

Indepth Description of the Itrim Program

The logo for Itrim features a horizontal row of seven dots above the brand name. The first dot is yellow, and the remaining six are white. The brand name 'itrim' is written in a bold, lowercase, white sans-serif font.

itrim

Living a lighter, healthier life.



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Scientific Advisory Board

Claude Marcus

Claude currently serves as a Professor at the Karolinska Institutet in Stockholm, Sweden and Chief Physician at Karolinska University Hospital in Huddinge, Sweden. He has been a member of Itrim's Scientific Advisory Board since 2003. Claude has, among other things, founded the National Center for Overweight Children at Karolinska University Hospital, where he continues to work as a director of research. He was a member of the group of experts who wrote a report on "Obesity -problems and actions" in 2002, and is a member of the Stockholm County Council Group of Experts for the development of action programs to fight obesity.

Martin Neovius, PhD

Martin is an Associate Professor of epidemiology at Karolinska Institutet in Stockholm, Sweden. He has been a member of Itrim's scientific advisory board since 2008. Martin's obesity research is currently focused on the economic evaluation of bariatric surgery versus conventional weight loss treatment, based upon data from the landmark Swedish Obese Subjects (SOS) study. Martin is also an expert in weight loss as a treatment for obstructive sleep apnea, as well as productivity losses associated with obesity.

Johan Sundström

Johan is an Associate Professor of cardiovascular epidemiology at Uppsala University, in Uppsala, Sweden. He is a specialist in internal medicine, and a physician in the Department of Cardiology at Uppsala University Hospital. He has been a member of Itrim's advisory board since 2005. Johan's research is aimed at mapping risk factors for heart attacks, heart failure and stroke, focusing on high blood pressure and lifestyle factors. He also evaluates treatment for persons with high blood pressure, diabetes or heart problems. Johan has participated in the Framingham Heart Study in Boston, MA and was recently a visiting Professorial Fellow at the George Institute of Global Health in Sydney, Australia.

Introduction: Long Term Weight Loss through Changed Eating and Exercise Behavior

Itrim provides weight loss for adults through lifestyle change and long-term, individualized support. The company was founded in 2003 and has grown to 37 centers in Sweden and one in Germany, and has served over 30,000 paying members of its program. In 2012, Itrim US was established to bring this successful sustained weight loss solution to the US. The Itrim program is being delivered through company-owned retail centers, as well as customized centers for corporations, medical groups, health and fitness centers, and accountable care organizations.

Itrim's weight loss program is based on scientific weight loss studies (see page 5), which allows the company to offer cutting edge services as new knowledge about weight loss and lifestyle change become available. We also work rigorously with our own R&D program (page 6), including analysis of our own member database by independent researchers, to optimize both content and structure of the program.

Itrim's management is regularly in touch with world leading experts on weight loss through Itrim's Scientific Advisory Board, consisting of three independent and active academic researchers within the field of obesity. Together with Itrim's Program Committee, the Scientific Advisory Board assess and discuss the continued development of Itrim's services and Research & Development Program.

Our business is committed to delivering sustained weight loss results for our members. We believe that providing eating, exercise and encouragement in a convenient and inspiring environment is the combination for success. If you have questions regarding the Itrim program or would like further information, please contact us. We look forward to speaking with you.

The Weight Loss Program

Itrim's weight loss program is based on the principle that weight (fat mass) is controlled by the laws of thermodynamics, i.e. eating and exercise habits. Because it takes time to change and maintain new eating and exercise habits, the program lasts two years. The aim is that the member should achieve a clinically meaningful weight loss of at least 5% of their body weight, and keep it off long term. Since weight loss maintenance is one of the hardest aspects of weight loss, the program is specifically tailored to assist with lasting behavior changes and minimization of weight regain.

Members pay a start up fee at the beginning of the program. The average price in the US is \$150 per month.

At the start of the program there is a 60 minute health assessment, including a discussion about current diet and exercise habits, daily routines and family situation. Key measurements are taken (waist, weight, body composition, blood pressure, cardiorespiratory fitness and pedometer-assessed physical activity). Members are assigned a personal health coach, and decide on weight loss goals and appropriate lifestyle changes including weight loss meal plan method. Follow-up sessions with the health coach are held after 3, 6, 9 and 12 months. Members also have the option of buying extra individual health coaching sessions during the course of the program. The members also attend regular support meetings and weigh-ins with their personal health coach, where the goals and appropriate behavioral changes are planned and monitored. Circuit training at the center is expected throughout the program, and members are encouraged to exercise at least 3 times a week and as often as they want to. No reservations are required, and small group classes are made available as well as personal training for those who want more exercise support.

Once the first year has been completed, members often continue with individual support and follow-up through Itrim's second year Balance Program (see below).

The weight loss program comprises three phases: the Weight Loss Phase (first 12 weeks), the Improvement Phase (from week 13 to the end of the first year), and the Balance Phase (year 2 onwards, for as long as the member wishes).

Throughout the program members exercise 30 minutes at the center 2–3 times each week (combined aerobic and strength training in a circuit), and use pedometers and fitness tracking devices to monitor and increase their daily exercise.

Weight Loss Phase

The initial focus of the Itrim program is on weight loss. Because a reduction in calorie intake is a more effective recommendation than just increased exercise for achieving weight loss, the content of the program during this phase focuses on reducing caloric intake.

Each member is offered three options for reducing their calorie intake (note that the results below are mean values for people who have completed the program). The member decides for him or herself which method to use in consultation with their personal health coach.

- **Rapid.** This method consists of meal replacements only, corresponding to 800 kcal/day (low calorie diet, LCD). LCD can only be used by persons with a BMI ≥ 27 kg/m² for a maximum of 12 weeks. The mean weight loss after 12 weeks is 14.1 kg (SD 5.7) after one year, the mean weight loss is 13.9 (8.1). The dropout rate is 18% after one year. Forty-two percent of all members choose this method.
- **Varied.** This method uses a combination of meal replacements, i.e. powder mixed with water (2 meals a day) and regular food with a limited caloric content (2 meals a day), providing 1200-1500 kcal/d. The mean rate of weight loss during the first twelve weeks is 7.7 kg (SD 3.7). After one year, the mean weight loss is 8.8 kg (SD 5.9), with a 23% dropout rate. Fifty-one percent of all members choose Varied as their method of weight loss.
- **Palm Portion Diet.** Regular, normal food with low energy density, corresponding to 1500-1800 kcal/d. The mean weight loss after 12 weeks is 5.5 kg (SD 3.8). After one year, the average weight loss is 6.9 kg (SD 5.9). The drop-out rate is 26% after one year. Seven percent of all members choose the Palm Portion Diet method.

Itrim has its own quality-assured range of meal replacement products, approved as LCD products by the Swedish National Food Administration and FDA. Meal replacements can be bought at any Itrim center or online.

Members meet in a group of about 15 people for five 60-minute sessions (one session every other week). Every group meeting is led by a trained health coach who gives a fact-based presentation on a relevant subject (e.g. regular mealtimes, fat & sugar, exercise, goals and expectations etc.). This is followed by a general discussion and homework planning for the week, plus review of last week's homework.

There are many health benefits to losing weight, but there are also side effects. Common side effects of rapid weight loss (approx. 1-2 kg weight loss/week) include gallstones, dizziness, feeling cold and hair loss.

The risks of side effects increase in relation to the rate of weight loss. We therefore recommend all members who choose the Rapid Meal Plan to consult their doctor before starting, and to have a follow-up medical consultation after returning to a stable weight. It is the member's responsibility to make sure that they are in sufficiently good health to undergo the program.

Improvement Phase

The Improvement phase starts directly after the Weight loss phase and continues until the end of the first year. The focus on exercise is increased during this phase, and there are ten new group meetings to help develop a stable diet and healthy exercise habits. The improvements that began during the weight loss phase continue and are augmented as behavior is improved and built into the member's personal habits. The recommended behavior improvements are established predictors for long-term weight loss, based on data from the National Weight Control Registry (see www.nwcr.ws).

NWCR is a study of individuals from the USA who, using a variety of methods, have succeeded in losing at least 13.6 kg and maintained the weight loss for an average of 5.7 years. The main weight loss strategies were a low-fat diet, daily weighing, a balanced breakfast, regular mealtimes, an hour's exercise each day, and limited relapses.

Balance Phase

In the second year, the emphasis shifts towards preventing lapses into old habits, and stabilizing the new body weight through healthy and balanced diet and exercise habits. Ten evenly-spaced group meetings and continued individual coaching help members maintain focus and solidify their new habits.

Background to Excess Weight and Weight Loss

The prevalence of overweight (BMI 25-29.9 kg/m²) and obesity (BMI ≥30 kg/m²) has increased internationally. The cause of overweight and obesity is a long-term positive energy balance, driven by excessive energy intake in relation to energy expenditure, ie. diet and exercise. Diet and exercise habits are in turn controlled by a number of factors such as genes, environment, psychology, sleep and stress.

The epidemic of overweight and obesity leads to an increased prevalence of obesity-related diseases, such as diabetes, hypertension, and depression, but also leads to reduced health-related quality of life and productivity, discrimination, and healthcare costs. Although exact numbers are difficult to estimate, studies indicate that 3-8% of healthcare costs can be attributed to overweight and obesity (SBU – The Swedish Council on Technology Assessment in Health Care. Fetma – problem och åtgärder. [Obesity - problems and interventions] Report no. 160, 2002).

There are a variety of scientifically proven methods for losing weight, all of which are based on the laws of thermodynamics, ie changed diet and exercise habits. Contrary to what many people believe, it has been established that the probability of long-term weight loss increases if the initial weight loss is rapid (1-2kg/week) compared to a more gradual rate of weight loss (0.5 kg/week), (SBU. Fetma – problem och åtgärder. Report no. 160, 2002).

There are two methods that stand out in delivering rapid weight loss: bariatric surgery (not discussed in more detail here) and low calorie diets (LCD, 800-1600 kcal/d for up to three months). Pharmaceutical anti-obesity drugs can also lead to sustained weight loss provided that they are combined with intensive lifestyle changes. There is currently a paucity of approved anti-obesity drugs, however.

LCD has been used as a weight loss method for more than 20 years without serious side effects, although transient side effects such as gallstones, constipation, dizziness, feeling cold, hair loss and bad breath can sometimes occur.

Consultation with a physician may be required for members who are on medication, which sometimes needs to be adjusted immediately after the start of the Rapid program. Doctors can also play an important role in boosting motivation for their patients, for example by testing risk factors for cardiovascular disease and diabetes before and after weight loss.

Because the LCD period is not in itself a long-term solution to overweight and obesity, the method must always be carried out as part of a long-term lifestyle change support program. This will improve diet and exercise habits as part of the daily routine, including how to prevent relapse. Itrim's weight loss program prides itself on its large focus on weight loss maintenance as part of a responsible and sensible use of LCD weight loss methods.

Healthy dietary habits include regular mealtimes, consumption of low-fat, low-sugar foods and a high intake of fruit and vegetables. Increased exercise is central and achieved through regular everyday activities (cycling, walking), and exercise sessions at the center 2-3 times/week. Weighing oneself regularly, keeping a diary, and basic stress management all further increase the chance of long-term success. These are the fundamental principles underlying Itrim's weight loss program.

Itrim Research and Development

At Itrim we understand the need to continuously evaluate the results our members achieve so that fact-based decisions can be taken on appropriate adjustments and improvements of our services. This process is done primarily through statistical analysis of Itrim's weight loss database, and keeping up to date with the peer review research literature. The Itrim data are stored on a password-protected server.

Itrim data are analysed in a number of different ways, including weight loss results, identification of predictors for dropout rate and weight loss, safety, and compliance with the program. Analyses arising from Itrim data are published by independent obesity academics, who also check and inspect the data carefully.

Two principal methods are then used to analyse the results of the program: outcomes for those who complete the program (completer analysis), and a more conservative analysis (intention-to-treat), which means that even those who do not complete the program are included, commonly with a no-change assumption (baseline observation carried forward).

To date (June 2013) Itrim has published two scientific research papers in top ranking international peer review journals. **Paper 1** was a primary effects analysis (weight loss and dropout). **Paper 2** was a safety analysis on the risk of developing symptomatic gallstones and cholecystectomy after rapid weight loss.

Note: Both Itrim research papers, and all published abstracts (see **Abstracts**), include data from Swedish weight loss participants enrolled between 1 January 2006-31 May 2009. During this time, the Rapid weight loss method consisted of a 500 kcal/d VLCD (very low calorie diet), as opposed to the 800 kcal/d LCD that is being used today.

Paper 1: Weight loss and dropout during a commercial weight loss program using VLCD, LCD and restricted normal food: observational cohort study (Hemmingsson et al., American Journal of Clinical Nutrition, 2012; 96: 953-961).

