowledgment .....</b>	<b>49</b>
<b>9</b>	<b>References.....</b>	<b>51</b>



# I INTRODUCTION

## I.1 OBESITY AND OVERWEIGHT

### I.1.1 Definition

Obesity and overweight are defined as abnormal or excessive fat accumulation that may impair health, and classified, according to the World Health Organisation (WHO), by use of the body mass index (BMI; kg/m<sup>2</sup>).<sup>1</sup> A BMI  $\geq 30.0$  is classified as obesity, while a BMI between 25.0 and 29.9 is classified as overweight, sometimes referred to as pre-obesity (**Table 1**).<sup>1</sup>

Classification	BMI (kg/m <sup>2</sup> )
<b>Underweight</b>	<b>&lt;18.5</b>
<b>Normal</b>	<b>18.5-24.9</b>
<b>Overweight</b>	<b>25.0-29.9</b>
<b>Obesity</b>	<b><math>\geq 30.0</math></b>
Obesity class I	30.0-34.9
Obesity class II	35.0-39.9
Obesity class III	$\geq 40.0$

Although BMI is used as a proxy for adiposity, it does not distinguish between fat and fat free mass, nor does it take fat distribution into account. Other more specific measures of body fat include measurement of body composition, such as dual energy X-ray absorptiometry, magnetic resonance imaging and bioelectrical impedance analysis. However, the costs, the limited availability, or the inaccuracy of some of these techniques limit their usefulness especially on the population level. BMI is therefore considered to provide a simple but useful measure of obesity.<sup>1</sup>

Waist circumference is commonly used as a surrogate measure for abdominal obesity (**Table 2**). Visceral fat has been described to be more metabolically active than fat in general, and abdominal obesity may therefore be associated with greater health risks than general obesity.<sup>1</sup> Studies have shown that waist circumference independently contributes to mortality risk beyond BMI.<sup>2</sup>

	Increased risk	High risk
<b>Men</b>	$\geq 94$ cm	$\geq 102$ cm
<b>Women</b>	$\geq 80$ cm	$\geq 88$ cm

### **1.1.2 Prevalence**

The prevalence of obesity has increased dramatically during the last decades worldwide. Between 1980 and 2008, the world prevalence has been reported to have doubled from 5% to 10% among adult men and from 8% to 14% among women.<sup>4</sup> The largest rise was seen in Oceania in both sexes, while the trend was almost flat for women in central Africa, central and eastern Europe and for men in southeast Asia during this time.<sup>4</sup> In 2008, it was estimated that 1.5 billion adults had a BMI  $\geq 25$  and 500 million of these were obese worldwide, with the highest prevalence of obesity in men seen in the United States (US) and in women in southern Africa.<sup>4</sup> According to the latest measured data from the US National Health and Nutrition Examination Survey (NHANES) in 2009-2010, almost 70% of the adult population was overweight or obese, of which half (36%) was obese.<sup>5</sup> In Sweden during the same time, 45% of the adult population was overweight or obese, of which one quarter (11%) was obese, according to self-reported data from Statistics of Sweden.<sup>6</sup> Self-reported data should, however, be interpreted with some caution, due to risk of systematic underestimations.<sup>7</sup> In both the US and Sweden, the most rapid increase of obesity during the last decades has occurred in the morbidly obese group (BMI  $\geq 35$ ).<sup>8,9</sup>

Several reports have suggested that the prevalence of obesity has levelled off since the early 2000s. For example, the prevalence has remained stable among women in the US since 1999, but not among men.<sup>10</sup> In an extensive review of the subject, Rokholm et al<sup>11</sup> concluded that a stabilisation or levelling off in the prevalence of obesity was seen in the majority of studies among children and adolescents. In adults the results were diverging, with some of the studies reporting stability, while increases were still observed in others. Despite a levelling of or not, the current prevalence is at all time high.

### **1.1.3 Health Consequences**

Overweight and obesity are associated with several adverse health consequences such as type 2 diabetes, cardiovascular disease including hypertension and hyperlipidemia, musculoskeletal disorders, obstructive sleep apnoea, psychiatric illness and several cancers (such as postmenopausal breast, colon, kidney, oesophagus cancers).<sup>1,12</sup> Some of these co-morbidities increase the risk of death, while others decrease quality of life or ability to work,<sup>13-15</sup> causing a major economic burden to society. Obesity alone has been estimated to be responsible for 0.7-2.8% of health care expenditures worldwide,<sup>16</sup> while in Sweden, the health care costs of obesity was in 2003 estimated to 3.6 billion SEK, that is 1.9% of the national health care expenditure.<sup>17</sup>

Obesity increases the risk for all-cause mortality,<sup>18,19,20</sup> while some controversy exists for this association in overweight.<sup>20,21</sup> It has been estimated that a BMI of 30-35 reduces life expectancy by two to four years, and a BMI of 40-45 with eight to ten years.<sup>18</sup> In US adults, diet and activity patterns were already in 2000 ranked as the second most important modifiable risk factor for preventable deaths after smoking, accounting for 17% and 18% of excess annual deaths, respectively.<sup>22</sup>

## **1.1.4 Treatment**

The main treatment options for obesity include lifestyle modification, very low energy diet (VLED), pharmacotherapy and bariatric surgery (weight loss surgery). These treatments will be discussed below, and VLED in particular in section 1.2.

### **1.1.4.1 Lifestyle Modification**

Lifestyle modification is always recommended as the first-line treatment option for overweight and obesity and includes dietary, physical activity and behavioral modification. The foundation of weight loss includes a negative energy balance over time that is achieved by decreasing the energy intake and/or increasing energy expenditure. The individual effect of behavioral treatment, diet, physical activity has been studied widely, but should according to the body of evidence be combined for the best treatment effect. A meta-analysis by Franz et al<sup>23</sup> concluded that diet and physical activity alone resulted in a modest weight loss after one year of -5 kg (-5%) and -1 kg (-1%), respectively. However, the weight loss was greater when combined -8 kg (-9%). In addition, the Look AHEAD (Action for Health in Diabetes) study of subjects with diabetes, reported one year weight losses of -9% of initial body weight in the intensive lifestyle intervention that included diet, physical activity, and behaviour modification,<sup>24</sup> and -6% of initial weight after four years.<sup>25</sup>

#### *1.1.4.1.1 Dietary Strategies*

Energy deficient diets are often aiming at a 500-1,000 kcal deficit of required energy intake per day to produce a weight loss of approximately 0.5-1 kg/week.<sup>26</sup> The impact of dietary macronutrient composition on weight loss has been investigated extensively and potential effects of high-protein diets, low-carbohydrate diets, high-fat diets, and low glycemic index, have been studied. One meta-analysis<sup>27</sup> and one review<sup>28</sup> comparing low-fat with low-carbohydrate diets both found that low-carbohydrate diets achieved greater weight loss during the first 6 months, but this difference was not present after 12 months. The authors of both papers concluded that the initial greater weight loss may have been linked to adherence, since a higher rate of adherence to low-carbohydrate diets was seen during 6 but not at 12 months, compared to the low-fat diet. In addition, large randomised controlled trials with different diet compositions have reported similar effects on weight loss after two years.<sup>29-31</sup> Data from these studies suggests that restricting total energy intake and adherence is more important than diet macronutrient composition for achieving weight loss.

For weight loss maintenance, however, there are data suggesting that diet composition could be important. The National Weight Control Registry (NWCR) in the US, containing over 4,000 individuals who have maintained a weight loss of 13.6 kg for a minimum of one year, found that a diet low in energy and fat was associated with long-term maintenance, according to self-reported data.<sup>32</sup> In addition, a large randomised controlled European study found that a modest increase in protein content and a modest reduction in the glycemic index, after an 800 kcal/day diet, led to improvements in study completion and maintenance of weight loss.<sup>33</sup>

#### *1.1.4.1.2 Weight Loss Maintenance*

In obesity treatment the greatest challenge is weight loss maintenance. Wing and Hill<sup>34</sup> have defined successful weight loss maintenance as an intentional weight loss of >10% that has been maintained for at least one year. Factors that have been associated with long-term weight loss maintenance, according to self-reported data from the NWCR, are:<sup>32 35 36</sup>

- 1) engaging in high levels of physical activity
- 2) eating a diet that is low in energy and fat
- 3) eating breakfast
- 4) self-monitoring weight regularly
- 5) maintaining a consistent eating pattern across the week
- 6) attending treatment sessions regularly

Factors associated with maintenance after weight loss with VLED are described in section 1.2.4.5.

#### *1.1.4.1.3 Commercial Weight Loss Programmes*

In addition to traditional obesity treatment within the health care system, commercial weight loss programmes are being used annually by millions. Randomised controlled studies evaluating the efficacy and safety of different commercial programmes are scarce.<sup>37</sup> The Weight Watchers programme has, however, been evaluated in three randomised controlled studies.<sup>38-40</sup> In a recent study<sup>41</sup> it was found that participants in the Weight Watchers group lost twice as much in weight after one year, compared to those in the standard care group (-4 vs -2 kg, with baseline carried forward for missing data).

### 1.1.4.2 Anti-Obesity Drugs

Anti-obesity drugs are (or have been) indicated in subjects with a BMI  $\geq 30$  or a BMI  $\geq 27$  with medically complicated obesity<sup>42</sup> who have failed to lose weight through lifestyle modification alone. Anti-obesity drugs should always be given in conjunction with a lifestyle modification programme.

#### 1.1.4.2.1 Anti-Obesity Drugs on or Recently Withdrawn from the Market

At present only one anti-obesity drug, orlistat, is available after withdrawal of rimonabant and sibutramine. The characteristics, mechanisms, weight loss and adverse events of the drugs are presented in **Table 3**.

Drug Trade Name	Mechanism	Weight loss <sup>43</sup> Placebo-adjusted	Adverse Events	Status
<b>Rimonabant</b> <i>Acomplia</i>	cannabinoid CB <sub>1</sub> antagonist <i>induces satiety, increases energy expenditure, decreases lipogenesis</i>	-4.7 kg (%not given)	depression and risk of suicide ideation	withdrawn
<b>Sibutramine</b> <i>Reductil/Meridia</i>	noradrenaline-serotonin-dopamine reuptake inhibitor <i>induces satiety, increases energy expenditure</i>	-4.2 kg (-4.3%)	increased blood pressure and pulse rate	withdrawn
<b>Orlistat</b> <i>Xenical</i>	lipase inhibitor <i>reduces dietary fat absorption by 30%</i>	-2.9 kg (-2.9%)	gastrointestinal	still on the market

Information from references.<sup>42-45</sup> Weight loss from a meta-analysis of pooled studies at one year. All participants in the weight loss trials, including those in the placebo-group, received comprehensive lifestyle education together with approximately a 500 kcal deficient diet.

*Rimonabant* was never approved in the US, and was withdrawn in Europe in 2008 after two years on the market due to reports of severe depression and increased risk of suicide ideation.<sup>44 46</sup> *Sibutramine* was withdrawn in Europe and the US in 2010<sup>44</sup> after 11 and 13 years on the market, respectively. The reason for the withdrawal was that the Sibutramine Cardiovascular Outcomes trial (SCOUT)<sup>47</sup> found that subjects with pre-existing cardiovascular conditions treated with sibutramine, that is subjects with contraindications for the drug, had an increased risk of nonfatal heart attacks and nonfatal stroke. *Orlistat* has been approved since 1998<sup>42</sup> and was recently also approved, in Europe and US, as an over-the-counter drug under the trade name *Alli*, but with half the dosage (60x3mg/day).<sup>48</sup> In Sweden *Xenical* is indicated in subjects with a BMI  $\geq 28$  with co-morbidity or a BMI  $\geq 30$ ,<sup>26</sup> while *Alli* in all with BMI  $\geq 28$ .

#### 1.1.4.2.2 Potential New Candidates

- *Qnexa*, a combination of phentermine and topiramate, was recently (February 2012) recommended to be approved as an anti-obesity drug in the US, but the final decision from the Food and Drug Administration (FDA) is awaiting.<sup>44</sup> Reported placebo-adjusted weight losses range between -8.9 to -10.9 kg.<sup>44</sup>
- *Liraglutide*, an injectable glucagon-like peptide-1 (GLP-1) receptor agonist, is approved under the trade name *Victoza* for treatment of diabetes. Liraglutide also induces weight loss with reported placebo-adjusted weight loss after one-year of -5.8 kg.<sup>49</sup>
- *Contrave*, a combination of bupropion and naltrexone, with placebo-adjusted weight losses of -4.2 to -5.2 kg.<sup>44</sup>
- *Cetilistat*, a newer lipase inhibitor (as orlistat) that has been reported to be associated with less gastrointestinal complications than orlistat, but similar weight loss.<sup>44</sup>

### 1.1.4.3 Bariatric Surgery

Bariatric surgery is indicated in obese subjects who have been unable to lose weight through lifestyle change alone, or in combination with anti-obesity drugs. The BMI indication in most guidelines is a BMI >40 kg/m<sup>2</sup> or a BMI >35 kg/m<sup>2</sup> with obesity-related co-morbidity.<sup>50</sup> In Sweden the current national guidelines stipulate a BMI >35 kg/m<sup>2</sup> with no further requirements regarding co-morbidity.<sup>51</sup>

Broadly, three classes of surgery exist: *restrictive* (e.g. gastric banding), *malabsorptive* (e.g. biliopancreatic diversion), and *combined procedures* (gastric bypass). **Table 4** outlines the principles, approximate weight loss and adverse events of the two most common procedures, globally.<sup>50</sup>

Procedure Class	Principle	Weight loss <sup>52</sup>		Main Adverse Events
		1-2y	10y	
<b>Gastric Banding</b> <i>Restrictive</i>	Adjustable band placed around the upper part of the stomach, creating a small pouch <i>Limiting the amount of food consumed</i>	-20%	-14%	Acid reflux Band erosion or migration Frequent vomiting Gastric pouch dilatation Reservoir leak
<b>Gastric Bypass</b> <i>Restrictive and malabsorptive</i>	The stomach is divided by staples creating a small pouch to which the small intestine is attached, while the first part of the intestine is bypassed <i>In addition to the restrictive and malabsorptive mechanism, increased levels of the gut hormones GLP-I and PYY are seen which increase satiety</i>	-32%	-25%	Abdominal pain Dumping syndrome Intestinal obstruction Nutritional deficiency Staple line leak Stomach ulcer Vomiting

Information from references.<sup>50 52 53</sup> GLP-I=Glucagon-like peptide-I; PYY= Peptide YY.

Gastric bypass leads to greater weight loss and weight loss maintenance compared with gastric banding.<sup>52 54</sup> In the Swedish Obese Subjects (SOS) study, the largest weight loss was seen the first and second year, and was followed by a weight regain that leveled off between year eight and ten.<sup>52</sup> In addition to weight loss, several other beneficial long-term effects are seen after bariatric surgery, such as reduced mortality<sup>52</sup>, reduced incidence of diabetes and cardiovascular events, major improvements or recovery in preexisting diabetes, hyperlipidemia, hypertension, obstructive sleep apnoea,<sup>54-56</sup> improved health-related quality of life,<sup>57</sup> and a reduced incidence of cancer.<sup>58</sup>

Until 2002 about 700 operations were performed annually in Sweden. Since then, an explosive growth has occurred, with 8,000 surgeries in 2010, of which 98% were gastric bypass procedures.<sup>59</sup>

## 1.2 VERY LOW ENERGY DIETS

Very low energy diets (VLEDs) or very low calorie diets (VLCDs) are defined as diets containing 450-800 kcal/day (1.9-3.3MJ/d) or <800 kcal/day (<3.3MJ/d) according to European<sup>60</sup> and American reports, respectively.<sup>61 62</sup> The diets are designed to be used as the sole source of nutrition and contain the recommended daily allowance for vitamins, minerals, electrolytes and essential fatty acids. Low energy diets (LEDs) or low calorie diets (LCDs), contain between 800 and 1,600 kcal/day (3.3-6.7MJ/day) depending on definition,<sup>60 63-65</sup> and often some of the regular meals during the day are substituted by liquid meal replacements.

### 1.2.1 History

The commercial liquid VLED formula was introduced in the 1970s. Unfortunately, the first products contained low quality protein and were deficient in vitamins and minerals, leading to several fatal dysrhythmias.<sup>61</sup> Modern VLEDs, containing high quality proteins and essential nutrients, were introduced in the 1980s and since then no deaths related to VLED have been reported in Europe, according to the European SCOOP-report on VLED use.<sup>60</sup> In addition, extensive studies on cardiac function have not found any adverse cardiac reactions after VLEDs.<sup>61 66</sup>

### 1.2.2 Composition

VLEDs are not defined as pharmaceutical agents, but as "foods for special medical purposes" with standardised values regarding their nutritional composition.<sup>60 67</sup> The standardised composition according to the SCOOP-report on VLED use is shown in **Table 5**.