The first Itrim contribution to the peer review literature was a primary effects analysis of the program, utilizing data from two sources: Itrim data on weight loss and other program parameters, and secondly data from Swedish National Quality Control Registers on comorbidities and drug dispensations. Linking Itrim data with Register data allow for a more complete understanding of the health of Itrim participants and enables analyses of how medical parameters influence program outcomes, such as weight loss and dropout. Paper 1 is attached as Appendix A.

Paper 2: Johansson et al., Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study. International Journal of Obesity; 2013; epub 22 May.

The second paper was an analysis of the safety of the Itrim program, specifically how use of VLCD (500 kcal/d) was associated with gallstone formation and cholecystectomy compared with LCD (1200-1500 kcal/d). In this study, the outcome variables were comprised of register data, with Itrim data being used as explanatory variables. Paper 2 is attached as Appendix B.

Abstracts: The results of Itrim's weight loss program were first presented at the national meeting of the Swedish Society of Medicine (Svenska Läkaresällskapet) in Gothenburg in 2006, in the section for obesity research. The abstract is attached in Appendix C. Itrim's results have since then continuously been presented at national and international conferences (see Appendices C–H).

Appendix A

Paper 1

**American Journal of Clinical Nutrition (2012):
Weight loss and dropout during a commercial weight-loss
program including a very low-calorie diet, a low-calorie diet,
or restricted normal food: observational cohort study.**

See corresponding editorial on page 949.

Weight loss and dropout during a commercial weight-loss program including a very-low-calorie diet, a low-calorie diet, or restricted normal food: observational cohort study^{1–3}

Erik Hemmingsson, Kari Johansson, Jonas Eriksson, Johan Sundström, Martin Neovius, and Claude Marcus

ABSTRACT

Background: The effectiveness of commercial weight-loss programs consisting of very-low-calorie diets (VLCDs) and low-calorie diets (LCDs) is unclear.

Objective: The aim of the study was to quantify weight loss and dropout during a commercial weight-loss program in Sweden (Itrim; cost: \$1300/€1000; all participants paid their own fee).

Design: This observational cohort study linked commercial weight-loss data with National Health Care Registers. Weight loss was induced with a 500-kcal liquid-formula VLCD [$n = 3773$; BMI (in kg/m^2): 34 ± 5 (mean \pm SD); 80% women; 45 ± 12 y of age (mean \pm SD)], a 1200–1500-kcal formula and food-combination LCD ($n = 4588$; BMI: 30 ± 4 ; 86% women; 50 ± 11 y of age), and a 1500–1800-kcal/d restricted normal-food diet ($n = 676$; BMI: 29 ± 5 ; 81% women; 51 ± 12 y of age). Maintenance strategies included exercise and a calorie-restricted diet. Weight loss was analyzed by using an intention-to-treat analysis (baseline substitution).

Results: After 1 y, mean (\pm SD) weight changes were -11.4 ± 9.1 kg with the VLCD (18% dropout), -6.8 ± 6.4 kg with the LCD (23% dropout), and -5.1 ± 5.9 kg with the restricted normal-food diet (26% dropout). In an adjusted analysis, the VLCD group lost 2.8 kg (95% CI: 2.5, 3.2) and 3.8 kg (95% CI: 3.2, 4.5) more than did the LCD and restricted normal-food groups, respectively. A high baseline BMI and rapid initial weight loss were both independently associated with greater 1-y weight loss ($P < 0.001$). Younger age and low initial weight loss predicted an increased dropout rate ($P < 0.001$). Treatment of depression (OR: 1.4; 95% CI: 1.1, 1.9) and psychosis (OR: 2.6; 95% CI: 1.1, 6.3) were associated with an increased dropout rate in the VLCD group.

Conclusion: A commercial weight-loss program, particularly one using a VLCD, was effective at reducing body weight in self-selected, self-paying adults. *Am J Clin Nutr* 2012;96:953–61.

INTRODUCTION

Because most US and European adults are overweight or obese (1, 2), health services are struggling to cope with the large number of individuals in need of weight loss. Bariatric surgery induces large weight losses and reduces type 2 diabetes and mortality (3–6) but is generally restricted to severely obese individuals with comorbidity, whereas antiobesity drugs are struggling to gain Food and Drug Administration approval (7). Many overweight

and obese individuals, therefore, find their options limited to commercial weight-loss programs, most of which have not been scientifically evaluated (8, 9).

Weight Watchers and Jenny Craig are 2 commercial weight-loss operators whose programs have been evaluated in long-term (≥ 1 y) randomized controlled trials (10, 11). A recent randomized trial found that a commercial weight-loss program (Weight Watchers) was twice as effective as standard care at reducing body weight after 2 y (-4.0 compared with -1.8 kg, intention-to-treat analysis with baseline carried forward) (12).

Research on commercial weight loss is still scarce, however, and there is a need to quantify the effectiveness of commercial weight-loss diets, especially in real-life settings. The aim was to evaluate weight loss and the dropout rate after 1 y of a commercial weight-loss program in Sweden, where weight loss was induced with a 500-kcal very-low-calorie diet (VLCD)⁴, a 1200–1500-kcal low-calorie diet (LCD), or a 1500–1800-kcal restricted normal-food diet followed by a diet and exercise maintenance program.

SUBJECTS AND METHODS

Recruitment

Participants were consecutively enrolled customers ($n = 9037$) from the commercial weight-loss company Itrim in Sweden from 1 January 2006 to 31 May 2009 (see Figure S1 under “Supplemental data” in the online issue). Data were collected from 28 centers across Sweden. All customers were enrolled in

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² Supported by a grant from Itrim International.

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⁴ Abbreviations used: ATC, Anatomic Therapeutic Chemical classification system; CVD, cardiovascular disease; LCD, low-calorie diet; VLCD, very-low-calorie diet.

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the Itrim weight-loss program. The regional ethics review board in Stockholm approved the study (registration numbers 2010/151-31/5 and 2010/1059-31/1).

Weight-loss programs

The 1-y weight-loss program consisted of an initial 3-mo weight-loss phase followed by a 9-mo weight-maintenance phase. At the start of the weight-loss phase, participants and their designated health coaches discussed and decided on an appropriate weight-loss diet that was largely based on baseline BMI, desired weight loss, and personal preference:

1) VLCD: consisted of a liquid-based formula diet of 500 kcal/d for 6 to 10 wk (Itrim; 125 kcal/sachet, 4 sachets/d, each sachet contained 13 g protein, 15 g carbohydrates, 2 g fat, and 3 g fiber; approved as the sole-source VLCD by the Swedish National Food Agency) followed by a 2-wk gradual introduction of normal food. Early introduction of normal food (6 as opposed to the full 10 wk) occurred when the participant was either satisfied with the achieved weight loss or had reached a normal-weight BMI (in kg/m²) of ≤ 25 .

2) LCD: consisted of 2 calorie-restricted normal-food meals and 2 formula-diet meal-replacement sachets providing a total caloric intake of ~ 1200 – 1500 kcal/d depending on body size and exercise levels.

3) Restricted normal-food diet: consisted mainly of food with high protein, low-glycemic-index carbohydrates, low fat intake, low energy density, and a high fiber content, providing a caloric intake of ~ 1500 – 1800 kcal/d depending on body size and exercise levels.

After the weight-loss phase, all 3 groups entered the same 9-mo weight-maintenance program, which included an exercise program (circuit training, with a mix of aerobic and strength-training workout stations, at the center 2–3 times/wk for 30 to 45 min; physically active transport to and from work; and use of a Yamax SW-200 pedometer to encourage walking), dietary advice, and behavioral changes. Dietary advice included the use of restricted portions sizes and consumption of a diet rich in protein, with a low glycemic index, and with a low overall energy density (eg, consumption of vegetables and water as opposed to caloric beverages).

TABLE 1

Baseline characteristics ($n = 9037$) of participants in a commercial weight-loss program including a VLCD (500 kcal/d), an LCD (1200–1500 kcal/d), or a restricted normal-food diet (1500–1800 kcal/d)¹

	VLCD ($n = 3773$)	LCD ($n = 4588$)	Restricted normal-food diet ($n = 676$)	<i>P</i>
Age (y)	45 \pm 12 (18–77) ²	50 \pm 11 (18–81)	51 \pm 12 (19–78)	<0.001 ^{3,4}
Female sex (%)	80	86	81	<0.001 ^{3,5}
Body weight (kg)	98 \pm 17 (64–195)	85 \pm 14 (54–190)	81 \pm 16 (51–166)	<0.001 ^{3–5}
Body weight, completers only (kg)	98 \pm 17 (64–188)	86 \pm 14 (54–190)	82 \pm 17 (51–166)	<0.001 ^{3–5}
BMI (%)	34 \pm 5 (22–58)	30 \pm 4 (21–68)	29 \pm 5 (18–54)	<0.001 ^{3–5}
<25 kg/m ²	0.4	4.8	21.6	
25–29 kg/m ²	16.9	53.0	49.4	
30–34 kg/m ²	47.9	30.3	19.1	
35–39 kg/m ²	23.5	9.3	6.8	
≥ 40 kg/m ²	11.3	2.6	3.1	
Waist circumference (cm)	110 \pm 12 (78–164)	101 \pm 11 (72–160)	98 \pm 13 (72–145)	<0.001 ^{3–5}
Waist circumference, completers only (cm)	110 \pm 12 (78–155)	102 \pm 11 (72–160)	98 \pm 13 (74–145)	<0.001 ^{3–5}
Waist circumference $\geq 102/88$ cm (%) ⁶	92	83	68	
BMI ≥ 30 kg/m ² or waist circumference $\geq 102/88$ cm (%) ⁶	98	88	74	
Comorbidities and drugs (%) ⁷				
History of CVD	7.9	8.0	10.9	0.026 ^{4,5}
History of cancer	1.6	2.6	3.7	<0.001 ^{3–5}
Antiobesity drugs				
Orlistat	1.0	0.5	1.0	0.038 ³
Sibutramine	1.7	0.8	0.9	<0.001 ^{3,4}
Diabetes	1.9	2.4	7.2	<0.001 ^{4,5}
Insulin	0.4	0.8	4.3	<0.001 ^{3–5}
Oral antidiabetes	1.8	2.0	5.8	<0.001 ^{4,5}
Antidyslipidemia drugs	5.8	7.9	9.2	<0.001 ^{3–5}
Antihypertension drugs	16.4	19.7	21.0	<0.001 ^{3–5}
Antidepressant drugs	11.6	13.2	12.0	0.095
Antipsychosis drugs	0.7	1.1	0.9	0.22

¹ CVD, cardiovascular disease; LCD, low-calorie diet; VLCD, very-low-calorie diet.

² Mean \pm SD; range in parentheses (all such values).

³ VLCD compared with LCD.

⁴ VLCD compared with restricted normal-food diet.

⁵ LCD compared with restricted normal-food diet.

⁶ Waist circumference ≥ 102 cm for men, ≥ 88 cm for women.

⁷ Drug use was assessed during the period 6 mo before baseline through register linkage with the Prescribed Drug Register, whereas comorbidity data (except for diabetes) were retrieved from the National Patient Register during the past 5 y. Because diabetes is, to a large extent, treated in primary care, it was defined as use of either insulin or oral antidiabetics. Group differences were analyzed by using ANOVA with a Scheffe post hoc test.

TABLE 2

Changes in absolute and percentage body weight and waist circumference in participants after 1 y in a commercial weight-loss program ($n = 9037$) including a VLCD (500 kcal/d), an LCD (1200–1500 kcal/d), or a restricted normal-food diet (1500–1800 kcal/d)¹

	Within-group changes		
	VLCD ($n = 3773$)	LCD ($n = 4588$)	Restricted normal-food diet ($n = 676$)
Intention to treat ($n = 9037$) ²			
Body weight (kg)	-11.5 (-11.7, -11.2)	-6.8 (-7.0, -6.6)	-5.0 (-5.6, -4.5)
Body weight (%)	-11.7 (-11.9, -11.4)	-7.7 (-7.9, -7.5)	-6.0 (-6.5, -5.4)
Waist circumference (cm)	-8.6 (-8.9, -8.3)	-5.9 (-6.1, -5.6)	-4.5 (-5.2, -3.9)
Completers only ($n = 7109$)			
Body weight (kg)	-13.8 (-14.0, -13.5)	-8.9 (-9.2, -8.7)	-7.0 (-7.6, -6.4)
Body weight (%)	-14.0 (-14.2, -13.8)	-10.1 (-10.4, -9.9)	-8.3 (-8.9, -7.7)
Waist circumference (cm)	-14.4 (-14.8, -14.1)	-10.1 (-10.4, -9.8)	-8.3 (-9.1, -7.5)

¹ All values are estimated marginal means; 95% CIs in parentheses. ANCOVA was conducted, and the values were adjusted for age, sex, center, calendar year, history of cardiovascular disease and cancer during the past 5 y, and dispensation of drugs for obesity, diabetes, hypertension, dyslipidemia, depression, and psychosis during the 6 mo preceding baseline. LCD, low-calorie diet; VLCD, very-low-calorie diet.

² With baseline substitution.

Behavioral changes were facilitated by using a structured support program, which included weekly 1-h group sessions during the weight-loss phase and every 4 wk during the weight-maintenance phase (20 in total). Each session was supervised by a company-trained health coach, who provided encouragement to participants throughout the program. Each group session covered a specific topic, such as health benefits of weight loss, healthy eating strategies, finding realistic eating and exercise routines, and stress management. There were also 30-min face-to-face counseling sessions at baseline and 3, 6, and 12 mo. Self-monitoring was facilitated through diaries, including diet and exercise plans, and graphs for plotting weight, waist circumference, planned and completed circuit training sessions, and steps per day.

Specific restrictions with use of a VLCD

Although participants were free to choose their method of weight loss, the company used criteria for use of VLCDs, consistent with the VLCD recommendations of the European Union Scientific Cooperation Task Report (13). First, individuals were required to have a BMI ≥ 30 or a BMI ≥ 27 with elevated waist circumference (≥ 102 cm for men and ≥ 88 cm for

women). In addition, unless they had signed approval from their physician, individuals with any of the following conditions were barred from following a VLCD: insulin-treated diabetes, gallstones, gout, cancer during the past 2 y, cardiovascular disease (CVD) during the past 3 mo, pregnancy, breastfeeding, catabolic disease, kidney disease, anorexia nervosa, or bulimia.

Cost

The cost for attending the 1-y weight-loss program (including the exercise program) was ~ 9000 Swedish krona (\sim US\$1300, $\text{€}1000$), excluding the liquid diets. At the start, all participants either paid for the whole 12-mo period or committed to paying the whole amount in monthly installments. All participants paid their own fees.

Observational data on weight loss and dropout

The primary outcome variable was weight loss after 1 y. Data on body weight and waist circumference were collected at baseline and 3, 6, and 12 mo. Body weight was measured with the TBF-300

TABLE 3

Adjusted between-group differences in absolute and relative body weight and waist circumference in participants after 1 y in a commercial weight-loss program ($n = 9037$) including a VLCD (500 kcal/d), an LCD (1200–1500 kcal/d), or a restricted normal-food diet (1500–1800 kcal/d)¹

	Between-group differences		
	VLCD compared with LCD	VLCD compared with restricted normal-food diet	LCD compared with restricted normal-food diet
Intention to treat ($n = 9037$) ²			
Body weight (kg)	-2.8 (-3.2, -2.5)	-3.8 (-4.5, -3.2)	-1.0 (-1.6, -0.4)
Body weight (%)	-3.0 (-3.4, -2.7)	-4.3 (-4.9, -3.7)	-1.3 (-1.9, -0.7)
Waist circumference (cm)	-3.0 (-3.4, -2.5)	-4.1 (-5.0, -3.3)	-1.1 (-1.9, -0.3)
Completers only ($n = 7109$)			
Body weight (kg)	-3.0 (-3.3, -2.6)	-3.9 (-4.5, -3.3)	-1.0 (-1.5, -0.4)
Body weight (%)	-2.9 (-3.3, -2.6)	-4.3 (-5.0, -3.7)	-1.4 (-2.0, -0.8)
Waist circumference (cm)	-2.1 (-2.5, -1.7)	-3.1 (-3.8, -2.4)	-1.0 (-1.7, -0.4)

¹ All values are estimated marginal means; 95% CIs in parentheses. ANCOVA was conducted, and the values were adjusted for age, sex, baseline BMI, center, calendar year, history of cardiovascular disease and cancer during the past 5 y, and dispensation of drugs for obesity, diabetes, hypertension, dyslipidemia, depression, and psychosis during the 6 mo preceding baseline. All between-group differences were $P < 0.05$. LCD, low-calorie diet; VLCD, very-low-calorie diet.

² With baseline substitution.

bioelectrical impedance scales (Tanita Corporation). Waist circumference was measured at the point midway between the iliac crest and the lower rib (exhaled). Height was measured with a wall-mounted stadiometer. Dropout was defined as missing data on body weight during 10–14 mo from baseline, including body weight measured at group sessions, and the 1-y follow-up.

Linkage with data from National Health Care Registers

Data on history of comorbidities during the past 5 y were collected from the Swedish National Patient Register, which includes virtually all inpatient and nonprimary outpatient care visits (14). Data on hospital visits for malignancies (*International Classification of Disease, Tenth Revision* code C00–C97) and CVD (code I00–I99) were also collected. Data on diabetes treated with insulin [Anatomic Therapeutic Chemical classification system (ATC) code A10A] or oral antidiabetic drugs (ATC A10B) were collected from the Prescribed Drug Register. Drug dispen-

sation data were retrieved from the Prescribed Drug Register during the 6 mo preceding the start of the program. We also collected data on dispensations of antihypertensive drugs (ATC C02, C03, C07, C08, and C09), lipid-lowering agents (ATC C10AA, C10AB, C10AC, C10AD, C10B, and C10AX), antipsychotics (N05A), antidepressants (ATC N06A), and the antiobesity drugs orlistat (A08AB01) and sibutramine (A08AA10). Finally, we collected data from the Causes of Death Register (for a data linkage outline, *see* Online Supplementary Material under “Supplemental data” in the online issue).

Statistical analyses

Weight loss was primarily analyzed with an intention-to-treat analysis by using baseline observation carried forward when follow-up data were missing. In sensitivity analyses, we also used last observation carried forward, multiple imputation (age, sex, and baseline value were used to predict missing values at 1 y), and

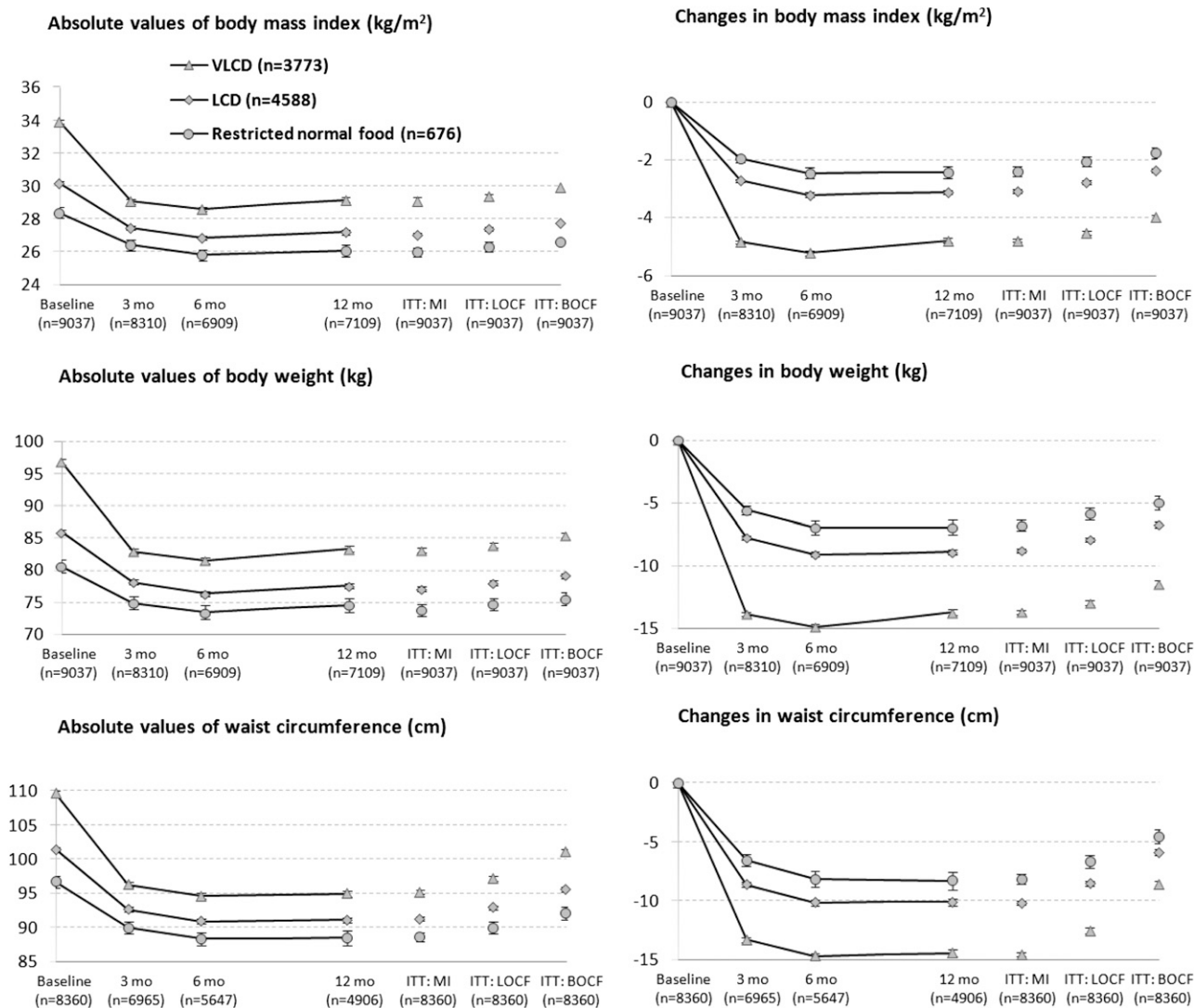


FIGURE 1. Absolute values for and changes in BMI, body weight, and waist circumference during a 12-mo commercial weight-loss program including a VLCD (500 kcal/d), an LCD (1200–1500 kcal/d), or a restricted normal-food diet (1500–1800 kcal/d). ANCOVA was conducted, and the data are estimated marginal means adjusted for age, sex, center, calendar year, history of cardiovascular disease and cancer, and dispensation of drugs for obesity, diabetes, hypertension, dyslipidemia, depression, or psychosis. Error bars represent 95% CIs. ITT: BOCF, intention to treat with use of baseline observation carried forward; ITT: LOCF, intention to treat with use of last observation carried forward; ITT: MI, intention to treat with use of multiple imputation; LCD, low-calorie diet; VLCD, very-low-calorie diet.

a completers-only analysis to see whether our findings were affected by the choice of data-imputation method.

When quantifying the within-group effects of the 3 weight-loss diets, we used a paired sample's *t* test. Between-group comparisons were performed by using ANCOVA with adjustment for age, sex, baseline body weight, center, calendar year, drug dispensations, and comorbidities. Multiple linear regression was used to study predictors of weight loss, and we used multivariable logistic regression to identify predictors of dropout.

When analyzing dropout within groups, we excluded data from the restricted normal-food group because of insufficient power. Because we wanted to study the potential influence of initial weight loss on dropout, we excluded participants who dropped out before the 3-mo follow-up. A 2-sided *P* value <0.05 was considered statistically significant. All data were analyzed with SPSS version 20 and SAS statistical software (version 9.3; SAS Institute Inc).

RESULTS

The mean age of the participants was 48 ± 12 y (range: 18–81 y), BMI was 32 ± 5 (range: 18–68), and waist circumference was 105 ± 13 cm (72–164); 83% of the participants were women, 4% were normal weight, 38% were overweight, 37% were class I obese, 15% were class II obese, and 6% were class III obese (Table 1).

During the 5 y preceding baseline, 8% of all participants had hospital visits listing diagnoses for CVD and 2% with cancer. During the 6-mo period preceding baseline, 18% were dispensed antihypertensives, 12% antidepressants, 7% lipid-lowering drugs, 2% oral antidiabetics, 1% insulin, and 1% anti-psychotics.

Weight loss after 1 y: intention-to-treat analysis

The unadjusted mean (\pm SD) weight change in the 3 weight-loss groups combined was -8.6 ± 8.0 kg (-9.5% of baseline body weight). Within-group weight changes were -11.4 ± 9.1 kg with the VLCD, -6.8 ± 6.4 kg with the LCD, and -5.1 ± 5.9 kg with the restricted normal-food diet ($P < 0.001$ for all within-group changes; Tables 2 and 3). BMI, percentage weight loss, and waist circumference were likewise reduced in a dose-response relation according to caloric intake (Figure 1). A higher proportion of participants in the VLCD group also lost $\geq 15\%$ body weight, and there were fewer participants who lost $< 5\%$ of body weight (Figure 2).