Nutrients	Content/day
<b>Protein</b>	≥50 grams of high quality
<b>Carbohydrate</b>	≥55 grams
<b>Fibre</b>	≥10 grams
<b>Fat</b>	≥7 grams , including essential fatty acids (linoleic- and alpha-linolenic acid of resp. 3.0 and 0.5 g)
<b>Vitamins and minerals</b>	recommended daily intake

VLEDs are generally strict liquid diets provided in powder form and mixed with water before consumption. Depending on the product, 3 to 6 sachets per day are consumed, replacing all meals. A more liberal VLED allows a restricted intake of other foods such as vegetables. VLEDs could also be based on normal food by combining lean meat, fish and fowl with vitamin and mineral supplements.<sup>66</sup> Studies have, however, found that strict adherence to a liquid VLED results in greater weight loss, both as compared to a more liberal approach allowing other foods<sup>68</sup> and as compared with normal food.<sup>69</sup>

## **1.2.3 Availability**

### **1.2.3.1 Europe**

In Europe VLEDs are available over-the-counter, except in Germany and France. In Germany VLEDs are used only under medical supervision, while in France VLEDs are only available on prescription. In other European countries VLEDs are freely available.<sup>60</sup> To ensure a safe use of VLEDs, the manufacturers should, according to the SCOOP-report,<sup>60</sup> include the following information for the consumer:

- 1) VLEDs should not be used for longer than three weeks without medical supervision
- 2) water intake should be at least 1.5 to 2 litre per day (in addition to that mixed with the powder)
- 3) a warning that VLEDs are unsuitable for children, adolescents, pregnant or lactating women and that elderly and patients with co-morbidities should consult their physician before starting a VLED

### **1.2.3.2 United States**

In the US, recommendations state that VLEDs should only be used under strict medical surveillance, managed by a physician. VLEDs should also be a part of a comprehensive intervention including medical monitoring and a lifestyle modification programme, preferably together with a dietician, psychologist and/or exercise physiologist.<sup>61 65</sup>

## **1.2.4 Treatment**

### **1.2.4.1 Indications**

According to the American report National Task Force on the Prevention and Treatment of Obesity,<sup>61</sup> VLED may be indicated in well-motivated individuals with a BMI >30 who have failed in previous weight loss attempts, or in individuals with a BMI ≥27 with obesity-related co-morbidity.

The European SCOOP-report does,<sup>60</sup> however, not report a unified indication. The report only states that VLED should be used in the treatment of obesity. In hospital-based obesity treatment programmes in Sweden, the reported indication is a BMI ≥30 or a BMI >27 with co-morbidity.<sup>70</sup> In addition, VLEDs could be indicated in situations where a rapid weight loss is clinically important, for example before bariatric surgery or other surgery, to reduce surgical risk and complications.<sup>66 71</sup>

### **1.2.4.2 Contraindications**

There is no total agreement about VLED indications and contraindications. **Table 6** lists the most common contraindications presented in European<sup>60</sup> and American reports.<sup>61</sup>



**Table 6** Common contraindications to very low energy diets (VLEDs)<sup>60 61</sup>

Contraindications	Relative Contraindications
<ul style="list-style-type: none"> <li>- Behavioural disorders (bulimia, anorexia, alcoholism or drug addiction)</li> <li>- BMI &lt;25</li> <li>- Cancer</li> <li>- Cardiovascular or cerebrovascular disease</li> <li>- Gallbladder disease</li> <li>- Liver disease and kidney disease</li> <li>- Major psychiatric disorder</li> <li>- Major depression</li> <li>- Type I diabetes mellitus</li> <li>- Pregnant and lactating women</li> </ul>	<ul style="list-style-type: none"> <li>- Children and adolescents <i>For children who are still growing VLED should be avoided. However, in selected cases of severe obese children, where other treatments have failed, VLED could be used under strict medical supervision.<sup>60 61</sup></i></li> <li>- Elderly <i>There are few reports on the effect of VLED in people over 65. Since elderly persons already are at increased risk for negative nitrogen due to normally depleted lean body mass, the increased risks must be balanced with the benefits of weight loss in older persons.<sup>61 66</sup></i></li> </ul>
<p>The SCOOP-report<sup>60</sup> also lists: Acute ischaemic cardiopathies, electrolyte disorders, gout, haemopathy, hereditary metabolic diseases, major surgery or serious accident within the last 3 months, orthostatic hypotension, porphyria.  The American National Task Force on the Prevention and Treatment of Obesity<sup>61</sup> also lists: Systemic infection or disease causing protein wasting.</p>	

### 1.2.4.3 Programme

The duration of a VLED-programme in a hospital-based obesity treatment programme usually range between eight and 16 weeks,<sup>66</sup> and performed in conjunction with lifestyle modification. After the VLED-period, a two to six week re-feeding period often follows to gradually introduce normal food again. The reasons for this are to prevent abrupt retention of fluid, to prevent abdominal discomfort and to adopt strategies to adjust eating behaviour. A longer re-feeding period has, in a randomised controlled trial,<sup>72</sup> been associated with better weight loss maintenance. The re-feeding period should be followed by a weight loss maintenance programme to prevent relapses in weight (further details in section 1.2.4.5).

### 1.2.4.4 Weight Loss

The amount of weight loss differs between subjects since the energy content of VLEDs is fixed and does not take sex, age, weight or lean body mass into account, which all are determinants of basal metabolic rate. Weight loss depends on the specific person's energy expenditure. For example, a 700 kcal/day VLED will lead to a much smaller energy deficit (and weight loss) in a sedentary female compared to an active male. Additionally, severely obese persons who expend more energy will lose more weight compared to moderately obese persons. An alternative definition of VLED has been suggested as approximately 10 kcal/kg of desirable body weight,<sup>73</sup> or <50% of an individual's predicted resting energy expenditure.<sup>65</sup> However, these definitions have not been used in practice. Due to the above mentioned factors weight loss could differ substantially between individuals. In general VLED results in an average loss of 1.5-2.0 kg/week in women and 2.0-2.5 kg/week in men.<sup>61</sup>

#### **1.2.4.5 Weight Loss Maintenance after VLED**

For all obesity treatment programmes weight loss maintenance is the greatest challenge. For VLED in particular, the effect of long-term weight loss maintenance has been questioned due to the reported poor long-term maintenance. In a meta-analysis<sup>65</sup> of six head-to-head studies comparing the long-term effect of VLEDs compared to LEDs, Tsai and Wadden concluded that VLEDs resulted in significantly greater short-term weight losses (-16% vs -10% over 13 weeks;  $p < 0.001$ ), but the maintenance at two years was poor (-6% vs -5%;  $p > 0.2$ ). However, neither of these trials included an extensive exercise programme,<sup>74 75</sup> pharmacotherapy,<sup>76-81</sup> a prolonged re-feeding period<sup>72 75</sup> or a low glycemic index and high protein diet<sup>33</sup> as a part of the maintenance programme, which are all proven to limit weight regain. In addition, early large weight loss has been shown to be a predictor of long-term weight loss maintenance in a meta-analysis.<sup>82</sup>

#### **1.2.5 Side-Effects**

Common side-effects of VLED include diarrhoea, constipation, headache, nausea, vomiting, dizziness, orthostatic hypertension, dry mouth, poor cold tolerance, dryness of skin and loss of hair.<sup>60 61</sup> These side-effects are all transient and related to the semi-starvation during VLED, but also due to inadequate fluid intake.<sup>60</sup> More serious side-effects, but not as common, are gallstones and gout.<sup>61 65 66 83</sup> Cardiac complications were, as previously described in section 1.2.1, a side effect with the old incomplete liquid formulas but not with the modern VLEDs.

As the risk of gallstones during treatment with VLED compared LED will be evaluated in *Study III* of this thesis, a further description of gallstones and their association to obesity is provided below.

##### **1.2.5.1 Gallstones**

Gallstones (cholelithiasis) develop in the gallbladder, and are clusters of crystallised pieces of bile consisting either of cholesterol or bilirubin, with cholesterol stones being the most common type in western countries.<sup>84</sup>

Multiple factors interact causing gallstone formation, the most commonly described mechanisms are:<sup>84</sup>

- 1) *Super-saturation of bile with cholesterol leading to cholesterol crystallisation*  
Supersaturation occurs if the liver excretes more cholesterol than the bile can dissolve, leading to aggregation of excess cholesterol into crystals that eventually form into gallstones.
  
- 2) *Insufficient gallbladder emptying due to impaired motility*  
Reduced ability to empty the gallbladder completely, or often enough, may result in concentrated bile, causing cholesterol aggregation and formation of gallstones.

#### *1.2.5.1.1 Risk Factors, Clinical Spectrum and Treatment*

Gallstone formation may be influenced by genetic and environmental factors, and common risk factors include: female sex, obesity, higher age (>40y), ethnic origin, and rapid weight loss.<sup>84-86</sup>

Gallstones may be asymptomatic or symptomatic. Asymptomatic gallstones are also called “silent gallstones”, and treatment is not recommended if these gallstones are found.<sup>84</sup> Approximately 15-20% of the asymptomatic gallstones develop into symptomatic stones.<sup>86</sup> Symptomatic gallstones manifest as attacks of biliary colic, lasting from 30 minutes to 6 hours, and typically occur 15 minutes to 2 hours after food intake. The primary treatment is analgesics drugs, with diclofenac being the most common. Cholecystectomy may be performed if the symptoms recur frequently, if the gallbladder wall has become calcified, or if the gallbladder bile ducts or pancreas have been inflamed.<sup>84</sup>

#### *1.2.5.1.2 Obesity and Rapid Weight Loss*

Obesity in itself is a risk factor of developing gallstones and the increased risk is particularly evident in women, but studies in men have also shown an increased risk.<sup>87-89</sup> Weight loss also increases the risk for gallstones, especially after rapid weight loss with VLED or bariatric surgery.<sup>87 88</sup>

The underlying mechanism for the increased risk of gallstones among obese persons may be associated with increased levels of cholesterol in the bile, that eventually leads to super-saturation of the bile.<sup>86 87</sup> <sup>88</sup> Rapid weight loss may increase the risk of gallstones by the same mechanism, that is by increased levels of cholesterol, but also by impaired gallbladder motility. The impaired motility during VLED is thought to be caused by reduced gallbladder stimulation due to the low fat content of a VLED.<sup>87 89</sup>

A majority of the clinical studies that have found an increased risk of gallstone formation during VLED have been American studies conducted in the late 1980s and early 1990s, using VLEDs with low levels of fat ( $\approx 1$  g/day).<sup>90-94</sup> In formulations containing higher amounts of fat (12-30 g/day), the incidence of gallstones has been much lower.<sup>95-98</sup> In a review, Festi et al<sup>89</sup> concluded that adequate fat content is important in gallstone prevention, with 10 g of fat/day as a threshold for obtaining efficient gallbladder emptying. A lower recommendation of 7 g fat/day has, however, been given by the European SCOOP-report on VLED use.<sup>60</sup>

## 1.3 OBESITY AND OBSTRUCTIVE SLEEP APNOEA

Obstructive sleep apnoea (OSA) is one of the most common sleep disturbances, affecting an estimated 24% of middle aged men and 9% of women, according to data from the Wisconsin Sleep Study.<sup>99</sup> In the same study, OSA with clinical symptoms as excessive daytime somnolence, that is obstructive sleep apnoea syndrome (OSAS) occurred in an estimated 4% and 2% of middle aged men and women, respectively.<sup>99</sup>

### 1.3.1 Definition, Risk Factors, Symptoms and Treatment

#### 1.3.1.1 Definition

OSA is caused by obstruction of the upper airway, either by total blockage (apnoea) or partial blockage (hypopnoea) of airflow for at least 10 seconds during sleep.<sup>100 101</sup> The apnoea-hypopnoea index (AHI), which measures the average numbers of apnoeas and hypopnoeas per hour of sleep, is used to classify the severity of OSA, according to the American Academy of Sleep Medicine (**Table 7**).<sup>100</sup> Occurrence of OSA is defined as an AHI  $\geq 5$  events/h.<sup>100</sup> The diagnosis is confirmed by a sleep study, either by an overnight laboratory polysomnography, or a by an ambulatory polygraphy equipment at home.

Severity	AHI (events/hour)
Mild	5-14.9
Moderate	15-30
Severe	>30

AHI=Apnoea-hypopnoea index.

#### 1.3.1.2 Risk Factors

A variety of factors, genetic as well as environmental, increase the risk of OSA. Frequently described risk factors include: male sex, increased age, obesity (especially abdominal), ethnicity, heritability, smoking, and alcohol consumption.<sup>101-103</sup> Body weight has widely been described as the strongest risk factor for OSA,<sup>101 104</sup> and data from the three largest epidemiological sleep studies, that is The Sleep Heart Health Study,<sup>105</sup> The Wisconsin Sleep Cohort Study,<sup>106</sup> and The Cleveland Family Study<sup>107</sup>, have all found weight gain to be associated with increased risk for OSA. Additionally, reports show that the majority (60-70%) of persons with OSA are either overweight or obese.<sup>101 103 108</sup>

#### 1.3.1.3 Symptoms and Consequences

Pauses in breathing caused by upper airway obstruction leads to hypoxemia, arousals and increased sympathetic activity, causing sleep fragmentation and potentially leading to adverse health outcomes. Associated features during sleep include loud snoring, frequent arousals, gasping and nocturia. Daytime symptoms due to sleep fragmentation are sleepiness, fatigue, impaired cognitive function, morning headache and impotence.<sup>109</sup>

Left untreated, OSA has been described to be associated with an increased risk of hypertension, cardiovascular and cerebrovascular diseases, decreased insulin resistance, metabolic syndrome, all-cause mortality, reduced quality of life and working capacity. Due to daytime sleepiness OSA also increases the risk for driving- and occupational-related accidents.<sup>101 110-112 103</sup>

### 1.3.1.4 Treatment

The most commonly used treatment for OSA is *continuous positive airways pressure (CPAP)*, a nasal mask connected to a compressor that keeps the airways open by a mild air pressure. The CPAP effectively relieves symptoms but has no or very short curative effect.<sup>109</sup> This also holds for treatment with oral devices mostly used for mild to moderate OSA. An *oral appliance* protrudes the lower jaw and thereby widens the airway. *Uvulopalatopharyngoplasty* is a surgical procedure where the tonsils and parts of the soft palate are removed. The method can be curative for the patient with correspondent anatomical conditions.<sup>109</sup> *Lifestyle modification including weight loss* should, according to guidelines, always be recommended in overweight or obese patients.<sup>113</sup> The beneficial effect of weight loss on OSA was recently demonstrated in three randomised controlled trials, one of which is included in this thesis (*Study I*), thus providing the first high quality evidence of the effectiveness of weight loss.<sup>114-116</sup>

### 1.3.2 Mechanisms

The epidemiological association between obesity and OSA is well documented,<sup>99 100</sup> but the mechanisms remain unclear.<sup>101 102</sup> Potential mechanisms include anatomical alterations caused by a mechanical load effect and/or disturbance in upper neuromuscular control caused by humoral factors:

- 1) *Mechanical Load Effect*: Due to fat accumulation in specific sites surrounding the upper airway, the thorax and abdomen, obesity may lead to OSA by altering airway anatomy and respiratory control. These alterations could lead to narrowing of the upper airway structure, reduced chest wall compliance, reduced lung volume, reductions in functional residual capacity and reduced tracheal traction, leading to upper airway narrowing, collapse and airflow obstruction.<sup>104 108</sup>
- 2) *Adipokine Effect*: It has been suggested that factors other than pure mechanical load may contribute to the pathogenesis of OSA.<sup>104</sup> Humoral factors, adipokines, produced by the metabolic active visceral adiposity may influence upper airway function. Most widely discussed is leptin, which in addition to regulation of food intake also regulates respiratory control. Also discussed are proinflammatory cytokines that may lead to alterations in upper airway function, causing disturbance in neuromuscular control, and increasing the risk of OSA.<sup>104 113 117</sup>

### 1.3.3 Previous Research regarding Weight Loss and Treatment

Weight loss has long been recommended as treatment option for overweight and obese patients with OSA, but without high quality evidence, and unclear compliance (both from treating doctors, and patients receiving weight loss advice).<sup>118 119</sup> The association between weight and AHI change has been well described in large epidemiological sleep cohort studies.<sup>105-107</sup> However, it was first in 2009 that evidence from randomised controlled trials supporting this concept was published (**Table 10**).<sup>114-116</sup> Previously published clinical studies had several methodological limitations, including lack of either randomisation,<sup>120-122</sup> or control group for comparisons<sup>123-137</sup> and limited follow-up (**Table 8-10**).<sup>119</sup>

### 1.3.3.1 Uncontrolled Studies

**Table 8** and **Table 9** presents uncontrolled studies of weight loss by surgery or a dietary intervention published between 1985 and 2010 (*Study II* in this thesis is included). The number of included subjects, duration and weight loss methods have differed between the studies; however all have found weight loss to be associated with improvements in OSA. Dietary weight loss studies have found a 24-68% reduction of AHI or ODI<sub>4</sub> with a weight loss (kg) between 8-14% of initial body weight, and surgery studies AHI improvements of between 49-78% with a weight loss of 29-37%.

Article Year Country	Dietary intervention	Follow- up months	BMI start	OSA start	N	Weight loss* kg, (%)	AHI/ODI <sub>4</sub> reduction
<b>Nerfeldt</b> <sup>138</sup> 2010 Sweden	<b>LED; 800 kcal/day</b> (8weeks LED+ 96weeks lifestyle)	24	40	AHI 43	33 <sub>ITT</sub> 23 <sub>comp</sub>	- -12kg (10%)	- -15 (35%)
<b>Johansson</b> <sup>139</sup> 2010 Sweden	<b>VLED; 554 kcal/day</b> (9weeks VLED+ 43weeks lifestyle)	12	35	AHI 36	63 <sub>ITT</sub> 44 <sub>comp</sub>	-12kg (11%) -16kg (14%)	-17 (47%) -22 (61%)
<b>Barnes</b> <sup>123</sup> 2009 Australia	<b>VLED; n/a</b> (8weeks VLED+ 8weeks re-feeding)	4	36	AHI 25 -	12 <sub>ITT</sub> 10 <sub>comp</sub>	-12kg (13%) -	-7 (27%) -
<b>Hernandez</b> <sup>128</sup> 2009 US	<b>LED; 1,000-1,500 kcal/day</b> (12weeks LED+ 12weeks lifestyle)	6	48	AHI 11	16 <sub>ITT</sub> 14 <sub>comp</sub>	- -16kg (12%)	- -6 (54%)
<b>Kajaste</b> <sup>129</sup> 2004 Finland	<b>VLED; 500 kcal/day</b> (6weeks VLED+90weeks CBT)	24	44	ODI <sub>4</sub> 51	33 <sub>ITT</sub> 29 <sub>comp</sub>	- -13kg (9%)	- -19 (38%)
<b>Hakala</b> <sup>127</sup> 2000 Finland	<b>VLED; 500 kcal/day</b>	1.5	35	ODI <sub>4</sub> 31	13 <sub>ITT</sub> 13 <sub>comp</sub>	- -16kg (14%)	- -21 (68%)
<b>Lojander</b> <sup>133</sup> 1998 Finland	<b>VLED; 500 kcal/day</b> (6weeks VLED+ 46weeks lifestyle)	12	36	ODI <sub>4</sub> 30	24 <sub>ITT</sub> 22 <sub>comp</sub>	- -11kg (10%)	- -18 (60%)
<b>Kansanen</b> <sup>131</sup> 1998 Finland	<b>VLED; 600-800 kcal/day</b>	3	38	ODI <sub>4</sub> 31	18 <sub>ITT</sub> 15 <sub>comp</sub>	- -9kg (8%)	- -12 (39%)
<b>Kajaste</b> <sup>130</sup> 1994 Finland	<b>CBT</b>	24	39	ODI <sub>4</sub> 36	36 <sub>ITT</sub> 26 <sub>comp</sub>	- -1kg/m <sup>2</sup> (4%)	- -1 (3%)
<b>Nosedal</b> <sup>134</sup> 1996 Belgium	<b>Dietary Advice</b> (N=36) <b>OR</b> <b>Bariatric Surgery</b> if BMI>40(N=3)	12	36	AHI 67	95 <sub>ITT</sub> 39 <sub>comp</sub>	- -9kg (8%)	- -16 (24%)
<b>Suratt</b> <sup>136</sup> 1992 US	<b>VLED; 420-800 kcal/day</b>	1-1.5	50	AHI 90	8 <sub>comp/ITT</sub>	-21kg (14%)	-28 (31%)

\* BMI reduction is given if weight loss in kg is not available.  
AHI=apnoea-hypopnoea index; CBT=cognitive behavioural treatment; Comp=completers analysis; ITT=intention-to-treat (missing data imputed); Lifestyle=behavioural modification programme; n/a=not available; ODI<sub>4</sub>=oxygen desaturation >4%/h of sleep.

**Table 9** Uncontrolled studies of bariatric surgery and obstructive sleep apnoea (OSA)

Article Year Country	Type of Surgery	Follow-up (months)	BMI start	OSA Start	N	Weight loss, kg (%)	AHI reduction
<b>Lettieri</b> <sup>132</sup> 2008 US	GBP	12	51	AHI 48	24	-54kg (37%)	-23 (49%)
<b>Haines</b> <sup>126</sup> 2007 US	GBP	11	56	RDI 51	101	-18kg/m <sup>2</sup> (32%)	-36 (71%)
<b>Fritscher</b> <sup>125</sup> 2007 Canada	GBP	24	52	AHI 47	12	-51kg (34%)	-31 (66%)
<b>Dixon</b> <sup>124</sup> 2005 Australia	GBP	18	53	AHI 62	25	-45kg (29%)	-48 (78%)
<b>Valencia-Flores</b> <sup>137</sup> 2004 Mexico	GBP	14	57	AHI 52	29	-17kg/m <sup>2</sup> (31%)	-38 (73%)
<b>Pillar</b> <sup>135</sup> 1994 Israel	GBP	90	45	AHI 40	14	-10kg/m <sup>2</sup> (22%)	-16 (40%)

\* BMI reduction is given if weight loss in kg is not available.  
AHI=apnoea-hypopnoea index; GBP=gastric bypass; n/a=not available; RDI=respiratory disturbance index.

### 1.3.3.2 Controlled Studies

Although controlled studies were published before 2009, none of these trials were randomised.<sup>120-122</sup> During 2009 three randomised studies were published. Tuomilehto et al<sup>115</sup> investigated the effect of VLED followed by supervised lifestyle counselling for one year in overweight or obese patients with mild obstructive sleep apnoea (**Table 10**). Thereafter Foster et al<sup>116</sup> investigated the effects of intensive lifestyle change in overweight or obese patients with type 2 diabetes and mild to severe OSA for one-year. Finally, we investigated the effects of VLED during nine weeks in obese men with moderate to severe OSA (*Study I*).<sup>114</sup>

All three trials found weight loss to result in clinically relevant AHI improvements. In 2010, Tuomilehto et al published a two-year follow-up study,<sup>140</sup> demonstrating that although there was some weight regain OSA remained improved and did not follow the trend of modest weight gain.

**Table 10** Controlled studies of weight loss and obstructive sleep apnoea (OSA)

Article Year Country	Intervention Control	N	AHI start	BMI start	Follow- up (months)	Weight change kg (%)	AHI change
<b>Randomised controlled trials</b>							
Tuomilehto <sup>115</sup> 2009 Finland	<b>1. VLED;600-800 kcal/day</b> (12weeks+lifestyle 40weeks) <b>2. Lifestyle only</b>	35 <sub>comp</sub>	10	33	12	-11kg (11%) -2kg (3%)	-4 (40%) +0.3 (+3%)
		37 <sub>comp</sub>	9	31			
Tuomilehto <sup>140</sup> 2010 Finland	<b>1. VLED;600-800 kcal/day</b> (12weeks+lifestyle 92weeks) <b>2. Lifestyle only</b>	35 <sub>comp</sub>	10	33	24	-7kg (7%) -3kg (3%)	-5 (46%) -0.5 (5%)
		36 <sub>comp</sub>	9	32			
Foster <sup>116</sup> 2009 US	<b>1. Intensive lifestyle</b> <b>2. Diabetes education</b>	125 <sub>ITT</sub>	23	37	12	-11kg (10%) -0.6kg (0.6%)	-5 (24%) +4 (+18%)
		139 <sub>ITT</sub>	24	37			
Johansson <sup>114</sup> 2009 Sweden	<b>1. VLED;554 kcal/day</b> <b>2. Controls</b>	30 <sub>ITT</sub>	37	34	2	-19kg (16%) +1kg (1%)	-25 (67%) -2 (5%)
		33 <sub>ITT</sub>	37	35			
<b>Controlled trials (non-randomised)</b>							
Smith <sup>122</sup> 1985 Australia	<b>1. Calorie restriction</b> <b>2. Matched controls</b>	15 <sub>comp</sub>	55	37	5	-10kg (9%)	-26 (47%)
		8 <sub>comp</sub>	66	37	9	+1.4kg (1%)	+5 (7%)
Schwartz <sup>121</sup> 1991 US	<b>1. Calorie restriction</b> <b>2. Matched controls</b>	13 <sub>comp</sub>	83	42	17	-7kg/m <sup>2</sup> (17%)	-51 (61%)
		13 <sub>comp</sub>	86	38	18	+0.1kg/m <sup>2</sup> (+0.3%)	-4 (5%)
Grunstein <sup>*120</sup> 2007 Sweden	<b>1. Bariatric surgery</b> <b>2. Matched controls</b>	1592	n/a* n/a	42.2	24	-28kg (23%) ±0kg	28% 71%
		1431		40.1			

AHI=apnoea-hypopnoea index.  
\*AHI was not measured, but a sleep questionnaire was used to evaluate the persistence of apnoeas.



## **2 OBJECTIVES**

### **2.1 OVERALL OBJECTIVE**

The overall objective of this thesis was to evaluate effects and side-effects of VLEDs in different obesity treatment settings, and to characterise discontinuation in obesity treatment programmes.

### **2.2 SPECIFIC OBJECTIVES**

1. To evaluate a weight loss programme as treatment option for patients with obstructive sleep apnoea
  - *Firstly*: to evaluate the effect of weight loss induced by a VLED on OSA in a randomised controlled trial (*Study I*)
  - *Secondly*: to determine whether initial improvements in OSA after the VLED were maintained after one year in a observational study (*Study II*)
2. To assess the risk of gallstones requiring hospital care, and cholecystectomy, in a commercial weight loss programme using VLED or LED (*Study III*)
3. To characterise overall discontinuation and discontinuation due to adverse events in obesity treatment programmes by analysing data from anti-obesity drug trials (*Study IV*)

## 2.3 RATIONALE FOR INCLUDED STUDIES

### 2.3.1 Study I&II: Weight Loss and Obstructive Sleep Apnoea

Few treatment options are available for OSA. The most commonly used strategy to facilitate breathing during sleep and to reduce morbidity and mortality is CPAP.<sup>109</sup> Although weight loss has long been advocated as a primary treatment strategy for the condition,<sup>113</sup> at the time of the study initiation/planning (spring 2008) no randomised controlled trials existed to support this concept.<sup>118 119</sup>

The rationale for *Study I* was, therefore, to assess potential improvement in OSA after VLED-induced weight loss in a randomised controlled trial including obese male patients with moderate to severe OSA, a patient group with increased mortality risk.<sup>111 112</sup> The rationale for *Study II* was to evaluate the extent to which initial improvements in OSA after the VLED-induced weight loss were maintained after one year.

### 2.3.2 Study III: Risk of Gallstones during VLED

Each year millions use commercial weight loss programmes, including intensive treatment schemes such as VLEDs.<sup>141</sup> Safety concerns exist for VLEDs, especially regarding gallstone development.<sup>88</sup> The magnitude of the risk is unclear: clinical studies evaluating the risk of gallstones associated with VLED have primarily been conducted in the late 1980s and early 1990s and using VLEDs containing low levels of fat ( $\approx 1$  g/day).<sup>90-94</sup> The few existing studies with VLEDs containing higher amounts of fat<sup>60</sup> show a much lower incidence of gallstones.<sup>95-98</sup> Major limitations of all published studies are lack of control groups, small sample sizes and short follow-up.

The rationale for this one-year cohort study conducted in a real-world setting was to investigate the risk of gallstones requiring hospital care, and cholecystectomy, during treatment with VLED (fat content 7-9 g/day) compared to matched controls using LED in a multi-centre commercial weight loss programme.

### 2.3.3 Study IV: Treatment Discontinuation

Weight loss treatment programmes in observational settings (hospital-based and commercial) as well as randomised trials are afflicted by high levels of attrition. In a systematic review of weight loss studies addressing factors associated with attrition,<sup>142</sup> one-year dropout rates of diet and lifestyle modification studies ranged between 16% and 77%. Pharmacotherapy trials could be used as benchmark of discontinuations rates in obesity treatment programmes, since these are strictly controlled and generally have significant resources to minimise attrition.

The rationale for *Study IV* was to characterise overall discontinuation, but also discontinuation due to adverse events and lack of effectiveness, in obesity treatment programmes by pooling data from randomised controlled anti-obesity drug trials.

### 3 METHODS

#### 3.1 STUDY DESIGNS AND STUDY POPULATIONS

Four different study designs and three different populations were included in this thesis (**Table I I**).

Study	Design	Population
<b>I</b>	<b>Randomised controlled trial</b>	Obese Swedish men with moderate to severe OSA undergoing a hospital-based weight loss programme
<b>II</b>	<b>Observational follow-up study</b>	
<b>III</b>	<b>Matched register-based cohort study</b>	Overweight and obese adult Swedish men and women enrolled in a commercial weight loss programme
<b>IV</b>	<b>Meta-analysis</b>	Pooled data from published randomised controlled trials, enrolling overweight and obese men and women, eligible for anti-obesity drugs

OSA=Obstructive sleep apnoea

#### 3.2 ETHICAL CONSIDERATIONS

In the clinical study of the effect of weight loss on OSA (*Study I&II*) obese patients were recruited from a patient database at the Aleris FysiologLab sleep clinic in Stockholm, Sweden. The patients who declared an interest in participating and met the inclusion criteria gave written informed consent to participate in the study. All patients were given a study identification number which was used throughout the study. The identification lists were kept in a locked room, with no access for research staff. Ethical approval was granted by the regional ethical review board, Stockholm, Sweden (reference number: 2008/1634-31).

In the commercial weight loss study (*Study III*) the database used by the commercial vendor ([www.itrim.se](http://www.itrim.se)) to track customer progress and compliance was used to retrieve participant data. By using the unique personal identification number assigned to each Swedish resident, these data were linked on an individual level to the National Patient Register, the Causes of Death Register and the Prescribed Drug Register. The integrity of the participants should always be considered when doing register-based research. For integrity protection purposes, the National Board of Health and Welfare anonymised all data before returning them to the research group. Furthermore, data were only presented on an aggregated level. Ethical approval was granted by the regional ethical review board, Stockholm, Sweden (reference number: 2010/1059-31/1).

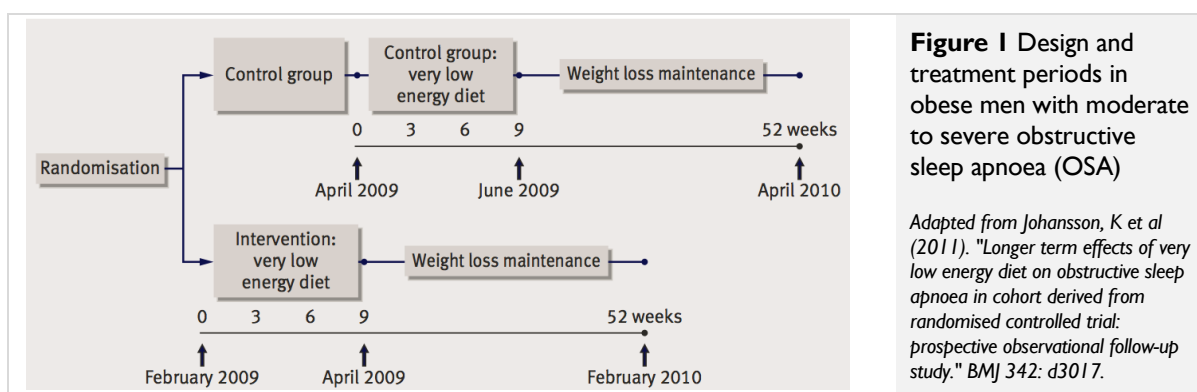
In the meta-analysis (*Study IV*) only previously published studies were analysed of which each individual study already reported that ethical permission was granted, hence ethical approval was not applied for.

### 3.3 STUDY I&II: WEIGHT LOSS AND OBSTRUCTIVE SLEEP APNOEA

The study was of one-year duration and consisted of a weight loss phase (0-9 weeks, RCT) and a weight loss maintenance phase (>9-52 weeks, observational) carried out between February 2009 and April 2010 at a specialist outpatient obesity clinic (hospital-based).

#### 3.3.1 Participants and Design

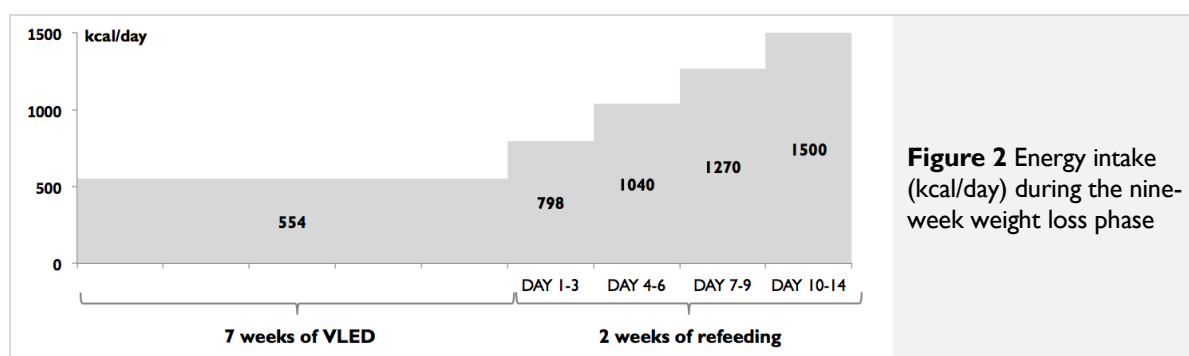
63 men aged 30-65 years with BMI 30-40 and moderate to severe obstructive sleep apnoea (OSA) defined as an AHI  $\geq 15$  events/hour, all treated with CPAP, were included in the study. Subjects were randomly assigned to intervention (weight loss by a VLED programme) or control groups in a 1:1 ratio. To reduce the likelihood of controls dropping out, control subjects were also offered the same treatment once the nine-week follow-up as controls was completed. After the weight loss programme, all patients were offered a standard care hospital-based outpatient weight loss maintenance programme (**Figure 1**).



#### 3.3.2 Intervention

##### 3.3.2.1 The Weight Loss Phase (Nine weeks)

The weight loss intervention consisted of a seven-week VLED, followed by a two-week re-feeding period (**Figure 2**), while the control group was instructed to adhere to their usual diet.



The VLED was a 554 kcal/day (2.3 MJ/day; 4 sachets per day à 138 kcal, 9-11 g fat/day) liquid energy intake formula (Cambridge Weight Plan, Northants, UK). To confirm dietary compliance, urinary ketosis was assessed at each visit. During the two weeks of re-feeding a gradual introduction of normal food in a strict manner to reach 1500 kcal/day (6.3 MJ/day) at week nine was carried out. Every other

week a one-hour group session, supervised by a research nurse and the study dietitians, was provided to build group support and provide motivation.