After adjustment for covariates (baseline body weight, age, sex, calendar year, center, comorbidities, and drug dispensations), the VLCD group lost 2.8 kg (95% CI: 2.5, 3.2) more than did the LCD group and 3.8 kg (95% CI: 3.2, 4.5) more than did the restricted normal-food diet. The LCD group lost 1.0 kg (95% CI: 0.4, 1.6) more than did the restricted normal-food diet group.

Weight loss after 1 y: completers-only analysis

In the completers-only analysis, the unadjusted mean (\pm SD) weight change for all 3 weight-loss groups was -10.9 ± 7.5 kg, equivalent to 12.0% of baseline body weight. Within-group, unadjusted weight changes were -13.9 ± 8.1 kg for the VLCD group, -8.8 ± 5.9 kg for the LCD group, and -6.9 ± 5.9 kg for the restricted normal-food diet.

By using linear regression we found that higher baseline body weight (Figure 3), greater initial weight loss, and female sex were associated with increased weight loss after 1 y across all weight-loss groups ($P < 0.01$ – 0.001 ; see Table S1 under

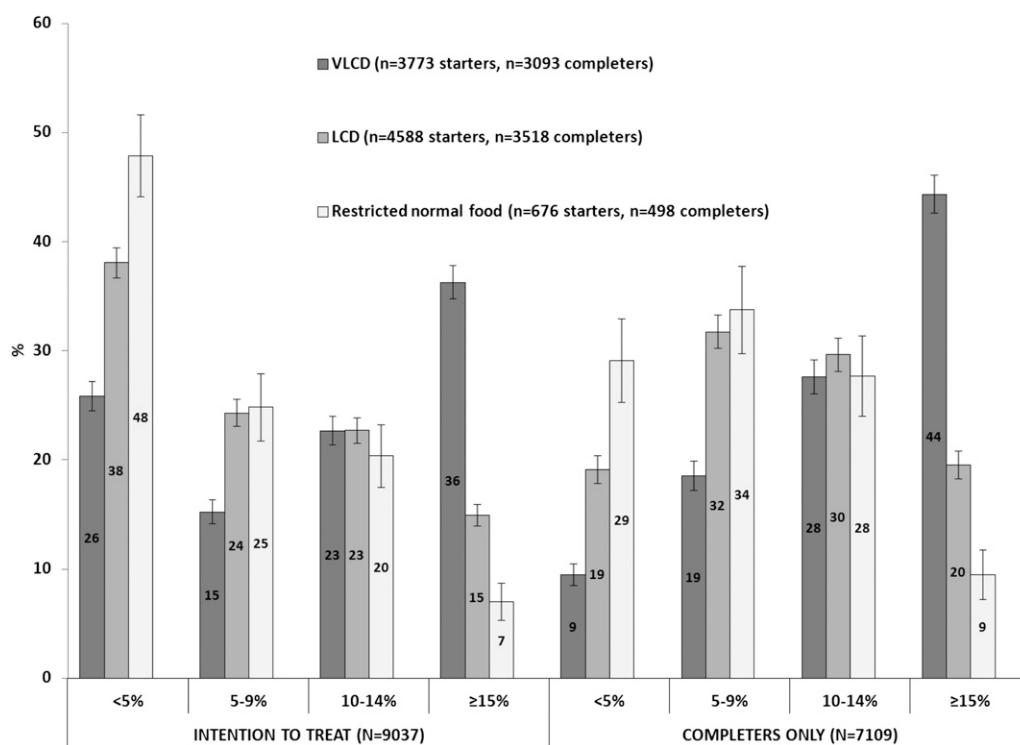


FIGURE 2. Categories of percentage weight loss at 1 y in a commercial weight-loss program including a VLCD, an LCD, or a restricted normal-food diet. The analyses were conducted as both intention to treat with baseline substitution and completers only. Error bars represent 95% CIs. LCD, low-calorie diet; VLCD, very-low-calorie diet.

“Supplemental data” in the online issue). A history of treatment with the previously available antiobesity drug sibutramine predicted a smaller weight loss after 1 y in the VLCD and LCD groups ($P = 0.026$ and $P = 0.008$, respectively).

Dropout after 1 y

Crude dropout rates were 18% in the VLCD group, 23% in the LCD group, and 26% in the restricted normal-food group. In multivariable analysis, with adjustment for age, sex, baseline BMI, center, calendar year, and comorbidities and drug dispensations, and with the use of the VLCD group as reference, dropout was significantly higher in the LCD group (OR: 1.43; 95% CI: 1.27, 1.62; $P < 0.001$) and restricted normal-food group (OR: 1.66; 95% CI: 1.37, 2.01; $P < 0.001$).

Within the VLCD group, younger age (<40 y) and low initial weight loss ($<5\%$) after 3 mo were associated with an increased dropout rate (Table 4). Drug dispensations for depression and psychosis were also associated with an increased risk of dropout. Within the LCD group, predictors of dropout were younger age (<40 y), a low BMI at baseline (<30), and a low initial weight loss ($<5\%$ of baseline body weight). Sex, history of treatment of CVD or cancer, or drug dispensation for hypertension, dyslipidemia, or diabetes were not associated with dropout.

Sensitivity analysis

To minimize the influence of choice of method for handling missing data, we carried out sensitivity analysis using last observation carried forward, a completers-only analysis, and multiple imputation. None of the 3 alternative data-imputation methods produced results that differed materially from the main analysis (Figure 1).

DISCUSSION

Main findings

Weight loss was largest in the 500-kcal VLCD group, followed by the 1200–1500-kcal LCD group, and finally the 1500–1800 restricted normal-food group, which demonstrated a linear, dose-response relation between energy intake and reduced body weight during commercial weight loss. The differences in effectiveness between weight-loss methods were similar when we analyzed waist circumference and percentage body weight as outcome variables. Moreover, the effects of weight-loss method were independent of covariate adjustment and the method for handling missing data.

Baseline body weight and rapid initial weight loss were also independently associated with greater weight loss after 12 mo, whereas treatment of CVD, cancer, hypertension, dyslipidemia,

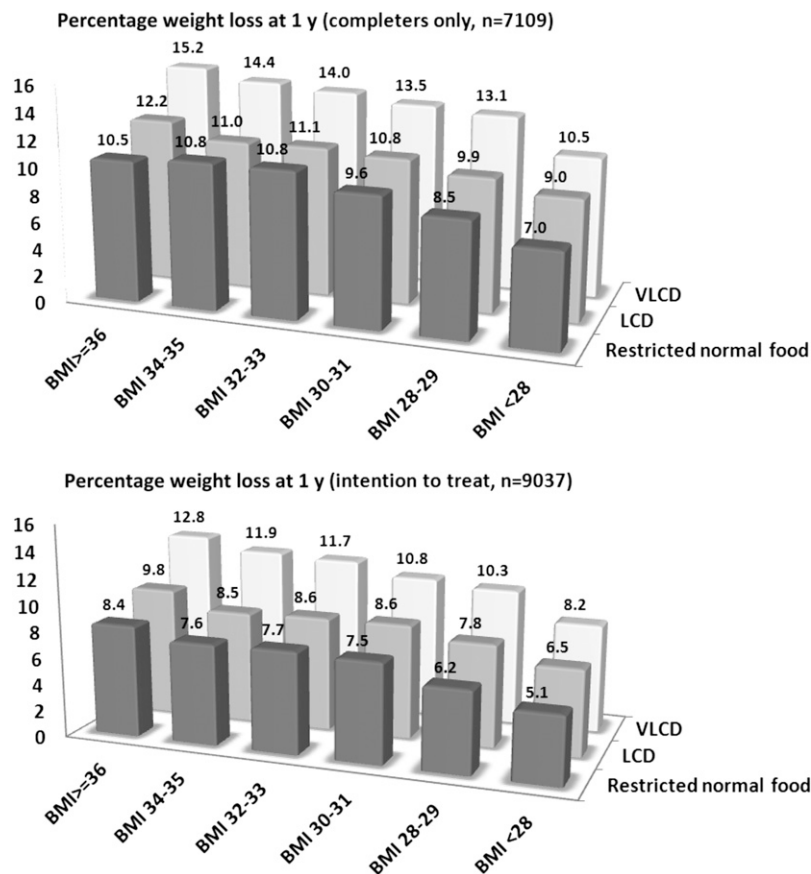


FIGURE 3. Independent effects of baseline BMI (in kg/m^2) and a VLCD (500 kcal/d; $n = 3773$), an LCD (1200–1500 kcal/d; $n = 4588$), and a restricted normal-food diet (1500–1800 kcal/d; $n = 676$) at predicting percentage weight loss after 1 y in a commercial weight-loss program. ANCOVA was conducted with adjustment for age, sex, center, calendar year, history of cardiovascular disease and cancer, and dispensation of drugs for obesity, diabetes, hypertension, dyslipidemia, depression, and psychosis. Data are estimated marginal means. LCD, low-calorie diet; VLCD, very-low-calorie diet.

TABLE 4Multivariable-adjusted ORs (95% CIs) of dropouts at 12 mo during a commercial weight-loss program including a VLCD (500 kcal/d) or an LCD (1200–1500 kcal/d)¹

	VLCD (<i>n</i> = 532 dropouts)		LCD (<i>n</i> = 818 dropouts)	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Male sex	0.84 (0.65, 1.09)	0.18	0.97 (0.76, 1.24)	0.81
Age				
≥60 y	Reference		Reference	
50–59 y	1.13 (0.71, 1.81)	0.61	1.24 (0.97, 1.59)	0.092
40–49 y	2.47 (1.57, 3.90)	<0.001	1.67 (1.28, 2.17)	<0.001
<40 y	4.12 (2.61, 6.50)	<0.001	2.68 (2.04, 3.51)	<0.001
<i>P</i> -trend	<0.001		<0.001	
Baseline BMI				
≥40 kg/m ²	Reference		Reference	
35–39 kg/m ²	1.17 (0.81, 1.68)	0.42	2.58 (1.29, 5.15)	0.007
30–34 kg/m ²	1.46 (1.04, 2.05)	0.027	2.50 (1.29, 4.84)	0.007
<30 kg/m ²	1.35 (0.92, 1.98)	0.13	3.02 (1.57, 5.81)	0.001
<i>P</i> -trend	0.082		0.003	
Weight loss at 3 mo				
≥15%	Reference		Reference	
10–14%	1.50 (1.19, 1.88)	0.001	1.39 (0.92, 2.11)	0.12
5–9%	2.49 (1.91, 3.24)	<0.001	2.51 (1.67, 3.76)	<0.001
<5%	3.41 (2.33, 5.00)	<0.001	4.99 (3.27, 7.63)	<0.001
<i>P</i> -trend	<0.001		<0.001	
Comorbidities and drug use				
History of cancer	1.24 (0.57, 2.73)	0.59	0.98 (0.58, 1.64)	0.98
History of CVD	1.04 (0.70, 1.55)	0.82	1.09 (0.80, 1.48)	0.60
Antihypertension drugs	1.00 (0.71, 1.42)	1.00	1.09 (0.85, 1.38)	0.50
Antidyslipidemia drugs	0.88 (0.51, 1.55)	0.66	0.89 (0.63, 1.25)	0.63
Antidiabetes drugs	1.31 (0.62, 2.74)	0.48	0.92 (0.52, 1.62)	0.76
Antidepressant drugs	1.44 (1.08, 1.91)	0.013	1.24 (0.99, 1.55)	0.065
Antipsychosis drugs	2.63 (1.09, 6.32)	0.031	0.55 (0.23, 1.33)	0.18
Antiobesity drugs	0.73 (0.32, 1.67)	0.49	1.25 (0.55, 2.84)	0.60

¹ Drug use was assessed during the period 6 mo before baseline through register linkage with the Prescribed Drug Register, whereas comorbidity data (except for diabetes) were retrieved from the National Patient Register during the past 5 y. Because diabetes is, to a large extent, treated in primary care, it was defined as use of either insulin or oral antidiabetics. We were not able to analyze the restricted normal-food diet group because of insufficient power and likewise for the antiobesity drug orlistat (only sibutramine was analyzed). There were 3466 participants with complete data on dropout predictors in the VLCD group (91.9%), of whom 532 dropped out, and 4163 in the LCD group (90.7%), of whom 818 dropped out. ORs were quantified by using multivariable logistic regression. CVD, cardiovascular disease; LCD, low-calorie diet; VLCD, very-low-calorie diet.

depression, diabetes, or psychosis did not influence weight loss. Dropout was lowest in the VLCD group, followed by the LCD group, and finally the restricted normal-food group. Younger age and low BMI (the latter for the LCD group only) were associated with increased dropout. Previous treatment of depression and psychosis was also associated with increased dropout in the VLCD group.