### **3.3.2.2 The Weight Loss Maintenance Phase (43 weeks)**

The maintenance programme started immediately after the weight loss phase and was based on standard behaviour modification group therapy with a self-help manual.<sup>143-146</sup>

*Behaviour Modification:* The programme consisted of monthly three-hour group therapy meetings (10 visits in total). Each group comprised 13-15 patients and was led by a research nurse and a dietitian. The behaviour modification focused on nutrition education, eating behaviour, hunger and craving, relapse situations, and increased physical activity. Other important aspects were evaluation of progress and identification of personal and environmental influences affecting eating and physical activity. In conjunction with the group sessions each patient was seen by a nurse for anthropometry measurements and by a dietitian for individual dietary advice.

*Energy Intake:* During the first two weeks of the maintenance phase the same diet as for the last days of the re-feeding period was followed, that is a 1500 kcal/day diet including normal food and one liquid meal replacement. Thereafter each patient's individual energy requirement for weight loss maintenance was calculated according to the Harris Benedict formula.<sup>147</sup> The recommended percentage of total energy intake (E%) for fat, carbohydrates and protein followed the 2005 Swedish Nutrition Recommendation,<sup>148</sup> that is to reduce fat to no more than 30E%, carbohydrates to 55E% (with a maximum of 10E% from pure sugar) and protein to 15E%. To achieve these recommendation the patients were recommended to increase the intake of fruits, vegetables, poultry, fish and lean meat, and by limiting dairy fats, fatty meat, sweets, pastries and desserts.

*Prevention of Weight Gain:* If a patient's weight had increased by more than 2 kg since the last visit, action to prevent further weight regain was taken. The first action was use of partial meal replacement, which included exchange of one or two daily meals with a 138 kcal VLED sachet (Cambridge Weight Plan, Northants, UK). As a secondary option sibutramine or orlistat was prescribed.

### **3.3.3 Outcomes**

#### **3.3.3.1 Obstructive Sleep Apnoea**

Sleep measurements were derived from two consecutive nocturnal sleep studies in the home, using a six channel ambulatory polygraphy equipment (Watch PAT100, Itamar Medical Ltd, Caesarea, Israel). Patients were carefully instructed not to use their CPAP the two nights before and during the nocturnal sleep studies. The sleep studies were performed at baseline, after the VLED, and at one year. The primary outcome was AHI, which is the major disease severity index for OSA. In addition, oxygen desaturation episodes of 4% or more per hour of sleep, the nadir of arterial oxygen saturation, and percentage of supine time were recorded. Daytime sleepiness was assessed with the Epworth sleepiness scale, an eight item self administered questionnaire.

#### **3.3.3.2 Body Composition**

Fat loss was assessed with anthropometry and body composition changes from baseline at weeks 1, 3, 5, 7, 9, during the weight loss phase and monthly during the weight loss maintenance phase. Percentage body fat and body weight were measured with the Tanita BC-418MA body fat analyser. Standing height was measured to the nearest centimetre with a wall mounted stadiometer. Waist circumference was measured in duplicate halfway between the iliac crest and the lower rib cage. Neck circumference was measured in duplicate at the level of the superior border of the cricothyroid membrane.

#### **3.3.3.3 Metabolic Measures**

Metabolic variables were measured at baseline, after the VLED, and after one year according to standard laboratory procedures after 12 hours fasting, including insulin, HbA<sub>1c</sub>, total cholesterol, LDL, HDL, triglycerides, TSH, urate, ALAT, creatinine, and glucose. Systolic and diastolic blood pressure were measured in duplicate after 5-minutes rest in supine position.

#### **3.3.3.4 Quality of Life**

Health-related quality of life was measured with the SF-12 health survey to allow quantification of a physical and a mental component score. Scores were compared with quality of life reference data for the male Swedish population.<sup>149</sup>

### **3.3.4 Side-Effects**

At each visit throughout the study side-effects from the VLED during the weight loss phase and the weight loss maintenance phase were noted by a nurse. The study physician then classified these events for potential causality (unlikely/possibly/likely).

## 3.4 STUDY III: RISK OF GALLSTONES DURING VLED

This matched cohort study on risk of gallstones requiring hospital care and cholecystectomy after VLED or LED was conducted in the commercial weight loss setting in Sweden. Participant data were retrieved from the database used by the commercial company. By using the unique personal identification number assigned to each Swedish resident, these data were linked on an individual level to the National Patient Register, Prescribed Drug Register and to the Causes of Death Register for follow-up of vital status. The National Board of Health and Welfare anonymised all data before sending the linked datasets to the research group. The commercial weight loss programme and the registers are described below.

### 3.4.1 Weight Loss Programme

#### 3.4.1.1 Participants

The study included consecutively enrolled adult customers (age  $\geq 18$  years;  $n=8,361$ , after matching 6,640) from the commercial weight loss company Itrim in Sweden ([www.itrim.se](http://www.itrim.se)) from January 1, 2006, until May 31, 2009. Data were collected from 28 centres across Sweden.

#### 3.4.1.2 Description of the Weight Loss Programme

The weight loss programme was of one-year duration and consisted of an initial three-month weight loss phase followed by a nine-month weight loss maintenance phase. During the weight loss phase, the participants were able to select, together with their health coach, one of four programmes (VLED, LED, normal food, or exercise). In this study only the VLED and LED programmes were included, since these are the two programmes including liquid formula products. Although all participants were paying customers and were free to choose weight loss method, the company used specific criteria for VLED use, consistent with the SCOOP-report recommendations.<sup>60</sup>

##### 3.4.1.2.1 Weight Loss Phase (Three Months)

During the weight loss phase the included participants attended either the VLED or the LED weight loss programme:

- **VLED:** Liquid-based formula diet of 500 kcal/day (2.1 MJ/day; 4 sachets per day à 125 kcal, 7-9 g fat/day, Itrim Sweden) for 10 weeks followed by two weeks gradual introduction of normal food. Early introduction of normal food occurred when the participant was either satisfied with the achieved weight loss or had reached normal weight (BMI 18.5-24.9 kg/m<sup>2</sup>).
- **LED:** Two regular meals consisting of normal food and two liquid meal replacements (à 125 kcal, Itrim Sweden) providing a caloric content of approximately 1,200-1,500 kcal/day (5.0-6.3 MJ/day) depending on body size and exercise levels.

Both groups attended a one-hour group session every other week to build group support and provide motivation. The group session was led by a trained health coach, and included information on nutrition, exercise, eating patterns, goals and expectations. Also, the participants were recommended to attend two to three weekly workout sessions for at least 30 minutes at the Itrim centre.

#### 3.4.1.2.2 *Weight Loss Maintenance Phase (Nine Months)*

After the weight loss phase, both groups entered the same nine-month weight loss maintenance phase with focus on exercise, but also including behavioural changes, dietary advice and self-monitoring.

*Behavioural Changes:* These were facilitated by a structured programme, including one-hour group sessions every other week during the maintenance phase (20 in total). Each session was supervised by a company trained health coach, who provided encouragement to participants throughout the programme. Each group session covered a specific topic, such as health benefits of weight loss, healthy eating strategies, finding realistic eating and exercise routines, health benefits of exercise, stress management, social support, etc. To further aid behaviour change, there were also four 30 minutes face-to-face counselling sessions with a company trained health coach at baseline, three, six and 12 months.

*Regular Exercise:* All participants were encouraged to continue to work out two to three times per week. Moreover, all participants used a validated pedometer (Yamax SW-200) and were given a tailored plan for increased walking during everyday living, such as walking to and from work.

*Dietary Advice:* These emphasised regular meal patterns, a diet rich in fruit and vegetables, and reducing the amount of dietary fat and sugar.

*Self-Monitoring:* This was facilitated by weight, diet and exercise diaries, including diet and exercise plans, and graphs for plotting weight, waist circumference, planned and completed circuit training sessions, and pedometer-assessed steps/day.

#### 3.4.1.2.3 *Programme Cost*

The cost for attending the one-year programme was approximately SEK 9,000 (≈\$1,300/€1,000), excluding liquid formulae diets and meal replacements, and was paid by the participants. Although Itrim headquarters provided all centres with recommendations for programme pricing, each centre was allowed to decide its own programme price tailored to local customer demand, rents for facilities, etc.

### **3.4.2 National Health Register Data**

#### **3.4.2.1 The National Patient Register**

The Swedish National Patient Register contains nationwide data on inpatient and non-primary outpatient care visits, including day surgery. The register was started in 1964 when the National Board of Health and Welfare started to collect information regarding inpatients at public hospitals in selected county councils. Nationwide coverage on all inpatient care was attained in 1987, day-surgery from 1997, and non-primary outpatient care was included in 2001. Primary care data are, however, so far not included. The register includes, among other things, personal identification number, visit date, and main as well as contributory diagnoses coded using International Classification of Diseases (ICD7-ICD10) and procedure codes for surgical interventions.



### 3.4.2.2 The Causes of Death Register

The Swedish Causes of Death Register contains deaths and causes of deaths of Swedish residents from 1961. The register contains personal identification number for the deceased, date of birth, date of death, and sex. The cause of death, with one underlying cause of death and several contributory causes, is available for >99% of all deaths occurring (including deaths occurring abroad).

### 3.4.2.3 The Prescribed Drug Register

The Prescribed Drug Register contains information on drugs dispensed on prescription or equivalent in Swedish pharmacies since July 2005. The register contains, among other things, data on the dispensed product (identity, quantity, price) and date of dispensing. ATC codes are used for identification of drugs.

## 3.4.3 Outcomes

### 3.4.3.1 Gallstone Problems

The primary outcome was gallstone problems requiring hospital care during the one-year weight loss programme, while cholecystectomy was investigated as secondary outcome. The primary and secondary outcomes were retrieved from the National Patient Register (**Table 12**).

Register Data	ICD 10 or Procedure Codes
Gallstones/Cholelithiasis	K80
Cholecystectomy	JKA20, JKA21

### 3.4.3.2 Body Composition

Body composition data were collected at baseline, 3, 6 and 12 months. Body weight and body fat percentage were measured in a non-fasting state with the Tanita TBF-300 bioelectrical impedance monitor. Waist circumference was measured midway between the iliac crest and the lower rib cage. Height was measured by a wall-mounted stadiometer without shoes.

## 3.5 STUDY IV: TREATMENT DISCONTINUATION

This study was a systematic review and meta-analysis including published placebo-controlled randomised trials<sup>a</sup> of orlistat (Xenical®), sibutramine (Reductil®) and rimonabant (Acomplia®).

### 3.5.1.1 Identification and Inclusion of Studies

A systematic search of three bibliographic databases (Medline, EMBASE and Cochrane controlled trials register) from 1990 to May 7, 2008, was performed to identify articles. The search was limited to humans, randomised placebo controlled trials, English-language publications and adults. The reference lists of identified articles were also searched for additional studies, as were reference lists of previously published systematic reviews. Two authors separately screened the abstracts for inclusion or exclusion of studies. Full-text articles were retrieved from all abstracts that were potentially relevant and were reviewed independently by the two authors. In case of conflicting views, a third person was asked to resolve matters. The criteria for included studies are presented in **Table 13**.

Study Inclusion	Study Exclusion
<b>Placebo-Controlled RCTs</b>	<b>Weight Loss Maintenance Studies</b>
<b>Licensed Doses for Clinical Use:</b>	<b>Not Licensed Doses for Clinical Use:</b>
- orlistat (3x120 mg/day)	- orlistat (180 mg/day)
- sibutramine (10–15 mg/day)	- sibutramine (>15 mg/day)
- rimonabant (20 mg/day)	- rimonabant (5 mg/day)
<b>Duration 12-24 months</b>	

The systematic search resulted in inclusion of 28 trials: 16 studies of orlistat (n=7,038), seven of sibutramine (n=1,475) and five of rimonabant (n=4,944).

### 3.5.1.2 Data Extraction and Synthesis

From the included studies data on participants, interventions, discontinuation and reason for discontinuation were extracted independently by two authors. The individual studies were then combined in a meta-analysis and the overall risk for discontinuation, lack of effectiveness and discontinuation due to adverse events were estimated compared to placebo.

### 3.5.1.3 Interventions in Included Trials

Pharmacotherapy trials are in general highly controlled and follow strict protocols according to Good Clinical Practice (GCP) guidelines. Hence, the interventions used in the 28 different studies were similar, with the participants in the active treatment group receiving an individual energy deficient diet (approximately 500 kcal/day deficit) in combination with exercise and lifestyle modification, in addition to the active drug or placebo.

<sup>a</sup> Two of the three anti-obesity drugs on the market when this study was performed have been withdrawn due to adverse events. Rimonabant was withdrawn in 2009 and sibutramine in 2010.

### 3.6 STATISTICAL ANALYSIS

The analyses conducted and reported in this thesis were performed by using three different statistical software programmes. The different tests and methods used in the studies are summarised below (Table 14).

	Study I	Study II	Study III	Study IV
<b>Statistical Tests/Methods</b>				
Student's T-Test	x	x	x	
Chi-Square Test			x	
ANCOVA			x	
Linear Regression	x	x		
Logistic Regression			x	
Conditional Cox Regression			x	
Matching			x	
Meta-Analysis				x
<b>Statistical Programmes</b>				
SPSS (version 17.0, Chicago, IL)	x	x		
Stata (version 10, CollegeStation, TX)	x	x	x	x
SAS Statistical Software (version 9.3, SAS Cary, NC, USA)			x	

#### 3.6.1 Student's T-Test – Continuous Data

Student's t-test is used for normally distributed data to determine if a difference between two means is greater than that expected by chance. Two-sample t-tests to estimate mean differences can be either unpaired (also called independent) or paired (also called dependent):

- *Unpaired/Independent*: The means of two independent groups are compared
- *Paired/Dependent*: The means at two different time points are compared within the same group

#### 3.6.2 Pearson's Chi-Squared Test – Categorical Data

The chi-square test is used to compare if there is a difference, other than that expected from chance, across categorical variables. The test is only regarded as valid for samples with at least 80% of expected frequencies greater than five. For smaller samples, where chi-squared tests may be invalid, the Fisher's exact test is recommended.

### 3.6.3 Linear Regression

Linear regression is used to estimate the relationship between a continuous outcome (dependent variable) and one or more predictor/-s (independent variable/-s). The predictor/-s can either be continuous, binary, or categorical variables. The regression line is given by the best fitted line through the observed data:

$$Y = \beta_0 + \beta_1 X_1 + \dots + \beta_k X_k$$

where Y is the outcome,  $\beta_0$  is the intercept,  $\beta_{1/k}$  is the regression coefficient for the X variable/-s, and X is the predictor variable/-s.

### 3.6.4 Logistic Regression

Logistic regression is a form of regression which is used when the outcome is a dichotomous variable (0/1). The independent variables, as for linear regression, can be either continuous, binary, or categorical. To allow a linear relationship to be modelled, the outcome variable is transformed into a logit variable (the natural log of the odds of the dependent variable occurring, or not occurring). In this way, logistic regression estimates the odds of a certain event occurring:

$$\log_e [P/(1 - P)] = \beta_0 + \beta_1 X_1 + \dots + \beta_k X_k$$

where P is the proportion with the outcome,  $\beta_0$  is the intercept,  $\beta_1$  is the regression coefficient for the X variable/-s (which when back-transformed from the log scale to the natural scale are odds ratios), X is the predictor variable/-s, and  $\log_e [P/(1 - P)]$  is the logit transformation.

### 3.6.5 Analysis of Covariance

Analysis of covariance (ANCOVA) is a combination of analysis of variance (ANOVA) and linear regression.<sup>150</sup> As for linear regression, the outcome variable has to be continuous, and at least two predictors has to be included; one continuous and one categorical. ANCOVA tests whether certain factors have an effect on the outcome variable after removing the variance of the added covariates.

### 3.6.6 Cox Regression

Cox regression, which uses the proportional hazards model, is designed for analysis of time to event data. Time to event data are generated when the measurement of interest is the time from a well-defined origin of measurement (for example treatment start) to occurrence of an event of interest (for example cholecystectomy). Time to event analysis is also known as lifetime analysis, and survival analysis.

One or more predictor variables are used to predict an event variable. The Cox model estimates the hazard ratio, that is the ratio of the instantaneous probability of a given event occurring in a given time period comparing two groups. In *Study III*, conditional Cox regression was used. This approach can be used when analysing matched data, that is when each case has one or more matched controls matched by certain variables by conducting the analysis in strata of the matching factors.

### 3.6.7 Matching

Matching is a statistical technique that is used in non-randomised studies to create two comparable groups with similar characteristics with respect to the matching variables.<sup>151</sup> For each observation in the treatment group, one or more controls are assigned with the same values on the matching factors, for example age, sex, and BMI. Matching can be done with or without replacement. In matching with replacement the controls could be matched to multiple treatment observations, while in matching without replacement each control can only be matched to one treatment observation.

### 3.6.8 Meta-Analysis

A meta-analysis is a statistical analysis which combines the results of several independent studies.<sup>152</sup> The statistical technique assigns different weight to the individual studies so that bigger and more precise studies have more influence on the final summary value, compared to smaller less precise studies. In the current thesis pooled risk ratios were assessed.

Two methods for estimating pooled effects from multiple studies are fixed and random effects meta-analysis. The most common method is the random effects model when studies are identified from the published literature. This method is used when it cannot be assumed that all studies are estimating the same underlying value, which would be the case if all the included studies would be functionally identical.

In the random effects model, two sources of variability are accounted for:

- *Within-Study Variability*: This is the variability between subjects within a study (sampling error)
- *Between-Study Variability*: This is the variability between study effects in different studies (true variation in study effect sizes)

When pooling studies in a meta-analysis, the presence of heterogeneity, the observed variability between study estimates, needs to be investigated and if it is large the source needs to be explored. Heterogeneity between studies is commonly assessed by the  $I^2$  statistic. If the  $I^2$  statistic exceeds 50%, it is recommended that the reason for heterogeneity among the studies should be investigated.<sup>153</sup> Possible clinical sources of heterogeneity include treatment differences, such as doses or other medications given, or variation in included patients, such as sex, age, diseases.<sup>152</sup>

### 3.6.9 Missing Data

Although there are several different statistical methods for addressing missing data, none of these have been deemed sufficient replacements for measured data, and ultimately may generate bias in one way or the other. The most common approaches to handle missing data are: completers analysis, last-observation-carried forward, baseline observation carried forward and multiple imputation, all potentially resulting in different treatment effect estimates.<sup>154</sup>

In *completers only analysis* only participants completing the trial are included in the analysis. Hence an overestimation of the treatment effect is likely since those remaining in the trial are more likely to have been successful regarding their weight loss.

*Last observation carried forward* includes the last measured value and will also, probably, lead to an overestimation of the treatment effect since the majority of the participants dropping out will most likely gain weight after discontinuation.

*Baseline observation carried forward* includes the baseline value of each missing value and therefore assumes that those who dropped out have returned to the baseline weight. This method is considered as the most conservative imputation approach.

*Multiple imputation* is a method to impute missing values by using the association between observed characteristics and the outcome from values of the participants remaining in the study (and sometimes from those discontinuing using their values prior to discontinuation). Hence multiple imputation will often result in similar estimates as for the completers analysis.

In the current thesis, baseline carried forward has been used as the main imputation method, while the other methods have been used in sensitivity analyses.

## 3.7 ROLE OF THE FUNDING SOURCES

*Study I&II* were partly supported by research grants from Cambridge Weight Plan, Northants, UK, and Novo Nordisk AS, Bagsværd, Denmark. The funders played no part in the analysis, write up of the papers, and did not read or comment on any version of the manuscript.

*Study III* was partly supported by a grant from Itrim International. The funders had no role in the design or conduct of the study; analysis or interpretation of the data; and did not read or comment on any version of the manuscript.

*Study IV* was conducted without any specific funding.

## 4 RESULTS

### 4.1 STUDY I: WEIGHT LOSS AND OBSTRUCTIVE SLEEP APNOEA

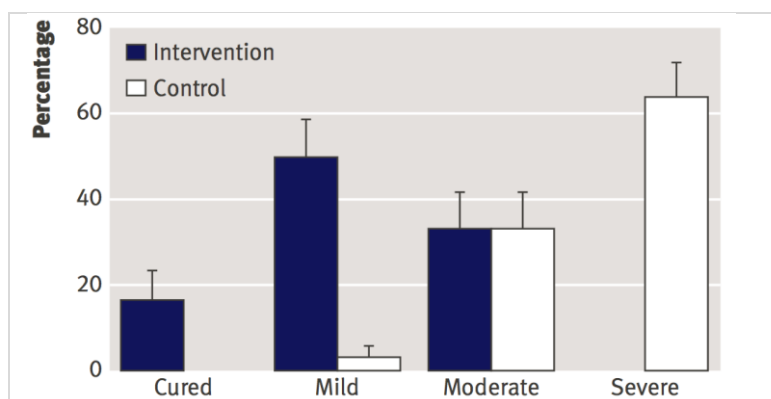
Of 63 eligible patients, 30 were randomised to intervention and 33 to control. Two patients in the control group were dissatisfied with allocation and immediately discontinued. All other patients completed the randomised phase of the trial. Data from all randomised patients were included in an intention-to-treat-analysis (baseline carried forward for missing data). Both groups had a mean AHI of 37 events/hour at baseline. At week nine, the difference between groups in AHI was -23 events/hour (95%CI -15 to -30) and -20 kg (95%CI -18 to -21) in body weight, favouring the intervention group (Table 15).

**Table 15** Changes in weight and obstructive sleep apnoea (OSA) between baseline and week nine

	Intervention (n=30)	Control (n=33)	Mean difference	P-value
AHI (events/hour)	-25 (17)	-2 (11)	-23 (-30 to -15)	< 0.001
Weight (kg)	-19 (4)	1 (2)	-20 (-21 to -18)	<0.001
Waist circumference (cm)	-19 (3)	-1 (2)	-18 (-19 to -16)	< 0.001
Neck circumference (cm)	-4 (1)	0 (1)	-4 (-5 to -4)	< 0.001

Data are mean (SD) or mean (95%CI); P values from independent sample t test; AHI=apnoea-hypopnoea index.

In the intervention group, 17% (5/30) were disease free (AHI <5) after the weight loss and 50% (15/30) had mild disease (AHI 5-14.9), whereas AHI remained at 15 or greater in all controls indicating moderate to severe disease (Figure 3). Significant treatment effect modification by baseline AHI was found (P<0.001), with greater improvement in AHI in the intervention group among patients with severe OSA (AHI >30) at baseline compared with those with moderate (AHI 15-30) sleep apnoea (AHI -38 vs -12, P<0.001), despite similar weight loss (-19 vs -18 kg, P=0.55).



**Figure 3** Proportions of patients defined as having no ("cured"), mild, moderate, or severe obstructive sleep apnoea at week nine. Error bars are 95% confidence intervals. Definitions: Cured defined as AHI <5 events/h, mild 5-14.9 events/h, moderate AHI 15-30 events/h, severe >30 events/h

Adapted from Johansson, K et al (2009). "Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial." *BMJ* 339: b4609.

## 4.2 STUDY II: MAINTENANCE AND OBSTRUCTIVE SLEEP APNOEA

In the pooled observational study of maintenance of OSA improvements over one year, 58 of the 63 participants completed the VLED period and started the weight loss maintenance programme, with 44 completing the full programme, and 49 with complete measurements at one year. In the main analysis, data from all patients were analysed (baseline carried forward for missing data). At baseline mean AHI was 36 events/hour, and mean weight was 113 kg. AHI changes after nine weeks of VLED were largely maintained at one year (**Table 16**).

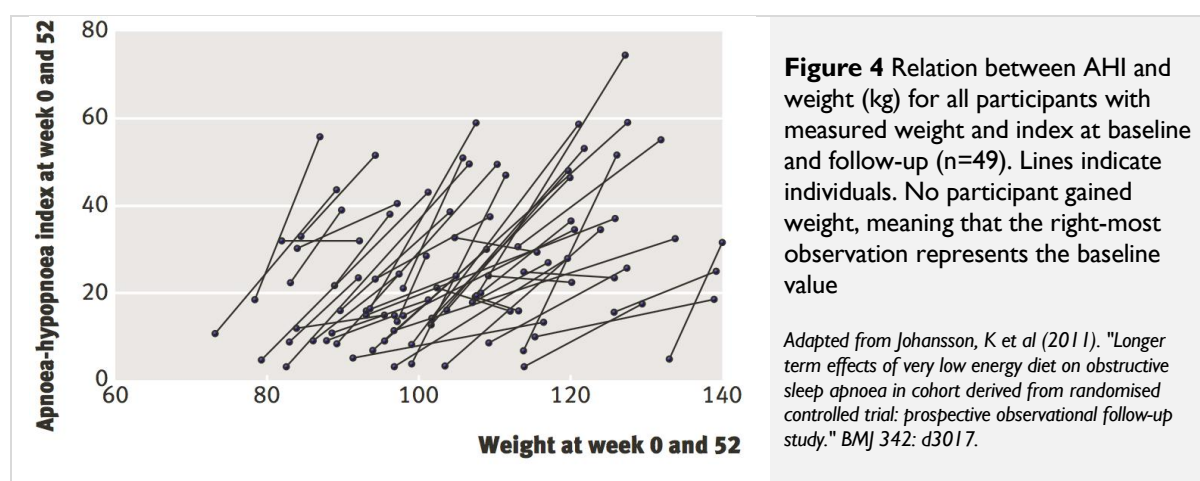
**Table 16** Changes in weight and apnoea-hypopnoea index (AHI) during the one-year programme

	VLED (0 to 9 weeks)		Maintenance (>9 to 52 weeks)		Full programme (0 to 52 weeks)	
	Change	P-value	Change	P-value	Change	P-value
<b>Weight (kg)</b>						
BOCF (n=63)	-18 (7)	<0.001	+6 (8)	<0.001	-12 (9)	<0.001
Completers (n=44)	-19 (4)	<0.001	+3 (6)	<0.001	-16 (7)	<0.001
<b>AHI (events/h)</b>						
BOCF (n=63)	-21 (16)	<0.001	+4 (12)	0.007	-17 (16)	<0.001
Completers (n=44)	-24 (15)	<0.001	+2 (8)	0.099	-22 (16)	<0.001

Data are mean (SD); P values from paired sample t test. BOCF=baseline carried forward for missing data.  
AHI=apnoea-hypopnoea index.

After one year, patients with severe obstructive sleep apnoea at baseline had greater improvements in AHI (-25 events/h; -54%) compared with patients with moderate disease (-7 events/h; -30%;  $P<0.001$ ). In addition, a dose-response association between weight loss and AHI at follow-up were seen ( $\beta=0.50$  events/kg,  $P=0.01$ ; **Figure 4**).

After one-year, 48% (30/63) no longer required CPAP during sleep and 10% (6/63) had achieved full remission (AHI<5).



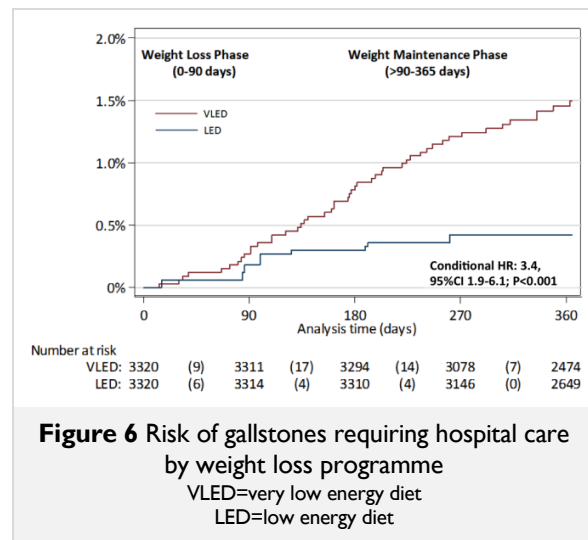
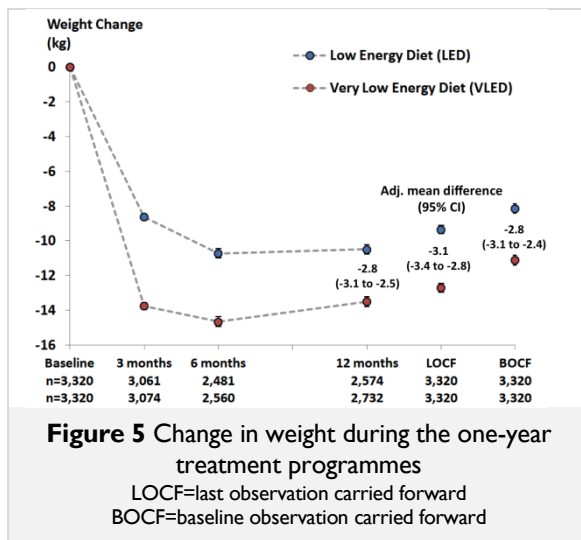
During the VLED period, 13 patients had an adverse event classified as probably causally linked with the VLED. Of the 13 adverse events three were constipation, six were increased ALAT activity, one was dizziness, two were gout and one was dry lips. All adverse events had disappeared by the visit two weeks after the VLED period. During weight loss maintenance there were five additional adverse events of which three were gallstones (all three resulting in cholecystectomy), one was gout and one was kidney stones. No patient discontinued treatment because of adverse events.



### 4.3 STUDY III: RISK OF GALLSTONES DURING VLED

After matching LED participants (n=4,588) with replacement to VLED participants (n=3,773) 1:1 by age, sex, BMI category, waist circumference category, and gallstone history, 3,320 participants remained in each group. At baseline mean age, weight and BMI were 46 years, 95 kg, and 33 kg/m<sup>2</sup>, respectively, while 83% were women. The majority were class I obese (51%), while 23% were class II obese, 8% class III obese, and 19% overweight.

82% of VLED participants and 78% of LED participants completed the one-year programme. Weight loss after one year was greater in the VLED than the LED group (-11 vs -8 kg, baseline carried forward for missing data, and among completers -14 vs -11 kg, both P<0.001; **Figure 5**).



During 3,163 and 3,198 person-years in the VLED and LED groups, 48 and 14 gallstones requiring hospital care occurred (152 vs 44 per 10,000 person-years; conditional hazard ratio 3.4, 95%CI 1.9 to 6.1; P<0.001; **Figure 6**). The risk difference was 108 per 10,000 person-years (95%CI 59 to 157), resulting in a number needed to harm of 92 (95%CI 63 to 168). That is, assuming a causal relationship, one avoidable gallstone requiring hospital care would be caused for every 92 patients treated with VLED instead of LED. Adjusting the analysis for weight loss during the first three months attenuated the hazard ratio, but the risk remained statistically significantly higher with VLED than LED (2.7, 95%CI 1.4 to 5.2).

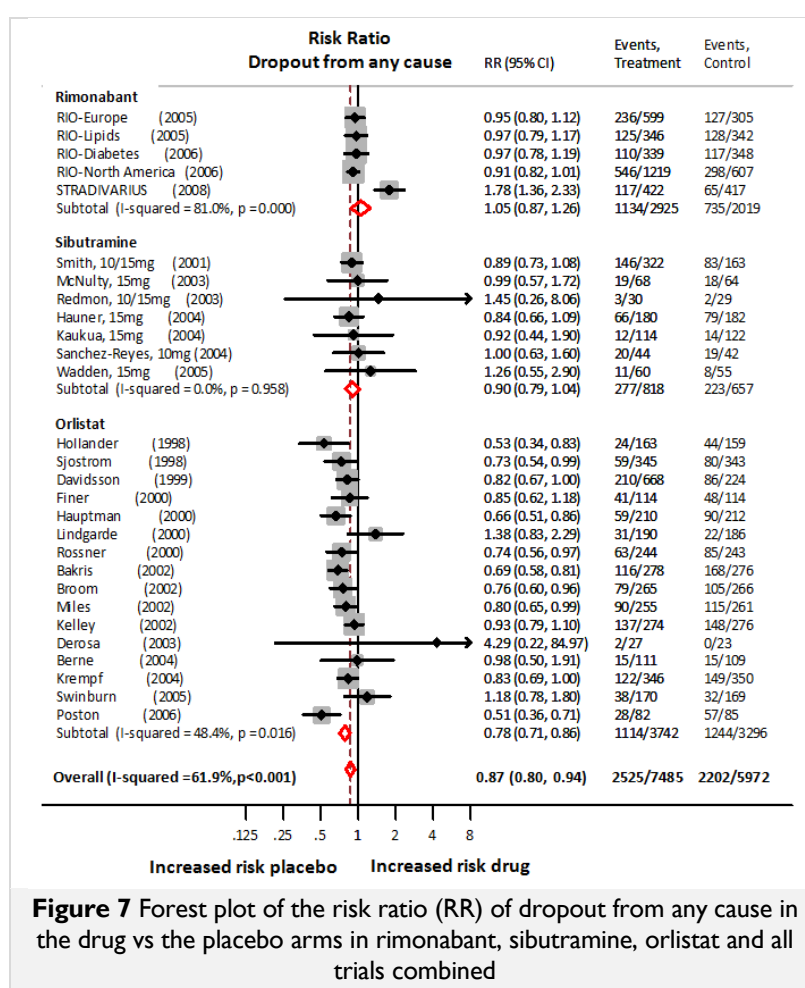
Of the 62 participants with gallstones requiring hospital care, 39 (63%) resulted in cholecystectomy, 29 in the VLED and 10 in the LED group (conditional hazard ratio 3.1, 95%CI 1.5 to 6.5; P=0.003; number needed to harm 151, 95%CI 94 to 377).

In a multivariable analysis including all subjects, the risk of developing gallstones requiring hospital care was higher in women than men, in participants with a higher baseline BMI, among those who lost ≥10kg, and in those with a history of gallstones (irrespective of cholecystectomy status).

## 4.4 STUDY IV: TREATMENT DISCONTINUATION

A total of 28 randomised controlled trials met the inclusion criteria: 16 studies of orlistat (n=7,038), 7 of sibutramine (n=1,475) and 5 of rimonabant (n=4,944). All included studies were between 12 and 18 months duration. Patients had similar demographic profiles across trials of all three drugs, with predominantly Caucasian subjects and a greater proportion of women than men in most of the studies. The mean age ranged between 41 and 59 years and the mean BMI between 33 and 38 kg/m<sup>2</sup>.

The overall combined dropout rates in the included studies were high in drug and placebo arms, with crude overall discontinuation rates of 30% for orlistat, 34% for sibutramine, 39% for rimonabant and 37% for placebo. In the overall pooled random effect model, the risk of dropout was marginally but statistically significantly lower in the active drug compared to the placebo arms (pooled risk ratio 0.9; 95% 0.8 to 0.9; P=0.001; **Figure 7**).