Potential mechanisms for the observed effects

The finding that weight loss was determined in a linear dose-response relation according to energy intake suggests that the laws of thermodynamics were the major determinants of weight loss. Moreover, there was no difference in exercise programs between weight-loss groups [Itrim also operates an exercise-only program, with a mean (\pm SD) weight and waist reduction of 1.6 ± 4.3 kg and 2.4 ± 5.2 cm after 1 y; completers-only analysis, $n = 570$, data not shown].

Greater initial weight loss during the first 3 mo was also associated with improved 1-y weight loss and reduced the dropout

rate, indicating that a good start promotes long-term compliance, possibly through increased motivation (15). The markedly increased risk of dropout associated with younger age needs to be studied further.

Comparisons with other commercial weight-loss programs

Weight Watchers and Jenny Craig have both evaluated their programs in randomized trials. Weight Watchers promotes a balanced, hypoenergetic, normal-food diet according to healthy-eating principles (12). In an intention-to-treat analysis with baseline carried forward, mean weight loss after 1 y was 4.1 kg (within-group analysis) and the dropout rate was 42% (12).

Jenny Craig initially uses prepackaged meals with a low fat and low energy content, typically 1200–2000 kcal/d, and then gradually reintroduces a greater proportion of normal food. In an intention-to-treat analysis with baseline carried forward, mean weight loss after 1 y was 6.6 kg (within group), and the dropout rate was 9% (16). In the completers-only analysis, weight loss was 7.3 kg—almost identical to the 7.0 kg lost by completers in



the restricted normal-food group in the current study. The greater weight losses seen in the current study suggest that liquid low-calorie formula diets that promote rapid initial weight loss can improve both weight loss and the dropout rate in commercial weight-loss programs.

However, differences in study protocols, participants, and payment complicate direct comparisons of the effectiveness of the Itrim program with Weight Watchers, Jenny Craig, and other commercial weight-loss programs. Observational studies, such as the current analysis, are likely to benefit from highly motivated, self-selected, and self-paying participants. Similarly, randomized trials may benefit from having a controlled environment and added visits with study personnel, doctors, and nurses.

Concerns with use of a VLCD

VLCDs have been associated with adverse events, such as gallstone formation and sudden death (17–19), which have contributed to stricter rules in the United States (where VLCD programs must be managed by a physician) than in Europe (8). Rapid weight loss, whether by VLCD or bariatric surgery, increases the risk of developing gallstones, and clinical recommendations advise physicians to inform patients about this risk (13, 17, 20). Gallstone formation has mainly been associated with VLCDs containing low amounts of fat (~1 g/d) (21–25), and a higher fat content (12–30 g/d) seems to reduce gallstone formation (26–29).

Another concern with VLCDs is weight regain. Although initial weight loss predicted lower body weight at follow-up in the current study and in others (30), rapid weight loss was also associated with greater regain during the weight-loss maintenance phase in all 3 weight-loss groups (see Figure S2 under “Supplemental data” in the online issue). Responsible use of VLCDs requires, at a minimum, a weight-loss maintenance program, transparency about the substantial efforts required to maintain weight loss (9, 31–34) and risk of regain, and exclusion of nonobese individuals.

Strengths and limitations of the study

First, it was not possible to randomly assign participants to different weight-loss methods, meaning that between-group comparisons are affected by selection bias and baseline differences. We tried to minimize confounding from baseline differences by using percentage weight loss in addition to absolute weight loss, and we performed a BMI-stratified analysis (Figure 3). We also adjusted for baseline body weight in between-group analyses. Our study was aided by a large sample size and the use of 3 different energy-intake methods. The data were furthermore collected in consecutively enrolled participants in a real-life setting, as opposed to data collected in a controlled research setting, where more strict inclusion criteria can limit external validity. We also supplemented the observational data on effectiveness with data from national health registers, which allowed us to describe the medical history of our participants and the influence of such data on effectiveness.

Conclusion

Both weight-loss and dropout rates were more favorable for the 500-kcal/d VLCD group than for the 1200–1500-kcal/d LCD

group and the 1500–1800-kcal/d restricted normal-food group, which suggests an approximately linear dose-response relation between initial caloric intake and long-term effectiveness during commercial weight loss.

The authors' responsibilities were as follows—EH: study conception and design, data acquisition, drafting of the manuscript, analysis and interpretation of the data, statistical analysis, critical revision of the manuscript for important intellectual content, and primary responsibility for final the content; KJ: data acquisition, statistical analysis, and revision of the manuscript for important intellectual content; JE: statistics and critical revision of the manuscript for important intellectual content; JS: study conception and design, interpretation of the data, critical revision of the manuscript for important intellectual content, and supervision; MN: data acquisition, study conception and design, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, and supervision; and CM: study conception and design, critical revision of the manuscript for important intellectual content, and supervision. All authors read and approved the final manuscript. The funding source (Itrim International) collected all data related to the program's effectiveness but was not involved in the design or conduct of the study; the management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript. EH has received consultancy fees from Itrim and was employed part-time by Itrim as program director during 2006–2008. MN, JS, and CM are paid members of Itrim's Scientific Advisory Board. KJ and JE had no conflicts of interest.

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Appendix B

Paper 2

*International Journal of Obesity (2013):
Risk of symptomatic gallstones and cholecystectomy after
a very low-calorie diet or low-calorie diet in a commercial
weight loss program: 1-year matched cohort study.*

ORIGINAL ARTICLE

Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study

K Johansson¹, J Sundström², C Marcus³, E Hemmingsson⁴ and M Neovius¹**BACKGROUND:** Concern exists regarding gallstones as an adverse event of very-low-calorie diets (VLCDs; <800 kcal per day).**OBJECTIVE:** To assess the risk of symptomatic gallstones requiring hospital care and/or cholecystectomy in a commercial weight loss program using VLCD or low-calorie diet (LCD).**DESIGN:** A 1-year matched cohort study of consecutively enrolled adults in a commercial weight loss program conducted at 28 Swedish centers between 2006 and 2009. A 3-month weight loss phase of VLCD (500 kcal per day) or LCD (1200–1500 kcal per day) was followed by a 9-month weight maintenance phase. Matching (1:1) was performed by age, sex, body mass index, waist circumference and gallstone history ($n = 3320:3320$). Gallstone and cholecystectomy data were retrieved from the Swedish National Patient Register.**RESULTS:** One-year weight loss was greater in the VLCD than in the LCD group (-11.1 versus -8.1 kg; adjusted difference, -2.8 kg, 95% CI -3.1 to -2.4 ; $P < 0.001$). During 6361 person-years, 48 and 14 gallstones requiring hospital care occurred in the VLCD and LCD groups, respectively, (152 versus 44/10 000 person-years; hazard ratio, 3.4, 95% CI 1.8–6.3; $P < 0.001$; number-needed-to-harm, 92, 95% CI 63–168; $P < 0.001$). Of the 62 gallstone events, 38 (61%) resulted in cholecystectomy (29 versus 9; hazard ratio, 3.2, 95% CI 1.5–6.8; $P = 0.003$; number-needed-to-harm, 151, 95% CI 94–377; $P < 0.001$). Adjusting for 3-month weight loss attenuated the hazard ratios, but the risk remained higher with VLCD than LCD for gallstones (2.5, 95% CI 1.3–5.1; $P = 0.009$) and became borderline for cholecystectomy (2.2, 95% CI 0.9–5.2; $P = 0.08$).**CONCLUSION:** The risk of symptomatic gallstones requiring hospitalization or cholecystectomy, albeit low, was 3-fold greater with VLCD than LCD during the 1-year commercial weight loss program.*International Journal of Obesity* advance online publication, 18 June 2013; doi:10.1038/ijo.2013.83**Keywords:** VLCD; LCD; commercial weight loss; gallstones; cholecystectomy; adverse events

INTRODUCTION

Bariatric surgery is currently the most effective treatment for obesity,¹ but all obese patients cannot undergo surgery because of guidelines, contraindications, capacity constraints and patient preferences. With the limited capacity of hospital-based obesity treatment, commercial weight loss programs including intensive treatment such as very-low-calorie diets (VLCDs; defined as <800 kcal per day)² are used by millions each year.^{2–4}

The effects of commercial weight loss programs have shown to equal or even outweigh primary-care programs,⁵ with initial rapid weight loss using VLCD compared with low-calorie diet program (LCD; 1200–1500 kcal per day) inducing greater 1-year weight losses and lower dropout rates.⁶ However, the safety of commercial programs has rarely been studied, and using VLCD in commercial weight loss programs is a particular concern given the risk of adverse events as well as weight regain.^{7–9}

A commonly described adverse event after rapid weight loss (including VLCD) is gallstones. Previous studies of VLCD-induced rapid weight loss have generally been small, of short duration, lacked control groups and used formulations with lower amounts of fat compared with the formulations used today.^{10–14} These

previous studies have all identified gallstone formation with ultrasonography after VLCD use. However, the majority of the gallstones found in these studies were asymptomatic, and few led to symptoms. The risk of symptomatic gallstones requiring hospital care and/or cholecystectomy, potentially serious adverse events after VLCD use, has not been studied. Further, to the best of our knowledge, there are no large-scale studies on the safety of commercial weight loss programs.

The aim of this matched cohort study was to investigate in a real-life setting the risk of symptomatic gallstones leading to hospitalization or cholecystectomy after using VLCD (500 kcal per day for 6–10 weeks) compared with participants on LCD (1200–1500 kcal per day for up to 3 months) during a 1-year commercial weight loss program.

METHODS

This matched cohort study was conducted in the commercial weight loss setting in Sweden. Participant data were retrieved from the database used by the commercial company to track customer progress and compliance. These data were linked to the National Patient Register,¹⁵ containing inpatient and nonprimary outpatient care, for outcome ascertainment, and

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to the Causes of Death Register for follow-up of vital status (Figure 1). The regional Ethics Committee in Stockholm, Sweden, approved the study.

Participants

Included participants were consecutively enrolled adult customers (age ≥ 18 years; $n = 8361$) from the commercial weight loss company Itrim in Sweden (www.itrim.se) from 1 January 2006 to 31 May 2009. Data were collected from 28 centers across Sweden, as described elsewhere.⁶

Interventions

The weight loss program was of 1-year duration and comprised an initial 3-month weight loss phase, followed by a 9-month weight maintenance phase. At enrollment, participants selected one of three programs (VLCD, LCD or normal food, as described elsewhere⁶). In this study, we report data from the VLCD and LCD groups, as these are the two programs including liquid formula diets. Although all participants were paying customers and were free to choose weight loss method, the company used criteria for VLCD use, similar to the recommendations in the European (Scientific Co-operation) SCOOP-report on VLCD use (Supplementary Table 1).¹⁶ VLCD participants needed to sign a form, where they had been informed that

VLCD use carries an increased risk of the adverse events listed in the SCOOP-report on VLCD use.¹⁶

Weight loss phase (0–3 months). VLCD: Liquid-based formula diet of 500 kcal per day for 6–10 weeks (Itrim, Stockholm, Sweden; 125 kcal per sachet, 4 sachets per day, each sachet contained 13 g protein, 15 g carbohydrates, 2 g fat and 3 g fiber; approved as sole source VLCD by the Swedish National Food Agency), followed by a 2-week gradual introduction of normal food. Early introduction of normal food (6 as opposed to the full 10 weeks) occurred when the participant was either satisfied with the achieved weight loss or had reached a body mass index (BMI) $< 25.0 \text{ kg m}^{-2}$.