**Figure 7** Forest plot of the risk ratio (RR) of dropout from any cause in the drug vs the placebo arms in rimonabant, sibutramine, orlistat and all trials combined

In the drug arms, the most common reasons for withdrawal were adverse events, patient request and poor compliance. In the placebo arms, withdrawal due to patient request and poor compliance were most common. Lack of effectiveness, as reason for dropout was specified in 10 studies. Patients in the drug arms tended to drop out less frequently as a result of lack of effectiveness compared with placebo (pooled risk ratio 0.5; 95% 0.4 to 0.7; P<0.001). The risk ratios for discontinuation due to adverse events were significantly elevated for rimonabant (2.0; 1.7-2.4) and orlistat (1.6; 1.2-2.1), but not sibutramine (1.0, 0.7-1.4), compared to placebo.

## 5 DISCUSSION

The overall objective of this thesis was to evaluate effects and side-effects of VLEDs in different obesity settings, and to characterise discontinuation in obesity treatment. Specific objectives were to evaluate weight loss as treatment option for patients with OSA (*Study I&II*); to assess the risk of gallstones requiring hospital care in a commercial weight loss programme using VLED or LED (*Study III*); and to characterise overall discontinuation in obesity treatment programmes by analysing data from anti-obesity drug trials (*Study IV*).

### 5.1 MAIN FINDINGS

The studies in this thesis were carried out at a specialist outpatient obesity centre (hospital-based; *Study I&II*), or in the commercial sector (*Study III*). The hospital-based trial included only men with OSA (*Study I&II*), while the commercial study (*Study III*) included both men and women with the majority being women. Analyses included all starting patients (baseline observation carried forward for missing data).

Initial weight loss after VLED in the hospital-based treatment was -16% (*Study I&II*), and -14% in the commercial weight loss programme (*Study III*). Hence the men in the hospital-based treatment programme lost slightly more weight during VLED, but regained more during the maintenance phase than the participants in the commercial programme (32% vs 19% regain of lost weight). A similar weight loss at one year in the hospital-based (-11%) and commercial programme (-12%) was therefore found.

Dropout from both the hospital-based and commercial programme was lower compared to the benchmark of 37% in placebo arms of anti-obesity drugs trials (*Study IV*), with 30% in the hospital-based and 18% in the commercial programme after one year. In the clinical care treatment programme, gallstones were reported in 5% (3/63; all three cholecystectomised; mean BMI 35) of the participants over one year compared to 1.4% (48/3320; 29 of 48 cholecystectomised; mean BMI 33) of the VLED participants of the commercial weight loss programme.

#### 5.1.1 Weight Loss and Obstructive Sleep Apnoea

The findings of the randomised trial of obese men with moderate to severe OSA (*Study I*) indicated that weight loss induced by a VLED significantly improved OSA. The mean AHI was reduced by two-thirds from 37 to 12 in the intervention group compared with no change in the weight stable control group after nine weeks. The pooled observational follow-up study (*Study II*) showed that the AHI changes after nine weeks of VLED (-58%) were largely maintained at one year (-47%) following the initial weight loss of -16% (-18kg), and -11% (-12kg) at one-year. In addition, a significant effect modification by baseline AHI was observed with patients with severe OSA at baseline having larger AHI improvements than patients with moderate disease. Moreover, a dose response association between weight loss and AHI improvement was found. After one year, half of the men no longer required CPAP, and one out of ten had total remission of OSA. There were also marked improvements in metabolic risk and the physical dimension of quality of life.

### 5.1.2 VLED and Risk of Gallstones

The absolute risk of gallstones requiring hospitalisation in overweight and obese participants enrolled in a one-year commercial weight loss programme (*Study III*), using either VLED or LED during the initial three-months weight loss phase, was found to be low (1.4% vs 0.4%). However, the risk was three times higher in the VLED than the LED programme with a number needed to harm of 92. That is, assuming a causal relationship between weight loss treatment and gallstone problems, one additional gallstone requiring hospital care would result per 92 patients on VLED instead of LED. The corresponding number for an additional cholecystectomy was 151. While the risks were greater in the VLED compared to the LED group, the benefit in terms of one-year weight loss was also greater -12% (-11 kg) vs -9% (-8 kg) of initial body weight, respectively. Also, a larger proportion of the participants in the VLED treatment programme completed one-year of treatment compared to participants in LED (82% vs 78%). These completion rates can be compared with the 63% in the placebo arms of randomised trials of anti-obesity drugs.

### 5.1.3 Dropout in Anti-Obesity Drug Trials

Attrition in anti-obesity drug trials including overweight and obese participants was found to be high in both the drug and placebo group, with overall discontinuation of 37% in the placebo arms only receiving diet and lifestyle modification (*Study IV*), and 30-39% in the drug arms, although slightly lower in the drug arm (pooled risk ratio 0.9). In the drug arms, the most common reasons for withdrawal were adverse events, patient request and poor compliance. In the placebo arms, withdrawal due to patient request and poor compliance were most common. Overall, patients in the drug arms tended to drop out less frequently as a result of lack of effectiveness compared with placebo (pooled risk ratio 0.5). The risk ratios for discontinuation due to adverse events were significantly elevated for rimonabant and orlistat, but not for sibutramine, compared to placebo.

## 5.2 COMPARISON WITH PREVIOUS RESEARCH

### 5.2.1 Weight Loss and Obstructive Sleep Apnoea

Before 2009, no randomised trial had shown weight loss to improve OSA, while observational studies of both dietary and surgical interventions indicated that this was the case.<sup>155</sup> In 2009, three randomised controlled trials were published,<sup>114-116</sup> one of which is included in this thesis (*Study I*).<sup>114</sup> All three trials found a positive effect of weight loss on OSA, but in different patient groups. A Finnish study by Tuomilehto et al<sup>115</sup> found a 40% reduction in AHI in patients with mild OSA after -11% (-11 kg) weight loss at one year, and a 46% AHI reduction with a -7% (-7 kg) weight loss after two years.<sup>140</sup> In a sub-sample of the American Look AHEAD study, Foster et al<sup>116</sup> found a 24% AHI reduction at one year with -10% (-11 kg) weight loss after an intensive lifestyle intervention in older (mean age 61y) patients with type 2 diabetes, while the AHI increased in control patients, resulting in a between group AHI difference of 42%. The dose-response association that was found in *Study I&II* between weight loss and OSA was also found by Foster et al and by Tuomilehto et al<sup>115 116</sup> Foster et al also found significantly greater improvements in patients with severe disease at baseline, as found in *Study I&II*.

In addition to dietary interventions, weight loss induced by bariatric surgery has also been shown in observational studies to result in long-term improvements in OSA. In the SOS study including matched controls, Grunstein et al<sup>120</sup> found that 30% of the surgery group reported self-reported persistent sleep apnoea at the two-year follow-up compared with 70% of the control group. Small uncontrolled studies (n<20) have also found long-term improvements in OSA after weight loss surgery.<sup>124 125 132 135 137</sup>

### 5.2.2 VLED and Risk of Gallstones

Few randomised trials investigating the effect of VLED on weight loss report side-effects. In a meta-analysis comparing the long-term efficacy and safety of VLEDs and LEDs, Tsai and Wadden<sup>65</sup> concluded that no symptomatic gallstones were reported among VLED participants in any of the included trials, but they also concluded that this may have been attributable to lack of assessment in the individual studies.

The majority of studies specifically investigating the risk of gallstones during VLED treatment have been conducted in the late 1980s and early 1990s with VLEDs containing low levels of fat ( $\approx 1$  g/day).<sup>90-94</sup> In a review of these studies,<sup>88</sup> Everhart reported that 10-25% of VLED participants developed gallstones, one third of which were symptomatic. However, the studies were of short duration (8-36 weeks),<sup>90-94</sup> and only one study included a weight stable control group.<sup>92</sup> Later studies have investigated VLEDs containing higher fat content,<sup>95-98</sup> including two randomized controlled trials,<sup>95 96</sup> and found that fewer participants developed symptomatic gallstones. In a review, Festi et al<sup>89</sup> concluded that adequate fat content is important in gallstone prevention, with 10 g/day as a threshold for obtaining efficient gallbladder emptying. A lower recommendation of 7 g/day has, however, been given by the European SCOOP-report on VLED use.<sup>60</sup> In our register-linkage study of a commercial weight loss programme using a liquid formula diet containing 7-9 g/day, we found a higher, albeit low, risk of symptomatic gallstones requiring hospitalisation in the VLED compared to the LED group, suggesting that more fat may be needed to eliminate the excess risk of gallstones compared to LED (*Study III*).

Bariatric surgery, however, also increases the risk of gallstones probably as a result of the rapid weight loss. The postoperative incidence has been reported to be between 3 to 28%.<sup>156</sup> This large span may be explained by different follow-up time and/or different methods of detecting gallstones. A Swedish population-based cohort study of bariatric surgery identified the risk of gallstones requiring hospitalisation by the use of the National Patient Register (that is, similar to the methodology in *Study III*), and found a fivefold increased risk of both gallstones requiring hospital care and cholecystectomy for the bariatric surgery group compared to that of the general population. In the SOS study the incidence of gallstones and cholecystectomy after 2 years was assessed using questionnaires.<sup>157</sup> Compared to conventional treatment, bariatric surgery significantly increased the risk of self-reported gallstones in men (4.0% vs 1.2%, odds ratio 4.2;  $P<0.001$ ), but not in women (5.5% vs 4.5%, odds ratio 1.1;  $P=0.33$ ). However, in both sexes, a greater weight loss in the surgery group was related to an increased incidence of gallstones.

### 5.2.3 Weight Loss Programme Discontinuation

Weight loss treatment programmes in observational settings (hospital-based and commercial) as well as randomised trials are generally associated with high levels of attrition, although reported dropout rates vary considerably. In a systematic review of weight loss studies addressing factors associated with attrition,<sup>142</sup> one-year dropout rates of diet and lifestyle modification studies ranged between 16-77%. In comparison, low attrition rates were reported in the Look AHEAD trial after 1 year (3% in the intensive lifestyle intervention and 4% in the diabetes support and education intervention),<sup>24</sup> and at four years (6% vs 7%, respectively).<sup>25</sup>

Lack of treatment effect is one of the most common reasons why participants discontinue treatment. In anti-obesity drug trials, adverse events are also a common reason in the active drug arm for withdrawal, as reported in *Study IV*. Identified predictors of dropout in weight loss intervention studies in general include young age, previous dieting attempts, too high weight loss expectations, poor mental health, body dissatisfaction, low self-efficacy, low social support, and low initial weight loss.<sup>142</sup>

Attrition has been reported as the major limitation of all weight loss trials.<sup>158</sup> Although there are several different statistical methods for addressing missing data, none of these have been deemed sufficient replacement for measured data, and ultimately generate bias in one way or the other.<sup>154</sup> When interpreting estimates of weight loss interventions it is important to consider how missing data have been handled, especially when comparing treatment effects of different studies.

## 5.3 STRENGTHS AND LIMITATIONS

**Study Design:** *Study I* was a randomised controlled trial of nine week duration, followed by an observational study of a total duration of one year (*Study II*). The strengths of *Study I* was the randomised study design with its low probability of selection bias and residual confounding.<sup>159</sup> The reason for not using a randomised design with a one-year follow-up was that our primary aim was to show, in the short term, a treatment effect from weight loss with a VLED in moderate to severe OSA. Our secondary aim was to see whether any improvements could be maintained in the long-term. We therefore wanted to minimise non-compliance in the control group in the nine week randomised phase by providing a strong incentive for controls to remain in the study by allowing patients to start the VLED programme immediately after serving as controls. The limitation of the observational design used for the one-year follow up means that our analysis is limited by the lack of comparison with natural progression regarding AHI and weight.

*Study III* was an observational cohort study with a large sample of participants in a commercial weight loss programme in a real-life setting. Because the risk of gallstones is low, one strength was the large sample which provided sufficient power for a comparison with LED. Also, by using a register-linkage design for assessment of events, we could follow-up a large number of participants at a relatively low cost. The main limitation was that participants were not randomised, but had self-selected to the VLED and LED programmes. However, the ensuing baseline differences in age, sex, BMI, waist circumference, and gallstone history were handled by performing a matched analysis. This design reduces the likelihood and impact of confounding, but residual confounding may remain beyond the matching factors.

*Study IV* was a meta-analysis which combined results from individual anti-obesity drug trials and assessed the risk of treatment discontinuation. The strengths of the meta-analysis include: increased statistical power, improved estimates of effect size and the ability to resolve controversies when different studies report conflicting results regarding both overall discontinuation and discontinuation due to adverse events.

**Identification/measurement of main outcomes:** In *Study I&II* the main outcome measure was AHI derived from two consecutive nocturnal sleep studies in the home. Because of the reported night-to-night variability,<sup>160</sup> a strength was that duplicate sleep studies were performed. A limitation was the use of a portable WatchPAT device instead of polysomnography, which is considered the gold standard for diagnosing OSA. However, high costs, limited access to sleep laboratories, and the increasing number of patients with OSA have led to the development of more accessible and cheaper methods, such as the portable monitors used in this study. Validation studies show that the WatchPAT device has high sensitivity and specificity for estimating sleep time and AHI compared with polysomnography.<sup>161 162</sup>

In *Study III*, the strength was the use of nationwide register data to identify the main outcome (gallstones requiring hospital care), the secondary outcome (cholecystectomy), and co-morbidity history and drug use of the cohort. The National Patient Register and the Prescribed Drug Register contain prospectively reported data collected routinely on a nationwide level in the universally accessible Swedish health care system, with virtually complete follow-up. One limitation, however, is that the National Patient Register only includes data on inpatient and non-primary outpatient visits and not visits in primary care. Hence, symptomatic gallstones treated in primary care could not be identified. However, our primary outcome was gallstones requiring hospital care, since symptomatic gallstones treated in primary care, at home, or not at all, are likely to be both less serious for the patient and less costly for society.

**Study Populations:** *Study I&II* included a patient group reported to have an increased risk for mortality.<sup>110-112</sup> However, since we only included obese men aged 30-65 years, our results might not be generalisable to subjects outside the inclusion criteria of the study, that is women, younger (<30 years) or older (>65 years) patients, overweight (BMI 25-29.9) or extremely obese patients (BMI  $\geq$ 40), or patients with mild sleep apnoea. The rationale for only including men was mainly to reduce risk of type 2 error, since we could not be certain that the effect of weight loss on OSA would be the same for men and women. The reason for choosing men instead of women was that the prevalence of OSA is much higher in men vs women (24% vs 9%, respectively).<sup>99</sup> The strengths of *Study III* included a large sample of weight loss participants in a real-life setting. The results from this study may limit generalisability to the wider overweight and obese population, since the participants had selected and paid for the treatment themselves, and could therefore be considered as a highly motivated group of higher socio-economic class.

## 5.4 CLINICAL IMPLICATIONS

The availability of obesity treatment is today limited mainly to lifestyle modification or bariatric surgery, since the withdrawal of two out of three previously approved anti-obesity drugs. Bariatric surgery is currently the most effective method for treating obesity and results in weight loss of about 14-25% after 10 years.<sup>52</sup> However, it is not realistic to treat all obese patients with surgery. According to current guidelines, only class II and class III obese qualify, that is patients with a BMI >35. Furthermore, due to both presence of contraindications and capacity constraints, not all in the class II/III obese group would be operated upon either. Other non-surgical treatment options, with strict maintenance programmes, are therefore needed. VLED in combination with a strict maintenance programme has been found to be a strong non-surgical candidate for achieving one-year maintenance results of 10-15% weight loss.<sup>33 72 74-81</sup>

The long-term effects of the use of VLED in the treatment of obesity vs LED have however been questioned. In the meta-analysis of Tsai and Wadden, they concluded that VLEDs induced significantly greater short-term weight loss than LEDs (mean difference of initial weight loss -6.4%,  $p < 0.001$ ) during a mean initial 13 weeks, but similar losses after 2 years (-1.3%,  $p > 0.02$ ).<sup>65</sup> They also concluded that VLEDs would be more attractive if sufficient weight loss maintenance programmes existed, but they did not recommend the use of VLEDs over LEDs. However, neither of the included studies of that meta-analysis included an extensive exercise programme,<sup>74 75</sup> pharmacotherapy,<sup>76-81</sup> a prolonged re-feeding period<sup>72 75</sup> or a low glycemic index diet in combination with high protein<sup>33</sup> as a part of the maintenance programme, which have all been proven to limit weight regain or even reduce weight further.<sup>33 74 76 80 81</sup>

In the VLED group of *Study III* 81% of the initial weight loss was maintained up to one-year (98% among completers), although the adjusted mean difference between VLED and LED was reduced from -5 kg at 12 weeks to -3kg at one-year. In *Study I&II* 68% (82% among completers) of initial weight was maintained up to one-year. The larger maintained weight loss in *Study III* could be explained by regular scheduled exercise as compared to *Study II* where increased exercise was emphasised but the programme did not include an exercise scheme. Also, *Study III* included a highly motivated group that had sought and also paid for treatment themselves.

Regarding the safety aspects of VLED, as shown in *Study III*, there is an increased risk of symptomatic gallstones requiring hospital care as well as cholecystectomy when using VLED instead of LED, although the absolute risk was low. Increased risk for gallstones is, however, also seen after bariatric surgery, which currently is considered the most effective treatment for obesity.