LCD: consisting of two calorie-restricted normal food meals and two formula diet meal replacement sachets (\hat{a} 125 kcal), providing a total caloric intake of ~ 1200 – 1500 kcal per day depending on body size and exercise levels. The normal food consisted of restricted portion sizes with a low overall energy density, high in protein, and with a low-glycemic index.⁶

Weight maintenance phase (3–12 months). After the weight loss phase, the two groups entered the same 9-month weight maintenance program that included an exercise program (circuit training, with a mix of aerobic

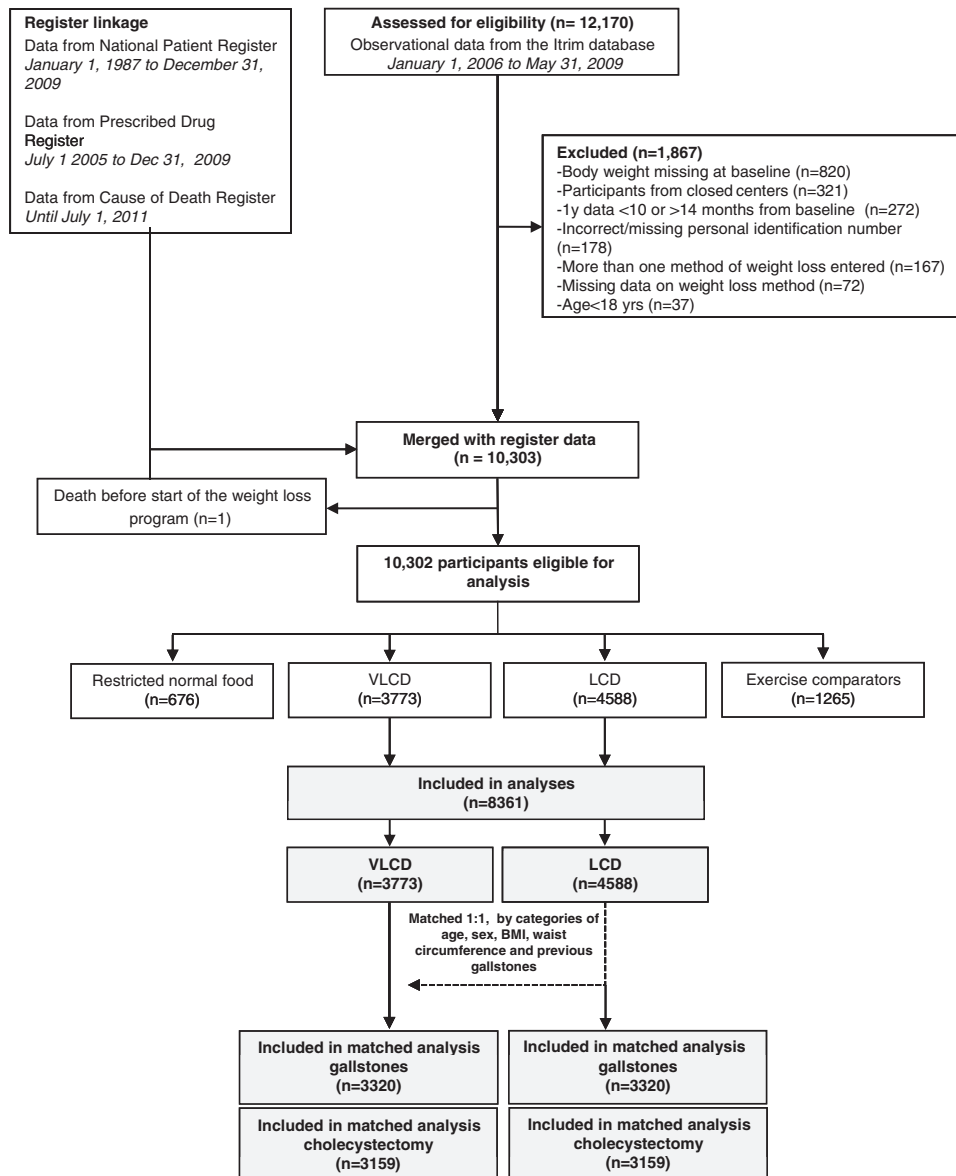


Figure 1. Flow chart of included participants and matching.

and strength training work-out stations, at the center 2–3 times per week for 30–45 min, physically active transport to and from work and using a Yamax SW-200 pedometer to encourage walking), dietary advice, self-monitoring and behavioral changes. Dietary advice included the use of restricted portion sizes, and eating a diet rich in protein and with a low-glycemic index, with a low overall energy density.⁶

Data collection

Participant data. Anthropometric data were collected by company-trained health coaches at baseline, 3, 6 and 12 months, and recorded into the database of the commercial company. Body weight was measured in a nonfasting state with the Tanita TBF-300 bioelectrical impedance monitor (Tanita Corporation, Tokyo, Japan). Waist circumference was measured midway between the iliac crest and the lower rib cage (exhaled) with a measuring tape and was classified as normal (<80 cm for women/<94 cm for men), increased risk (80–87/94–101 cm) and high risk ($\geq 88/102$ cm).¹⁷ Height (without shoes) was measured by a wall-mounted stadiometer. World Health Organization BMI criteria (kg m^{-2}) were used to classify participants as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9) and obese class I/II/III (30.0–34.9/35.0–39.9/ ≥ 40).¹⁸

Register data. Data on gallstones requiring hospital care, cholecystectomy, mortality and comorbidity were retrieved from National registers via register linkage. In Sweden, all the residents have a 10-digit personal identification number recorded in the medical files and nationwide health and census registers, enabling deterministic linkage.

History of gallstones, comorbidity and drug use. Data on the history of gallstones requiring hospital care during the 5 years before program were collected from the National Patient Register, which contains nationwide data on inpatient and nonprimary outpatient care in Sweden. Cholecystectomy history was retrieved from the same source from 1987 and onward. Data on hospital visits for malignancies (International Classification of Diseases [ICD] version 10 codes C00–C97) and circulatory disease (I00–I99) were also collected.

Drug dispensation data were retrieved from the nationwide Prescribed Drug Register during the 6 months preceding program start for antidiabetic drugs (Anatomical Therapeutic Classification [ATC] classification system codes A10A and A10B), antihypertensive drugs (C02, C03, C07, C08, C09), lipid-lowering drugs (C10AA, C10AB, C10AC, C10AD, C10B, C10AX), antidepressants (N06A), the antiobesity drugs orlistat (A08AB01), sibutramine (A08AA10) and rimonabant (A08AA11) and ursodeoxycholic acid (A05A).

Outcome and follow-up data. The primary outcome was gallstones requiring hospital care (cholelithiasis, ICD10 code K80). Cholecystectomy (procedure codes JKA20/JKA21) and all-cause mortality were investigated as secondary outcomes. Participants were followed from program start until first event, death, program end or 31 December, 2009, whichever came first. Cholecystomized patients were excluded in the analysis of cholecystectomy but included in the analysis of gallstones requiring hospital care, as gallstones still can form in the gall ducts.

Gallstone and cholecystectomy data were retrieved from the National Patient Register.¹⁵ Mortality data were retrieved from the Causes of Death Register, which contains information on >99% of all deaths in Sweden.¹⁹

Statistical analysis

LCD participants were matched with replacement to VLCD participants 1:1 by age (+/–1-year), sex, BMI category, waist circumference category and previous gallstones. Analyses included all matched patients and were analyzed by intention to treat.

Kaplan–Meier curves were constructed to illustrate the absolute risk. To compare the risk of gallstones and cholecystectomy between the programs, we used conditional Cox regression to estimate hazard ratios over the 1-year follow-up (conditioned on the matching factors and adjusted for factors with significant differences at baseline).

A sensitivity analysis was conducted restricting the study population to participants without gallstones requiring hospital care during the 5 years preceding program start. Mortality was not analyzed due to few cases (one death due to unknown cause occurred in the VLCD group after the weight loss phase).

An exploratory analysis, combining the two intervention groups, was also conducted using multivariable Cox regression to investigate

factors potentially associated with gallstones requiring hospital care, or cholecystectomy, including age, sex, baseline BMI, history of gallstones and weight loss during the rapid weight loss phase (0–3 months).

Data were analyzed using SAS (version 9.3). All reported *P*-values are two-sided and *P*-values <0.05 were regarded as statistically significant.

RESULTS

After matching LCD participants ($n=4588$) with replacement to VLCD participants ($n=3773$) 1:1 by age, sex, BMI, waist circumference, and previous gallstones, 3320 participants remained in each group (Figure 1).

Baseline characteristics

At baseline, the mean age was 46 years, mean BMI 33.4 kg m^{-2} and 83% were women. Fifty-one percent of the participants were class I obese, 23% were class II obese, 8% were class III obese and 19% were overweight.

The two treatment groups were balanced regarding circulatory disease, malignancy history and the use of lipid-lowering drugs and antidepressants. There were fewer users in the VLCD than in the LCD group of antidiabetic drugs (1.8 versus 3.3%; mean difference, -1.4% , 95% CI -0.7 to -2.2% ; $P<0.001$) and antihypertensives (16.7% versus 19.4%; mean difference, -2.7% , 95% CI -0.8 to -4.5% ; $P=0.005$; Table 1). At baseline, 0.9% ($n=58/6640$) had a history of gallstones requiring hospital care, of which 74% ($n=43/58$) had been cholecystomized (Table 1).

Weight change

Eighty-two percent of the VLCD group and 78% in the LCD group completed the 1-year program (odds ratio, 1.3, 95% CI 1.2–1.5; $P<0.001$). After the initial weight loss phase (0–3 months; baseline observation carried forward), weight loss was 12.7 versus 7.9 kg (adjusted mean difference, 4.6, 95% CI 4.4–4.9; $P<0.001$). After the entire 1-year program, weight loss was 11.1 versus 8.1 kg (adjusted mean difference, 2.8, 95% CI 2.4–3.1; $P<0.001$; Figure 2). Data for the unmatched population have been described elsewhere.⁶

Risk of gallstones requiring hospital care

During 6361 person-years of follow-up, 48 gallstones occurred in the VLCD group and 14 in the LCD group (152 versus 44 per 10000 person-years; conditional hazard ratio, 3.4, 95% CI 1.8–6.3; $P<0.001$; Figure 3; Table 2). The risk difference was 108 per 10000 person-years (95% CI 59–157; $P<0.001$), resulting in a number-needed-to-harm of 92 (95% CI 63–168; $P<0.001$). Adjusting the main analysis for weight loss during the first 3 months attenuated the hazard ratio, but the hazard ratio remained higher with VLCD than LCD (2.5, 95% CI 1.3–5.1; $P<0.001$).

Risk of cholecystectomy

Including only participants who did not undergo a cholecystectomy preceding program start ($n=3159$ in the VLCD group and 3159 in the LCD group), 38 cases of cholecystectomy were performed during 6067 person-years of follow-up, of which 29 were in the VLCD group and 9 in the LCD group (96 versus 30 per 10000 person-years; conditional hazard ratio, 3.2, 95% CI 1.5–6.8; $P=0.003$; number-needed-to-harm, 151, 95% CI 94–377; $P<0.001$; Figure 3; Table 2). Adjustment for weight loss during the first 3 months attenuated the hazard ratio (2.2, 95% CI 0.9–5.2; $P=0.08$).

Sensitivity analysis

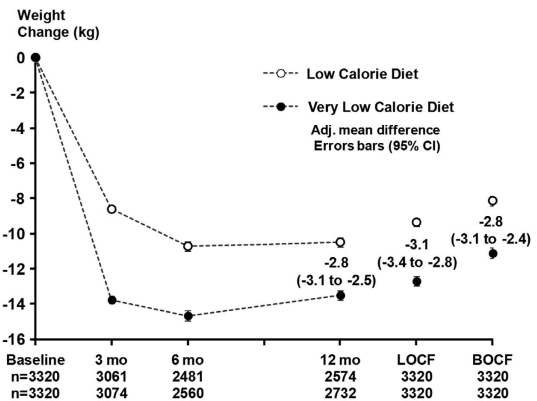
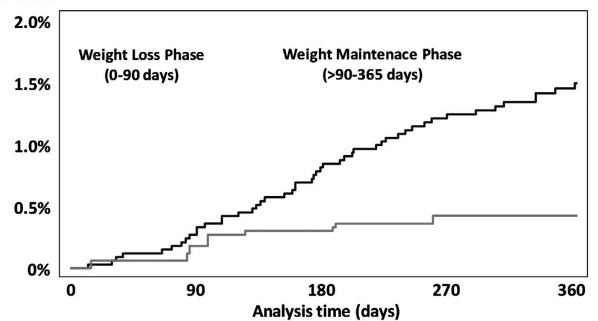
Excluding participants with gallstones requiring hospital care during the 5 years preceding program start ($n=58$) resulted in

Table 1. Baseline characteristics of matched participants enrolled in a commercial weight loss program using very-low-calorie diet or low-calorie diet

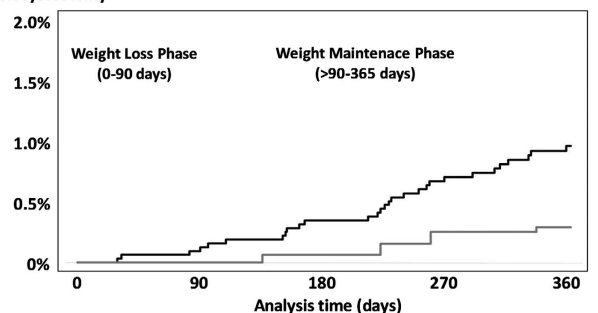
	Very-low-calorie diet (n = 3320)	Low-calorie diet (n = 3320)	P-value ^a
Women	2764 (83%)	2764 (83%)	1.00
Age (years)	46 (11), 18–75	46 (11), 18–76	0.85
Body weight (kg)			
Women	93 (13), 64–168	92 (15), 59–190	0.002
Men	111 (14), 77–180	109 (15), 77–188	0.003
BMI (kg m⁻²)			
18.5–24.9	13 (0%)	13 (0%)	1.00
25–29.9	616 (19%)	616 (19%)	
30–34.9	1692 (51%)	1692 (51%)	
35–39.9	748 (23%)	748 (23%)	
≥40	251 (8%)	251 (8%)	
Waist circumference (cm)			
Women			
80–87	37 (1%)	37 (1%)	1.00
≥88	2615 (95%)	2615 (95%)	
Men			
94–101	2 (0%)	2 (0%)	1.00
≥102	541 (97%)	541 (97%)	
Event history			
Gallstones (last 5 years)	29 (0.9%)	29 (0.9%)	1.00
Cholecystectomy (since 1987)	137 (4.1%)	180 (5.4%)	0.01
Comorbidity history			
Circulatory Disorders	267 (8.0%)	272 (8.2%)	0.82
Malignancy	54 (1.6%)	70 (2.1%)	0.15
Drug use (last 6 months)^b			
Any antidiabetes drug	61 (1.8%)	108 (3.3%)	<0.001
Insulin	12 (0.4%)	43 (1.3%)	<0.001
Oral antidiabetics	56 (1.7%)	93 (2.8%)	0.002
Lipid-lowering agents	195 (5.9%)	217 (6.5%)	0.26
Antihypertensives	556 (16.7%)	645 (19.4%)	0.005
Any antiobesity drug	87 (2.6%)	82 (2.5%)	0.70
Orlistat	31 (0.9%)	38 (1.1%)	0.40
Sibutramine	56 (1.7%)	49 (1.5%)	0.49
Rimonabant	0 (0.0%)	0 (0.0%)	1.00
Antidepressants	391 (11.8%)	432 (13.0%)	0.13
Ursodeoxycholic acid	0 (0.0%)	2 (0.1%)	0.16

Data for continuous variables are mean (s.d.), min–max, and n (%) for categorical variables. ^aP-values are from independent samples t-tests for continuous variables and from χ^2 tests for categorical variables. Waist circumference was missing for n = 348 (5%). N = 124 (4%) for VLCD and N = 124 (4%) for LCD. ^bDrug use during the last 6 months was assessed via register linkage to the Prescribed Drug Register, while comorbidity, gallstones and cholecystectomies were retrieved from the National Patient Register during the last 5 years (comorbidity and gallstones), or from 1987 and onwards (cholecystectomy history).

similar results for gallstones (46 versus 13 in the VLCD and LCD group, respectively; 147 versus 41 per 10 000 person-years; hazard ratio, 3.4, 95% CI 1.8–6.3; number-needed-to-harm, 94, 95% CI 65–173; $P < 0.001$) and cholecystectomy (28 in the VLCD group compared with 9 in the LCD group; 93 versus 30 per 10 000 person-years; hazard ratio, 3.2, 95% CI 1.5–6.8; number-needed-to-harm, 158, 95% CI 97–420; $P = 0.002$).

**Figure 2.** Weight change during the 1-year program LOCF, last observation carried forward (to 12 months); BOCF, baseline observation carried forward (to 12 months).**Cumulative Incidence of Gallstones****Number at Risk (Gallstones requiring hospital care)**

	0	90	180	270	360
VLCD: 3320	(9)	3311 (17)	3294 (14)	3078 (7)	2474
LCD: 3320	(6)	3314 (4)	3310 (4)	3146 (0)	2649

Cumulative Incidence of Cholecystectomy**Number at Risk (Cholecystectomies)**

	0	90	180	270	360
VLCD: 3159	(3)	3156 (8)	3148 (10)	2947 (7)	2371
LCD: 3159	(0)	3159 (2)	3157 (6)	2987 (1)	2523

Figure 3. Risk of gallstones requiring hospital care (upper panel) and cholecystectomy (lower panel) by weight loss program. VLCD, very-low-calorie diet; LCD, low calorie diet.

Exploratory analysis: predictors of gallstones and cholecystectomy during follow-up

In multivariable analysis, the risk of developing gallstones requiring hospital care was higher in women than in men, in younger than in older participants, in those with a higher baseline BMI, among those who lost the most weight and in those with a history of gallstones (irrespective of cholecystectomy status; Supplementary Table 2). For cholecystectomy, the same factors as for gallstones requiring care were associated with an increased risk for cholecystectomy (Supplementary Table 3).

Table 2. Risk of gallstones requiring hospital care and cholecystectomy

	Participants at risk (n)	Observation years (sum)	Events (n)	Events/10 000 person-years (95% CI)	Hazard ratio (95% CI)	Hazard ratio ^a (95% CI) additionally adjusted for 3-month weight loss
<i>Gallstones requiring hospital care</i>						
VLCD	3320	3163	48	152 (110–194)	3.4 (1.8–6.3) <i>P</i> < 0.001	2.5 (1.3–5.1) <i>P</i> = 0.009
LCD	3320	3198	14	44 (21–66)	1.0 (ref.)	1.0 (ref.)
<i>Cholecystectomy</i>						
VLCD	3159	3021	29	96 (62–130)	3.2 (1.5–6.8) <i>P</i> = 0.003	2.2 (0.9–5.2) <i>P</i> = 0.08
LCD	3159	3046	9	30 (11–48)	1.0 (ref.)	1.0 (ref.)

Abbreviations: VLCD, very-low calorie diet; LCD, low-calorie diet. ^aHazard ratios were estimated conditioned on age, sex, gallstone history, baseline BMI, waist circumference and additionally adjusted for drug-treated diabetes and use of antihypertensives for the last 6 months. The analysis of gallstones requiring hospital care was also conditioned on history of cholecystectomy.

DISCUSSION

In our analysis of symptomatic gallstones requiring hospital care or cholecystectomy in participants using either VLCD or LCD for the first 3 months of a 1-year commercial weight loss program, we found the absolute risk of gallstones as well as cholecystectomy to be low but approximately three times higher in the VLCD than in the LCD group. After adjusting for weight loss during the first 3 months, the risk was attenuated but remained higher with VLCD than LCD, suggesting a direct effect of VLCD on gallstone disease. To the best of our knowledge, this is the largest controlled study of VLCD and of the risk of severe gallstone problems and the first large-scale safety analysis of a commercial program.

Previous research

Previous studies have investigated the association between VLCD and ultrasonography-assessed gallstone formation, rather than the risk of gallstones as a serious adverse event requiring hospital care and/or cholecystectomy. The majority of these studies were conducted in the late 1980s and early 1990s using VLCDs containing low levels of fat (≈ 1 g per day).^{10–14} In a review of these studies,²⁰ Everhart reported that 10–25% of VLCD participants developed gallstones, one-third of which were symptomatic. Limitations of these studies were the lack of control groups, small sample sizes and short follow-up (8–36 weeks).^{10–14} Later studies included VLCDs containing higher fat content (12–30g per day),^{21–24} two of which were randomized controlled trials.^{21,22} None developed systematic gallstones in the high-fat group in either of the studies, suggesting that an adequate fat intake reduces gallstone formation. The fat content of the VLCD in our study was 7–9g per day, consistent with the 7g per day recommendation given by the European SCOOP-report on VLCD use.¹⁶ The higher risk with VLCD in our study suggests that fat content may need to be increased even further to reduce the risk to LCD levels.

Mechanisms

Increased risk for gallstone formation during VLCDs could be explained by inadequate fat content of the diet and/or the rapid weight loss associated with VLCDs. Rapid weight loss, either by VLCD or bariatric surgery, is a known risk factor for gallstone formation.²⁰ The two most commonly suggested mechanisms for gallstone formation are supersaturation of bile with cholesterol, leading to cholesterol crystallization and stone formation, and the insufficient gallbladder emptying due to impaired motility.²⁵ Rapid weight loss induced by VLCDs is believed to affect both the mechanisms: Supersaturation is believed to be caused by decreased bile salt levels and increased cholesterol levels, and impaired motility due to reduced gallbladder stimulation because of the low-fat content.^{26,27} However, as described previously, a fat

intake of 7–10g per day has been reported as a threshold for maintaining an efficient gallbladder emptying.^{16,26} The majority of the gallstones requiring hospital care occurred during the maintenance phase (37/48 in the VLCD group and 8/14 in the LCD group). This was also the case in a previous study of VLCD as a treatment for sleep apnea (3/3 gallstones reported during the maintenance phase).^{28,29}

Clinical implications

Increased risk of gallstone formation during and after VLCD-induced rapid weight loss is incorporated in clinical recommendations as an adverse event, advising physicians to inform patients about this risk, but the risk magnitude has been unclear.^{7,16,20} Our findings indicate a small, absolute but substantially elevated relative risk of gallstones requiring hospital care and/or cholecystectomy when using VLCD instead of LCD.

Whether the benefits of the additional weight loss in the VLCD group are worth the extra risk for gallstones and cholecystectomy may depend on patients' disease and risk factor status, as well as their preferences. Supplementation with omega-3 fatty acids and/or the use of ursodeoxycholic acid during the rapid weight loss phase could possibly reduce gallstone formation.^{26,30}

Strengths and limitations

The strengths of the current study include the large sample of weight loss participants in a real-life setting, with a direct VLCD and LCD comparison. With the risk of symptomatic gallstones being low, statistical power may become an issue in smaller studies. Our large study made it possible to study the risk of symptomatic gallstones leading to hospitalization and/or cholecystectomy as a serious adverse event to VLCD. Further, the outcomes were prospectively reported and data were collected routinely on a nationwide level in the universally accessible Swedish health-care system, with virtually complete follow-up.

The main limitation was the nonrandomized design. Baseline differences in age, sex, BMI, waist circumference and gallstone history were handled by matching. Multivariable adjustment was used for handling remaining baseline imbalances. However, residual confounding may exist. The results appeared to be robust in our sensitivity analyses.

Second, participants had selected and paid for the treatment themselves, possibly limiting generalizability to the wider overweight and obese population. Finally, the National Patient Register contains data on inpatient and nonprimary outpatient visits for gallstones, not visits in primary care, or undetected asymptomatic gallstones. Our results may therefore not be generalizable to mild or asymptomatic gallstones. However, our primary outcomes were gallstones requiring hospital care and cholecystectomies. Gallstones

treated in the primary care, at home, or not treated at all, are likely both less serious for the patient and less costly for society.

CONCLUSION

The absolute risk of gallstones as well as cholecystectomy was found to be low but approximately three times higher in the VLCD than in the LCD group during the 1-year commercial weight loss program. After adjusting for weight loss during the first 3 months, the risk was attenuated but remained higher with VLCD than LCD, suggesting a direct effect of VLCD on gallstone disease.

CONFLICT OF INTEREST

All authors have completed ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Hemmingsson report that he has received consultancy fees from Itrim and was employed part-time by Itrim as program director during 2006-2008. Drs Neovius, Sundström and Marcus report that they are members of Itrim's Scientific Advisory Board. Dr Johansson has no financial relationships with Itrim, but received a grant from Cambridge Weight Plan, Northants, (manufacturer of another VLCD formula) for two studies examining the effect of weight loss on obstructive sleep apnea.^{28,29}

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AUTHOR CONTRIBUTIONS

Dr Johansson and Dr Neovius had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Johansson, Neovius. Acquisition of data: Johansson, Neovius, Hemmingsson. Analysis and interpretation of data: Johansson, Neovius, Sundström. Drafting of the manuscript: Johansson, Neovius. Critical revision of the manuscript for important intellectual content: Johansson, Neovius, Sundström, Hemmingsson, Marcus. Statistical analysis: Johansson, Neovius. Obtained funding: Hemmingsson. Study supervision: Johansson, Neovius.

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Supplementary Information accompanies this paper on International Journal of Obesity website (<http://www.nature.com/ijo>)

Appendix C. Abstract for the Annual Meeting of the Swedish Society of Medicine (Svenska Läkaresällskapet), Section for Obesity Research, Gothenburg, 2006.

Weight Loss and Lifestyle Change within the Commercial Sector – a Good Complement to Healthcare?

Erik Hemmingsson, Johan Sundström, Claude Marcus

Background: Only a small proportion of overweight patients currently get state-financed help with weight loss and lifestyle changes. The quality of commercial weight loss programs is still relatively unknown.

Method: 340 participants (BMI 31.9 ± 5.3 kg/m²; age 47.4 ± 11.8 years, 89.7% female) underwent a commercial 12-month weight loss program (Itrim) comprising 20 one-hour lectures on diet and exercise, 30-45 minutes of aerobic and strength training 2-3 times/week, individual coaching at every weigh-in (at the start, 10, 20 and 52 wks), and homework tasks/diaries. The participants, who all had a BMI >25 kg/m², were recruited consecutively between 2004-2005 from six centres in different parts of the country. The participants had all paid for the program themselves (cost approx. SEK 700/month). The participants could choose one of three specific low-calorie diets during the first ten weeks of the program (after which they gradually returned to energy balance): 1) VLCD; 2) 2 meals of normal food + 2 VLCD meals ("2+2"); and 3) normal food with a restricted fat and sugar content ("Normal food"). The intention to-treat principle was used (baseline carried forward). RM ANOVA with baseline weight as a covariate was used for hypothesis testing.