Whether the benefits of the additional weight loss in the VLED group compared to the LED group are worth the extra risk for gallstones and cholecystectomy, as well as the extra health care costs, may depend on patients' disease and risk factor status as well as their preferences. For some patients, VLED could however be difficult to adhere to and/or result in significant weight regain after the weight loss phase, while others will benefit from VLEDs both in the short and long-term. Although little is known about which patients are most likely to benefit from different treatments, a study by Gripeteg et al<sup>163</sup> has investigated predictors of VLED outcome. The authors found that social support and walking capacity were important determinants of successful weight loss with VLED in men, whereas psychosocial function were important for VLED success in women. They also found that patients with low perceived health who lack a close social network may need extra support during treatment.



## 5.5 FUTURE RESEARCH

- **Weight loss maintenance after VLED:** Further long-term randomised studies, including comparison of the effect of different weight loss maintenance strategies after VLED or LED are needed to optimise weight loss maintenance.
- **Composition of VLED:** The effect of different fat contents of VLEDs has not been studied in detail in long-term studies. Hence comparisons between products containing about 7 g/day of fat as recommended by the European SCOOP-report on VLED use, and higher intakes (>12 g/day) are needed to evaluate associated risk for gallstones with a lower fat intake of VLEDs.
- **Long-term effect of weight loss on OSA:** Weight loss may have a long-term effect on OSA despite a rebound in weight. Tuomilehto et al<sup>140</sup> demonstrated in their two-year follow-up study that AHI remained improved and did not relapse and follow the trend of modest weight gain. Also, unpublished data of the four-year follow-up of the study by Foster et al<sup>116</sup> demonstrated the same trend. Further long-term studies of the effect of weight loss in OSA are therefore needed to investigate this long-term response to weight loss.
- **Prevention of discontinuation:** The majority of published weight loss studies focuses on the effects of weight loss and/or the resolution of obesity-related co-morbidities, and reasons for dropout are often either not reported, or not explored in any depth. The few studies that have investigated reasons for dropout have been limited to data not collected for the purpose of evaluation of dropout.<sup>142</sup> Studies are therefore needed to identify strategies to prevent dropout.

## 6 CONCLUSION

The overall conclusions of this thesis are:

- I) VLED-induced weight loss resulted in a significant reduction of moderate to severe OSA in obese men. Patients with severe OSA benefited most from the VLED-induced weight loss.
- II) In patients with moderate to severe OSA who had lost weight by a VLED, the majority of the initial improvement in AHI was maintained at one year. Almost half of the patients no longer required CPAP after one year, and one out of ten had total remission of OSA.
- III) Although VLED, compared to LED, is associated with a three times increased risk of gallstones requiring hospital care or cholecystectomy, the absolute risk was low (1.4% for VLED vs 0.4% for LED). While these risks were greater for VLED compared to LED, sustained weight loss reduction was approximately 30% greater at one year in the VLED group.
- IV) One-year treatment discontinuation was lower in both the sleep apnoea study using a hospital-based outpatient weight loss programme (30%) and in the commercial weight loss programme (18%) compared to the pooled data from placebo arms of anti-obesity drug trials (37%).

## 7 SVENSK SAMMANFATTNING

**Bakgrund** Förekomsten av fetma har ökat dramatiskt under de senaste decennierna, både i Sverige och i övriga världen. Fetma är associerat med ökad risk för sjuklighet och dödlighet, vilket leder till stor belastning för sjukvården. Den för närvarande mest effektiva fetmabehandlingen är fetmakirurgi. Eftersom alla individer med fetma inte kan genomgå fetmakirurgi är behovet av icke-kirurgiska behandlingsmetoder stort.

**Syfte** Det övergripande syftet med denna avhandling var att utvärdera effekter och bieffekter av "very low energy diets" (VLEDs), men också att karakterisera avhopp från fetmabehandling. Specifika syften var att utvärdera effekten av viktminskning med VLED som behandling för patienter med obstruktiv sömnapné (OSA; *Studie I&II*) i ett kliniskt viktminskningsprogram, att utvärdera risken för sjukvårdskrävande gallstensbesvär efter VLED eller "low energy" diet (LED, *Studie III*) i ett kommersiellt viktminskningsprogram, och att karakterisera avhopp från fetmabehandling genom att analysera data från fetmaläkemedelsprövningar (*Studie IV*).

**Metoder** *Studie I&II* bestod av en nio veckor lång randomiserad kontrollerad studie följt av 43 veckors observationell uppföljning. Män med fetma (n=63, BMI 30-40, 30-65 år) och måttlig till svår OSA (apnea-hypopnea index (AHI)  $\geq 15$ ) behandlade med CPAP inkluderades. Interventionen bestod av VLED (554 kcal/dag) under nio veckor. Efter den randomiserade fasen erhöll kontrollgruppen samma intervention. VLED-perioden följdes av sedan av ett viktstabiliseringsprogram. *Studie III* var en ettårig matchad kohortstudie, bestående av män och kvinnor som deltog i ett kommersiellt viktminskningsprogram i Sverige mellan 2006 och 2009 (n=6,640; medelålder 46 år, 83% kvinnor, BMI 33). Programmet inkluderade en tremånaders viktminskningsperiod bestående antingen av VLED (500 kcal/dag) eller LED (1,200-1,500 kcal/dag). Viktminskningsfasen följdes av ett nio månaders viktstabiliseringsprogram. Data om sjukvårdskrävande gallstensbesvär ellerolecystektomi under det ettåriga programmet hämtades från patientregistret på Socialstyrelsen. *Studie IV* var en systematisk genomgång och metaanalys som inkluderade publicerade randomiserade placebokontrollerade läkemedelsprövningar av orlistat, sibutramin och rimonabant (n=13,457).

**Resultat** *Studie I&II*: Efter den nio veckor långa randomiserade fasen var interventionsgruppens genomsnittliga kroppsvikt 20 kg lägre än kontrollgruppens, och medelvärdet för AHI var 23 uppehåll/timme lägre. Totalt så fullföljde 70% (44/63) av alla deltagare den observationella uppföljningsstudien. Merparten av de initiala förbättringarna i AHI (-58%) efter ett år bibehölls (-47%) efter den initiala viktminskningen på 18 och 12 kg efter ett år. *Studie III*: Den absoluta risken för gallsten ocholecystektomi var låg, men tre gånger högre i VLED än LED programmet (hasardkvot 3.4 och 3.1;  $P < 0.001$ ). Medan riskerna för gallsten var större i VLED- jämfört med LED-gruppen så var viktminskningen också större (11 vs 8 kg;  $P < 0.001$ ) och fler fullföljde studien (82% vs 78%). *Studie IV*: Avhoppsfrekvensen från fetmaläkemedelsprövningar var hög både i läkemedels- (30-39%) och kontrollgrupperna (37%) men något lägre i läkemedelsgruppen (poolad riskkvot 0.9;  $P = 0.001$ ).

**Slutsats** VLED-inducerad viktnedgång resulterade i en signifikant reduktion av måttlig till svår OSA, med majoriteten av den initiala förbättringen bibehållen efter ett år. Risken för gallsten var högre efter VLED än LED, medan viktminskningen också var större i VLED-gruppen. Frekvensen behandlingsavhopp var lägre i både det kliniska och det kommersiella viktminskningsprogrammet jämfört med poolade data från kontrollgrupperna i fetmaläkemedelsprövningar.

## 8 ACKNOWLEDGMENT

I would like to thank,

My supervisor, *Martin Neovius*, for everything you have taught me; for always being available regardless the time of the day (and night); for the uncountable hours and endless commitment; for always pushing me and for never letting me give up. Simply lots of thanks for being a fantastic main supervisor.

*Erik Hemmingsson*, co-supervisor, for all your support and encouragement; for never being further away than a phone call and for all the inspiring discussions.

*Stephan Rössner*, co-supervisor, for always believing in me; for always saying your opinion; for your extremely rapid response in proof-reading; for making the OSA-study happen; and finally for your humour and fun discussions.

Finally to *all my supervisors* for believing in me and allowing me to take responsibility; for placing high expectations on me while at the same time giving me all the help I ever needed. Thank you for four wonderful years.

*Kristian Neovius* for sharing the PhD-student time with me; for being a fantastic friend ever since we shared office at the Obesity Unit; for all the fun discussions; for all your help and support with everything from KI-forms to bicycle repairs to cooking.

*Anna Laumann, Jenny Dygve and Sara Yllö*, for the fantastic years at the Obesity Unit; for all the laughter; for showing the importance of having a calendar; for putting up with me when I did not have the time for coffee breaks or anything else; for making work a wonderful place; and finally for being fantastic friends ever since that time.

*Lena Mannström* for all the lovely discussions; for always having the time for me and helping me when everything was new; for giving me a hand with everything from paper jams to study-planning and of course for doing an excellent job in the OSA-study.

*Jonas Eriksson* for all your SAS support. It is a true honour to share office with a human SAS-encyclopaedia; and for all the inspiring cross-country skiing discussions.

*Viveca Petré* for help with everything from administration to study-planning and for all the nice chats during the years at the Obesity Unit.

*Mary Hyll* for all the interesting discussions and for excellent proof-reading of manuscripts.

*Richard Harlid* for great collaboration in the OSA-study; for all your hard work with everything from patient inclusion to manually reviewing all the sleep data; for delivering the data under time pressure; and finally for all your help, guidance and patience with all my questions about sleep apnoea.

*Ylva Trolle Lagerros* for interesting research discussions and help with the OSA-study.

*All colleagues at the Obesity Unit, Huddinge, for making the time so fun and educational. A special thanks to Lena Mannström, Jenny Dygve, Mary Hyll, Ylva Trolle Lagerros, Viveca Petré, Anna Laumann and Sara Yllö for your hard, dedicated and thorough work in the OSA-study.*

*The staff at Aleris Fysiologlab, for performing the sleep studies.*

*The study patients in the OSA-study for participating in the study.*

*Fredrik Granath for statistical expertise.*

*Birgitta Thörn, Itrim, for all the work with the data extraction in the commercial weight loss study.*

*Johan Sundström and Claude Marcus for co-authorship, great comments and new ideas.*

*Friends and Family,*

*To Johanna, my oldest friend, for making me somewhat more spontaneous and for your support throughout all years. Astrid, my "big sister", for always guiding me and helping me see things from new perspectives; for your endless encouragement and support; and for always giving me your honest opinion. Anna for always being there for me; always supporting me; and for always reminding me to take care of myself when I become absorbed in work or other projects.*

*Last but not least, to my family, to Björn for your patience, endless support and encouragement; for always believing in me and my abilities; and for putting up with all my ideas and projects. To my parents, Agneta and Svante, for always encouraging me to do what I believe in and for your everlasting support.*

## 9 REFERENCES

1. WHO. *Obesity: preventing and managing the global epidemic: report of a WHO consultation*. Geneva: World Health Organization, 2000.
2. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *The New England journal of medicine* 2008;359(20):2105-20.
3. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120(16):1640-5.
4. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;377(9765):557-67.
5. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA : the journal of the American Medical Association* 2012;307(5):491-7.
6. Statistiska-centralbyrån. Levnadsförhållanden - Hälsa, sjukdom och vård efter region, indikator och kön. Andelar i procent och skattat antal i tusental. 3-årsmedelvärde. Fetma och övervikt. 2008-2010;<http://www.ssd.scb.se/databaser/makro/MainTable.asp?yp=tansss&xu=C9233001&omradekod=LE&omradetext=Levnadsf%F6rh%E5llanden&lang=1>. Accessed 2012-03-30.
7. Gorber SC, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007;8(4):307-26.
8. Sturm R. Increases in morbid obesity in the USA: 2000-2005. *Public Health* 2007;121(7):492-6.
9. Neovius M, Teixeira-Pinto A, Rasmussen F. Shift in the composition of obesity in young adult men in Sweden over a third of a century. *Int J Obes (Lond)* 2008;32(5):832-6.
10. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA : the journal of the American Medical Association* 2010;303(3):235-41.
11. Rokholm B, Baker JL, Sorensen TI. The levelling off of the obesity epidemic since the year 1999--a review of evidence and perspectives. *Obes Rev* 2010;11(12):835-46.
12. Haslam DW, James WP. Obesity. *Lancet* 2005;366(9492):1197-209.
13. Neovius K, Johansson K, Kark M, Neovius M. Obesity status and sick leave: a systematic review. *Obes Rev* 2009;10(1):17-27.
14. Neovius K, Johansson K, Rossner S, Neovius M. Disability pension, employment and obesity status: a systematic review. *Obes Rev* 2008;9(6):572-81.
15. Neovius K, Neovius M, Rasmussen F. The combined effects of overweight and smoking in late adolescence on subsequent disability pension: a nationwide cohort study. *Int J Obes (Lond)* 2010;34(1):75-82.
16. Withrow D, Alter DA. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. *Obes Rev* 2011;12(2):131-41.
17. Odegaard K, Borg S, Persson U, Svensson M. The Swedish cost burden of overweight and obesity--evaluated with the PAR approach and a statistical modelling approach. *Int J Pediatr Obes* 2008;3 Suppl 1:51-7.

18. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373(9669):1083-96.
19. Neovius M, Sundstrom J, Rasmussen F. Combined effects of overweight and smoking in late adolescence on subsequent mortality: nationwide cohort study. *BMJ* 2009;338:b496.
20. McGee DL. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol* 2005;15(2):87-97.
21. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *JAMA : the journal of the American Medical Association* 2005;293(15):1861-7.
22. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA : the journal of the American Medical Association* 2004;291(10):1238-45.
23. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc* 2007;107(10):1755-67.
24. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes care* 2007;30(6):1374-83.
25. Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010;170(17):1566-75.
26. Lindroos A-K, Rössner S. *Fetma : från gen- till samhällspåverkan*. Lund: Studentlitteratur, 2007.
27. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Jr., Brehm BJ, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166(3):285-93.
28. Astrup A, Meinert Larsen T, Harper A. Atkins and other low-carbohydrate diets: hoax or an effective tool for weight loss? *Lancet* 2004;364(9437):897-9.
29. Foster GD, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, Brill C, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* 2010;153(3):147-57.
30. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *The New England journal of medicine* 2008;359(3):229-41.
31. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *The New England journal of medicine* 2009;360(9):859-73.
32. Wing RR, Phelan S. Long-term weight loss maintenance. *Am J Clin Nutr* 2005;82(1 Suppl):222S-25S.
33. Larsen TM, Dalskov SM, van Baak M, Jebb SA, Papadaki A, Pfeiffer AF, et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. *The New England journal of medicine* 2010;363(22):2102-13.
34. Wing RR, Hill JO. Successful weight loss maintenance. *Annual review of nutrition* 2001;21:323-41.
35. Wadden TA, Neiberg RH, Wing RR, Clark JM, Delahanty LM, Hill JO, et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)* 2011;19(10):1987-98.
36. Wing RR, Tate DF, Gorin AA, Raynor HA, Fava JL. A self-regulation program for maintenance of weight loss. *The New England journal of medicine* 2006;355(15):1563-71.

37. Tsai AG, Wadden TA. Systematic review: an evaluation of major commercial weight loss programs in the United States. *Ann Intern Med* 2005;142(1):56-66.
38. Heshka S, Anderson JW, Atkinson RL, Greenway FL, Hill JO, Phinney SD, et al. Weight loss with self-help compared with a structured commercial program: a randomized trial. *JAMA : the journal of the American Medical Association* 2003;289(14):1792-8.
39. Truby H, Baic S, deLooy A, Fox KR, Livingstone MB, Logan CM, et al. Randomised controlled trial of four commercial weight loss programmes in the UK: initial findings from the BBC "diet trials". *BMJ* 2006;332(7553):1309-14.
40. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA : the journal of the American Medical Association* 2005;293(1):43-53.
41. Jebb SA, Ahern AL, Olson AD, Aston LM, Holzapfel C, Stoll J, et al. Primary care referral to a commercial provider for weight loss treatment versus standard care: a randomised controlled trial. *Lancet* 2011;378(9801):1485-92.
42. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. *Lancet* 2007;369(9555):71-7.
43. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ* 2007;335(7631):1194-9.
44. Heal DJ, Gosden J, Smith SL. What is the prognosis for new centrally-acting anti-obesity drugs? *Neuropharmacology* 2012.
45. Johansson K, Sundstrom J, Neovius K, Rossner S, Neovius M. Long-term changes in blood pressure following orlistat and sibutramine treatment: a meta-analysis. *Obes Rev* 2010;11(11):777-91.
46. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007;370(9600):1706-13.
47. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *The New England journal of medicine* 2010;363(10):905-17.
48. EMEA. European Medicines Agency: European Medicines Agency recommends first switch from prescription only to non-prescription for a centrally authorised medicine. 2008; [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2009/11/WC500014828.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014828.pdf). Accessed 2012-03-30.
49. Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2011.
50. Dixon JB, Straznicky NE, Lambert EA, Schlaich MP, Lambert GW. Surgical approaches to the treatment of obesity. *Nature reviews. Gastroenterology & hepatology* 2011;8(8):429-37.
51. Nationella-indikationer-för-obesitas-kirurgi. 2009; [www.sfoak.se/wp-content/niok\\_2009.pdf](http://www.sfoak.se/wp-content/niok_2009.pdf). Accessed 2012-03-30.
52. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *The New England journal of medicine* 2007;357(8):741-52.
53. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. *Cochrane Database Syst Rev* 2009(2):CD003641.
54. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrenbach K, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association* 2004;292(14):1724-37.



55. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351(26):2683-93.
56. Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. *JAMA : the journal of the American Medical Association* 2012;307(1):56-65.
57. Karlsson J, Taft C, Ryden A, Sjöström L, Sullivan M. Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *Int J Obes (Lond)* 2007;31(8):1248-61.
58. Sjöström L, Gummesson A, Sjöström CD, Narbro K, Peltonen M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *The lancet oncology* 2009;10(7):653-62.
59. Näslund I. Accelererande utveckling av obesitaskirurgi i Sverige. *Lakartidningen* 2011;108(49):2574-7.
60. SCOOP-VLCD Task 7.3. Scientific Co-operation on Questions Relating to Food: Directorate-General Health and Consumer Protection, European Union. 2002; [http://ec.europa.eu/food/fs/scoop/7.3\\_en.pdf](http://ec.europa.eu/food/fs/scoop/7.3_en.pdf). Accessed 2012-03-20.
61. National Task Force on the Prevention and Treatment of Obesity NIOH. Very low-calorie diets. *JAMA : the journal of the American Medical Association* 1993;270(8):967-74.
62. National Institutes of Health NIOH. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998;6 Suppl 2:51S-209S.
63. NIH. Obesity guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children (NICE Clinical Guideline 43). 2006:4S-80S.
64. Sharma AM, Freedhoff Y. *Best Weight- Practical Guide to Office-Based Obesity Management*: Canadian Obesity Network 2010.
65. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)* 2006;14(8):1283-93.
66. Mustajoki P, Pekkarinen T. Very low energy diets in the treatment of obesity. *Obes Rev* 2001;2(1):61-72.
67. Codex Stan 203-1995. Codex Standard for formula foods for use in very low energy diets for weight reduction. 1995; [www.codexalimentarius.net/download/standards/296/CXS\\_203e.pdf](http://www.codexalimentarius.net/download/standards/296/CXS_203e.pdf). Accessed 2012-03-20.
68. Torgerson JS, Agren L, Sjöström L. Effects on body weight of strict or liberal adherence to an initial period of VLCD treatment. A randomised, one-year clinical trial of obese subjects. *Int J Obes Relat Metab Disord* 1999;23(2):190-7.
69. Heymsfield SB, van Mierlo CA, van der Knaap HC, Heo M, Frier HI. Weight management using a meal replacement strategy: meta and pooling analysis from six studies. *Int J Obes Relat Metab Disord* 2003;27(5):537-49.
70. Torgerson JS. Very Low Calorie Diets In: Lindroos A-K, Rössner S, editors. *Fetma : från gen- till samhällspåverkan*. Lund: Studentlitteratur, 2007:253-64.
71. Van Nieuwenhove Y, Dambrauskas Z, Campillo-Soto A, van Dielen F, Wiezer R, Janssen I, et al. Preoperative very low-calorie diet and operative outcome after laparoscopic gastric bypass: a randomized multicenter study. *Arch Surg* 2011;146(11):1300-5.
72. Gripeteg L, Torgerson J, Karlsson J, Lindroos AK. Prolonged refeeding improves weight maintenance after weight loss with very-low-energy diets. *The British journal of nutrition* 2010;103(1):141-8.

73. Atkinson RL. Low and very low calorie diets. *The Medical clinics of North America* 1989;73(1):203-15.
74. Fogelholm M, Kukkonen-Harjula K, Nenonen A, Pasanen M. Effects of walking training on weight maintenance after a very-low-energy diet in premenopausal obese women: a randomized controlled trial. *Arch Intern Med* 2000;160(14):2177-84.
75. Bischoff SC, Damms-Machado A, Betz C, Herpertz S, Legenbauer T, Low T, et al. Multicenter evaluation of an interdisciplinary 52-week weight loss program for obesity with regard to body weight, comorbidities and quality of life-a prospective study. *Int J Obes (Lond)* 2011.
76. Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *The American journal of medicine* 1999;106(2):179-84.
77. LeCheminant JD, Jacobsen DJ, Hall MA, Donnelly JE. A comparison of meal replacements and medication in weight maintenance after weight loss. *Journal of the American College of Nutrition* 2005;24(5):347-53.
78. Mathus-Vliegen EM. Long-term maintenance of weight loss with sibutramine in a GP setting following a specialist guided very-low-calorie diet: a double-blind, placebo-controlled, parallel group study. *European journal of clinical nutrition* 2005;59 Suppl 1:S31-8; discussion S39.
79. Richelsen B, Tonstad S, Rossner S, Toubro S, Niskanen L, Madsbad S, et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. *Diabetes care* 2007;30(1):27-32.
80. Astrup A, Caterson I, Zelissen P, Guy-Grand B, Carruba M, Levy B, et al. Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res* 2004;12(10):1658-69.
81. Wadden TA, Fujioka K, Toubro S, Gantz I, Erondu NE, Chen M, et al. A randomized trial of lifestyle modification and taranabant for maintaining weight loss achieved with a low-calorie diet. *Obesity (Silver Spring)* 2010;18(12):2301-10.
82. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr* 2001;74(5):579-84.
83. Saris WH. Very-low-calorie diets and sustained weight loss. *Obes Res* 2001;9 Suppl 4:295S-301S.
84. Maddrey WC, Schiff ER, Sorrell MF, Ovid. Schiff's diseases of the liver. *Chapter 22. Gallstone Disease: Pathogenesis and Treatment*. 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2007:p.640-63.
85. Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. *Journal of long-term effects of medical implants* 2005;15(3):329-38.
86. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. *Gastroenterology clinics of North America* 2010;39(2):157-69, vii.
87. Erlinger S. Gallstones in obesity and weight loss. *European journal of gastroenterology & hepatology* 2000;12(12):1347-52.
88. Everhart JE. Contributions of obesity and weight loss to gallstone disease. *Annals of internal medicine* 1993;119(10):1029-35.
89. Festi D, Colecchia A, Larocca A, Villanova N, Mazzella G, Petroni ML, et al. Review: low caloric intake and gall-bladder motor function. *Alimentary pharmacology & therapeutics* 2000;14 Suppl 2:51-3.
90. Broomfield PH, Chopra R, Sheinbaum RC, Bonorris GG, Silverman A, Schoenfield LJ, et al. Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. *The New England journal of medicine* 1988;319(24):1567-72.
91. Kamrath RO, Plummer LJ, Sadur CN, Adler MA, Strader WJ, Young RL, et al. Cholelithiasis in patients treated with a very-low-calorie diet. *The American journal of clinical nutrition* 1992;56(1 Suppl):255S-57S.

92. Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight-reduction dieting. *Archives of internal medicine* 1989;149(8):1750-3.
93. Shiffman ML, Kaplan GD, Brinkman-Kaplan V, Vickers FF. Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. *Annals of internal medicine* 1995;122(12):899-905.
94. Yang H, Petersen GM, Roth MP, Schoenfield LJ, Marks JW. Risk factors for gallstone formation during rapid loss of weight. *Digestive diseases and sciences* 1992;37(6):912-8.
95. Festi D, Colecchia A, Orsini M, Sangermano A, Sottili S, Simoni P, et al. Gallbladder motility and gallstone formation in obese patients following very low calorie diets. Use it (fat) to lose it (well). *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 1998;22(6):592-600.
96. Gebhard RL, Prigge WF, Ansel HJ, Schlasner L, Ketover SR, Sande D, et al. The role of gallbladder emptying in gallstone formation during diet-induced rapid weight loss. *Hepatology* 1996;24(3):544-8.
97. Hoy MK, Heshka S, Allison DB, Grasset E, Blank R, Abiri M, et al. Reduced risk of liver-function-test abnormalities and new gallstone formation with weight loss on 3350-kJ (800-kcal) formula diets. *The American journal of clinical nutrition* 1994;60(2):249-54.
98. Spirt BA, Graves LW, Weinstock R, Bartlett SJ, Wadden TA. Gallstone formation in obese women treated by a low-calorie diet. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 1995;19(8):593-5.
99. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328(17):1230-5.
100. The-report-of-an-American-Academy-of-Sleep-Medicine-Task-Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22(5):667-89.
101. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5(2):136-43.
102. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165(9):1217-39.
103. Lindberg E, Gislason T. Epidemiology of sleep-related obstructive breathing. *Sleep Med Rev* 2000;4(5):411-33.
104. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc* 2008;5(2):185-92.
105. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med* 2005;165(20):2408-13.
106. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000;284(23):3015-21.
107. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA : the journal of the American Medical Association* 2003;289(17):2230-7.
108. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care* 2008;31 Suppl 2:S303-9.
109. Banno K, Kryger MH. Sleep apnea: clinical investigations in humans. *Sleep Med* 2007;8(4):400-26.

110. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6(8):e1000132.
111. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep* 2008;31(8):1079-85.
112. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008;31(8):1071-8.
113. de Sousa AG, Cercato C, Mancini MC, Halpern A. Obesity and obstructive sleep apnea-hypopnea syndrome. *Obes Rev* 2008;9(4):340-54.
114. Johansson K, Neovius M, Lagerros YT, Harlid R, Rossner S, Granath F, et al. Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *BMJ* 2009;339:b4609.
115. Tuomilehto HP, Seppa JM, Partinen MM, Peltonen M, Gylling H, Tuomilehto JO, et al. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2009;179(4):320-7.
116. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med* 2009;169(17):1619-26.
117. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90(1):47-112.
118. SBU-rapport. *Obstructive sleep apnoea syndrome : a systematic literature review*. Stockholm: SBU, 2007.
119. Shneerson J, Wright J. Lifestyle modification for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2001(1):CD002875.
120. Grunstein RR, Stenlof K, Hedner JA, Peltonen M, Karason K, Sjostrom L. Two year reduction in sleep apnea symptoms and associated diabetes incidence after weight loss in severe obesity. *Sleep* 2007;30(6):703-10.
121. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;144(3 Pt 1):494-8.
122. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Annals of internal medicine* 1985;103(6 ( Pt 1)):850-5.
123. Barnes M, Goldsworthy UR, Cary BA, Hill CJ. A diet and exercise program to improve clinical outcomes in patients with obstructive sleep apnea--a feasibility study. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2009;5(5):409-15.
124. Dixon JB, Schachter LM, O'Brien PE. Polysomnography before and after weight loss in obese patients with severe sleep apnea. *Int J Obes (Lond)* 2005;29(9):1048-54.
125. Fritscher LG, Canani S, Mottin CC, Fritscher CC, Berleze D, Chapman K, et al. Bariatric surgery in the treatment of obstructive sleep apnea in morbidly obese patients. *Respiration* 2007;74(6):647-52.
126. Haines KL, Nelson LG, Gonzalez R, Torrella T, Martin T, Kandil A, et al. Objective evidence that bariatric surgery improves obesity-related obstructive sleep apnea. *Surgery* 2007;141(3):354-8.
127. Hakala K, Maasilta P, Sovijarvi AR. Upright body position and weight loss improve respiratory mechanics and daytime oxygenation in obese patients with obstructive sleep apnoea. *Clin Physiol* 2000;20(1):50-5.

128. Hernandez TL, Ballard RD, Weil KM, Shepard TY, Scherzinger AL, Stamm ER, et al. Effects of maintained weight loss on sleep dynamics and neck morphology in severely obese adults. *Obesity (Silver Spring)* 2009;17(1):84-91.
129. Kajaste S, Brander PE, Telakivi T, Partinen M, Mustajoki P. A cognitive-behavioral weight reduction program in the treatment of obstructive sleep apnea syndrome with or without initial nasal CPAP: a randomized study. *Sleep Med* 2004;5(2):125-31.
130. Kajaste S, Telakivi T, Mustajoki P, Pihl S, Partinen M. Effects of a cognitive-behavioural weight loss programme on overweight obstructive sleep apnoea patients. *Journal of sleep research* 1994;3(4):245-49.
131. Kansanen M, Vanninen E, Tuunainen A, Pesonen P, Tuononen V, Hartikainen J, et al. The effect of a very low-calorie diet-induced weight loss on the severity of obstructive sleep apnoea and autonomic nervous function in obese patients with obstructive sleep apnoea syndrome. *Clin Physiol* 1998;18(4):377-85.
132. Lettieri CJ, Eliasson AH, Greenburg DL. Persistence of obstructive sleep apnea after surgical weight loss. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2008;4(4):333-8.
133. Lojander J, Mustajoki P, Ronka S, Mecklin P, Maasilta P. A nurse-managed weight reduction programme for obstructive sleep apnoea syndrome. *J Intern Med* 1998;244(3):251-5.
134. Nosedá A, Kempnaers C, Kerkhofs M, Houben JJ, Linkowski P. Sleep apnea after 1 year domiciliary nasal-continuous positive airway pressure and attempted weight reduction. Potential for weaning from continuous positive airway pressure. *Chest* 1996;109(1):138-43.
135. Pillar G, Peled R, Lavie P. Recurrence of sleep apnea without concomitant weight increase 7.5 years after weight reduction surgery. *Chest* 1994;106(6):1702-4.
136. Suratt PM, McTier RF, Findley LJ, Pohl SL, Wilhoit SC. Effect of very-low-calorie diets with weight loss on obstructive sleep apnea. *Am J Clin Nutr* 1992;56(1 Suppl):182S-84S.
137. Valencia-Flores M, Orea A, Herrera M, Santiago V, Rebollar V, Castano VA, et al. Effect of bariatric surgery on obstructive sleep apnea and hypopnea syndrome, electrocardiogram, and pulmonary arterial pressure. *Obes Surg* 2004;14(6):755-62.
138. Nerfeldt P, Nilsson BY, Mayor L, Udden J, Friberg D. A two-year weight reduction program in obese sleep apnea patients. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2010;6(5):479-86.
139. Johansson K, Hemmingsson E, Harlid R, Trolle Lagerros Y, Granath F, Rossner S, et al. Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. *BMJ* 2011;342:d3017.
140. Tuomilehto H, Gylling H, Peltonen M, Martikainen T, Sahlman J, Kokkarinen J, et al. Sustained improvement in mild obstructive sleep apnea after a diet- and physical activity-based lifestyle intervention: postinterventional follow-up. *Am J Clin Nutr* 2010;92(4):688-96.
141. Tsai AG, Wadden TA. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Annals of surgery* 2005;242(2):290.
142. Moroshko I, Brennan L, O'Brien P. Predictors of dropout in weight loss interventions: a systematic review of the literature. *Obes Rev* 2011;12(11):912-34.
143. Melin I, Karlstrom B, Lappalainen R, Berglund L, Mohsen R, Vessby B. A programme of behaviour modification and nutrition counselling in the treatment of obesity: a randomised 2-y clinical trial. *Int J Obes Relat Metab Disord* 2003;27(9):1127-35.
144. Melin I, Reynisdottir S, Berglund L, Zamfir M, Karlstrom B. Conservative treatment of obesity in an academic obesity unit. Long-term outcome and drop-out. *Eat Weight Disord* 2006;11(1):22-30.

145. Melin I. *Obesitas : Arbetsbok - för dig som vill gå ner i vikt*. 2. uppl. ed. Lund: Studentlitteratur, 2001.
146. Melin I. *Obesitas : handbok för praktisk klinisk behandling av övervikt, fetma och metabolt syndrom baserad på kognitiv beteendemodifikation och konventionell behandling*. 2. uppl. ed. Lund: Studentlitteratur, 2001.
147. Harris JA, Benedict FG. *A Biometric Study of Basal Metabolism in Man*. Washington DC: The Carnegie Institute 1912.
148. Livsmedelsverket. *Svenska näringsrekommendationer - Rekommendationer om näring och fysisk aktivite*. 4. uppl. ed. Uppsala: Livsmedelsverket, 2005.
149. Sullivan M, Karlsson J, Taft C. *SF-12 Health Survey: Swedish User Handbook*. Gothenburg: Sahlgrenska University Hospital, 1997.
150. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;323(7321):1123-4.
151. Bland JM, Altman DG. Matching. *BMJ* 1994;309(6962):1128.
152. Borenstein M. *Introduction to meta-analysis*. 1st ed. U.K.: Chichester, West Sussex, 2009.
153. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58.
154. Ware JH. Interpreting incomplete data in studies of diet and weight loss. *The New England journal of medicine* 2003;348(21):2136-7.
155. Veasey SC, Guilleminault C, Strohl KP, Sanders MH, Ballard RD, Magalang UJ. Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. *Sleep* 2006;29(8):1036-44.
156. Jonas E, Marsk R, Rasmussen F, Freedman J. Incidence of postoperative gallstone disease after antiobesity surgery: population-based study from Sweden. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery* 2010;6(1):54-8.
157. Torgerson JS, Lindroos AK, Naslund I, Peltonen M. Gallstones, gallbladder disease, and pancreatitis: cross-sectional and 2-year data from the Swedish Obese Subjects (SOS) and SOS reference studies. *The American journal of gastroenterology* 2003;98(5):1032-41.
158. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. *Cochrane Database Syst Rev* 2003(4):CD004094.
159. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *BMJ* 2000;321(7256):255-6.
160. Levendowski DJ, Zack N, Rao S, Wong K, Gendreau M, Kranzler J, et al. Assessment of the test-retest reliability of laboratory polysomnography. *Sleep Breath* 2009;13(2):163-7.
161. Bar A, Pillar G, Dvir I, Sheffy J, Schnall RP, Lavie P. Evaluation of a portable device based on peripheral arterial tone for unattended home sleep studies. *Chest* 2003;123(3):695-703.
162. Zou D, Grote L, Peker Y, Lindblad U, Hedner J. Validation a portable monitoring device for sleep apnea diagnosis in a population based cohort using synchronized home polysomnography. *Sleep* 2006;29(3):367-74.
163. Gripegteg L, Karlsson J, Torgerson J, Lindroos AK. Predictors of very-low-energy diet outcome in obese women and men. *Obesity facts* 2010;3(3):159-65.