Result: 249 participants completed the 12 months. The dropout rate was 20.6% in the VLCD group (20/97), 30.2% in the 2+2 group (54/189) and 25.9 % in the normal food group. After 12 months the VLCD group had lost 12.3 kg (95% CI 10.4 to 13.7), the 2+2 group 7.6 kg (6.4 to 8.8), and the normal food group 5.7kg (3.5 to 7.9). The VLCD group had significantly better weight loss than both the 2+2 and the normal food groups ($P < 0.001$ for both). The 2+2 group achieved significantly better weight loss than the normal food group ($P < 0.05$).

Summary: All groups achieved clinically relevant weight loss. The greatest weight loss was achieved when meal replacement was used at the start of the program. Commercial weight loss programs may be an important complement to public healthcare.

Note: Both Itrim research papers, and all published abstracts, include data from Swedish weight loss participants enrolled between 1 January 2006-31 May 2009. During this time, the Rapid weight loss method consisted of a 500 kcal/d VLCD (very low calorie diet), as opposed to the 800 kcal/d LCD that is being used today.

Appendix D Abstract for European Congress on Obesity, Geneva, May 2008.

Efficacy and Consistency of a Franchising Weight Loss Program in the Swedish Commercial sector

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Background: Commercial weight loss programs with a scalable structure, operating according to a defined manual including regular quality controls, can partner health professionals when public care is lacking.

Aim: To clarify consistency of weight loss (across years and locations) of a commercial franchise company (Itrim) in Sweden.

Methods: Weight loss at 12 months was analysed for the years 2004-2006, across 11 centres (6 cities), before and after adjustment for baseline body weight, age, gender, and group session attendance. 970 consecutively recruited participants (BMI 31.5 kg/m² [sd 5.5], age 47.1 yrs [11.4], 86 % women) were included. The program consisted of 20 one hour group sessions on diet and exercise behavior change, physical activity (circle training 2-3 times/wk á 30-45 min + pedometers), individual coaching at 0, 10, 26 and 52 weeks, meal replacements, home assignments, and food and exercise diaries. Participants paid their own fee (approx. Euro1000/yr.).

Results: Mean weight loss at 12 months was 10.5 kg (95 % CI: 10.0 to 11.1). In unadjusted analysis, there was a significant weight loss difference between centers (p=0.03) but not between years (p=0.16). After adjustment for covariates, the difference in weight loss between centers was attenuated (p=0.10). Predictors of weight loss were instead baseline body weight (Beta=-0.3 per baseline kg, p<0.001), group session attendance (Beta=-0.49 per session, p<0.001), gender (Beta=2.4 men>women, p<0.002), and age (Beta=0.06 younger>older, p<0.008).

Conclusions: Commercial companies, operating according to a defined manual including regular quality controls, can provide consistent weight loss results across time and locations.

Conflict of interest: EH works part time as Itrim's Program Director. JS and CM are members of Itrims Scientific Advisory Board.

Note: Both Itrim research papers, and all published abstracts, include data from Swedish weight loss participants enrolled between 1 January 2006-31 May 2009. During this time, the Rapid weight loss method consisted of a 500 kcal/d VLCD (very low calorie diet), as opposed to the 800 kcal/d LCD that is being used today.

Appendix E. Abstract for The Obesity Society, Phoenix, 2008.

Multi-Center Commercial Weight Loss through Caloric Restriction, Behaviour Modification and Exercise: Results Across Time and Location

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Background: Commercial weight loss programs based on diet and exercise behaviour change with a scalable structure can partner health professionals in the treatment of obesity and prevention of obesity co-morbidities.

Aim: To clarify consistency of weight and waist loss (across years and locations) of a commercial franchise company (Itrim) in Sweden.

Methods: Weight loss and waist loss at 12 months were analysed for the years 2004, 2005, 2006 and 2007 across 12 commercially operated weight loss centers in 7 cities. 1726 participants who completed one year were included (BMI 31.6 [sd 5.5] kg/m², waist 105.0 [12.9] cm, age 47.0 [11.6] yrs, 86 % women). The one-year program consisted of 20 one-hour group sessions on diet and exercise behaviour change, physical activity (circle training 2-3 times/week à 30-45 min, fitness testing and pedometers), individual coaching at 0, 10, 26 and 52 weeks, meal replacements, home assignments, and food and exercise diaries. Participants paid their own fee (approx \$1500/year).

Results: Overall weight loss (all mean values are age and sex adjusted) at 12 months was 10.8 kg (95 % CI: 10.4 to 11.4). The mean waist loss was 11.8 (95 % CI: 11.4 to 12.3) cm. Both weight loss and waist loss were stable across years (P=0.43 and P=0.81, respectively) but differed across centers (P<0.001 for both). Mean weight loss across centers ranged from 7.5 (95 % CI: 5.3 to 9.6) to 12.5 (95 % CI: 11.4 to 13.6) kg, with waist loss ranging from 7.1 cm (95 % CI: 3.9 to 10.2) to 16.3 (95 % CI: 14.5 to 18.1).

Conclusions: Commercial weight loss programs can provide stable results across time. Consistency between centers, however, remains a challenge in multi-center commercial weight loss.

Conflict of interest: At the time of submission, EH was employed part time by Itrim International as Program Director. MN, JS and CM are members of Itrim's Scientific Advisory Board.

Note: Both Itrim research papers, and all published abstracts, include data from Swedish weight loss participants enrolled between 1 January 2006-31 May 2009. During this time, the Rapid weight loss method consisted of a 500 kcal/d VLCD (very low calorie diet), as opposed to the 800 kcal/d LCD that is being used today.

Appendix F. Abstract for the Annual Meeting of the Swedish Society of Medicine (Svenska Läkaresällskapet), Section for Obesity Research, Stockholm, 2009.

Evaluation of a franchising weight loss program: 2-year results and drop-out

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Background: Commercial weight loss through lifestyle modification is a growing industry. Results of commercial weight loss programs are seldom published, especially data on long-term weight loss and drop-out.

Method: Data on body weight from 4917 participants (BMI 31.8 ± 5.2 kg/m²; age 46.7 ± 11.9 y, 86% women) on the Itrim weight loss program in Sweden were available for analysis through a member database. All participants were enrolled consecutively from 21 centers during 2004-2007. The program consists of group sessions, circle training, fitness testing, individual coaching sessions, home assignments, and diaries. All participants paid their own fee (cost ca €1 000/yr). In September 2006 the company added a 1-year voluntary maintenance program to the existing 1-year weight loss program, thereby also providing 2-year follow-up data.

Results: Of the 4917 starters during 2004-2007, 3390 completed the 1-year follow-up, giving a 31% drop-out rate. In an intention to treat analysis, using baseline carried forward for drop-outs, the average weight loss at 1 year was 7.3 kg (SD 7.9) (10.6 kg in completers only analysis). Sixteen percent (n=248) of the members enrolling on the weight loss program at or after September 2005 (n=248 of n=1414) started the maintenance program. Eighty-nine percent (n=220) completed the 2-year follow-up (drop-out: 11 %), with an average weight loss of 10.9 kg from baseline (1-year data carried forward for second year drop-outs; -12.3 kg in completers only analysis).

Conclusion: Commercial weight loss programs, where participants pay their own fee, can provide clinically relevant results long-term. A common problem in obesity treatment is drop-out before enrolling on a maintenance program, which is a major challenge for commercial weight loss programs.

Note: Both Itrim research papers, and all published abstracts, include data from Swedish weight loss participants enrolled between 1 January 2006-31 May 2009. During this time, the Rapid weight loss method consisted of a 500 kcal/d VLCD (very low calorie diet), as opposed to the 800 kcal/d LCD that is being used today.

Appendix G. Abstract presented at the European Congress of Obesity, Lyon, 2012.

Dropout during commercial weight loss: Observational cohort study with register linkage

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Introduction: Dropout during commercial weight loss is unclear.

Methods: Observational data on weight loss and dropout from the commercial weight loss company Itrim (Sweden) were linked with national health registers. The cohort consisted of 8361 consecutively-enrolled participants on a 1-year weight loss program (cost: \$1300/€1000). Weight loss was induced by 6-10 weeks VLCD (n=3773; BMI 34±5kg/m², 80% women; age 45±12y) or meal replacements (n=4588; BMI 30±4kg/m², 86% women, age 50±11y), followed by a diet and exercise maintenance program. At baseline, 18% were treated for hypertension, 12% for depression, 8% for CVD, 7% for dyslipidemia, 3% for diabetes, 2% for cancer, and 1% for psychosis. Logistic regression was used to identify predictors of dropout at 1 year.

Results: In crude analysis, weight change for VLCD (completers) was -13.9±8.1kg with 18% dropout. Weight change for meal replacements (completers) was -8.8±5.9kg with 23% dropout. In multivariable analysis, use of meal replacements remained associated with dropout compared to VLCD (odds ratio, OR: 1.5). Independent predictors of dropout within the VLCD group were low age <40y vs ≥60y (OR: 4.4), low BMI <30kg/m² vs ≥40kg/m² (OR: 1.6), depression (OR: 1.4), and psychosis (OR: 2.6). Within the meal replacement group, predictors of dropout were low age <40y vs ≥60y (OR: 2.6), low BMI <30kg/m² vs ≥40kg/m² (OR: 2.2), and depression (OR: 1.4). Treatment for CVD, cancer, hypertension, dyslipidemia, and diabetes was not associated with dropout.

Conclusion: While dropout was generally low, we noted an increased risk of dropout with low age, low BMI, depression and psychosis.

1. Conflict of interest: Erik Hemmingsson has received consultancy fees from Itrim. Martin Neovius, Johan Sundström and Claude Marcus are members of Itrim's Scientific Advisory Board.

2. Funding: Itrim International. The funding source was not involved in the analysis of data, and did not read or comment on any version of the abstract.

Note: Both Itrim research papers, and all published abstracts, include data from Swedish weight loss participants enrolled between 1 January 2006-31 May 2009. During this time, the Rapid weight loss method consisted of a 500 kcal/d VLCD (very low calorie diet), as opposed to the 800 kcal/d LCD that is being used today.

Appendix H. Abstract presented at The Obesity Society, San Antonio, Texas, 2012.

Risk of Gallstones in a Commercial Weight Loss Program using Very Low Energy Diet or Low Energy Diet: Matched Cohort Study

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Background: Very-low-energy diet (VLEDs; <800kcal/day) guidelines recommend a daily fat content >7g to prevent gallstone formation, but data supporting this threshold are scarce. The objective was to assess the risk of gallstones requiring hospital care in a commercial weight loss program using VLED or low energy diet (LED).

Method: One-year prospective cohort study of consecutively enrolled adults in a commercial weight loss program, conducted in 28 centres in Sweden between 2006 and 2009. LED participants were matched to VLED participants by age, sex, BMI, waist circumference, and previous gallstones resulting in 3,320 LED and 3,320 VLED participants. The intervention consisted of either VLED (500kcal/day; 7-9g fat/day) or LED (1,200-1,500kcal/day) for three-month, followed by a weight maintenance phase for nine-month. The main outcome measure was gallstones requiring hospital retrieval from the Swedish National Patient Register. Cholecystectomy was investigated as secondary outcome.

Results: Weight loss was greater in the VLED than the LED group (-11.1 versus -8.1kg; adjusted mean difference -2.8kg, 95%CI-3.1,-2.4; p<0.001). During 3,163 and 3,198 person-years in the VLED and LED groups, 48 and 14 gallstones requiring hospital care occurred (152 versus 44 per 10,000 person-years; hazard ratio 3.4, 95%CI 1.9-6.1; p<0.001; number-needed-to-harm 92, 63-168). Of the 62 events, 39(63%) resulted in cholecystectomy (29 versus 10; hazard ratio 3.1, 95%CI 1.5-6.5; p=0.003; number-needed-to-harm 151, 94-377).

Conclusion: The risk of gallstones requiring hospitalisation or cholecystectomy, albeit low, was greater with VLED than LED treatment, as was weight loss. The threshold of 7g fat/day appears insufficient to prevent gallstones when comparing with LED.

Note: Both Itrim research papers, and all published abstracts, include data from Swedish weight loss participants enrolled between 1 January 2006-31 May 2009. During this time, the Rapid weight loss method consisted of a 500 kcal/d VLCD (very low calorie diet), as opposed to the 800 kcal/d LCD that is being used today.

