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Title: Does the rate of weight loss influence the success of long term weight maintenance?
1. BACKGROUND

1.1 The obesity epidemic

Obesity and overweight are physical conditions that result from excessive storage of fat in the body as a consequence of an energy imbalance, where energy intake exceeds energy expenditure. Overweight is defined as a body mass index (BMI; kg/m²) greater than 25 and obese as a BMI of 30 or greater [1]. Over the last decade the prevalence of obesity and overweight have increased significantly, and the conditions now represent a major health problem worldwide in both developed and developing nations [2]. In 2006 the World Health Organization estimated that there were 1.6 billion overweight and 400 million obese adults (age 15+) [3].

Although obesity should be considered a disease in its own right, it is associated with a variety of serious medical conditions, such as diabetes [4], cardiovascular disease [5, 6], gallbladder diseases [7], and obstructive sleep apnoea [8]. Other health issues associated with obesity include respiratory difficulties [9], infertility [10, 11], skin problems [12], and musculoskeletal problems [13, 14], that not only impact on quality of life but may lead to an increased risk of premature death [15].

BMI has been shown to correlate positively with fasting blood glucose, circulating concentrations of total and low-density lipoprotein (LDL) cholesterol, triglycerides, and blood pressure [16]. Large prospective studies have demonstrated that even modest increases in BMI increase the risk of developing type two diabetes mellitus (T2DM) [4, 17]. Data from eight years of follow-up of over 110,000 women in the US Nurses’ Health Study showed the risk of T2DM was lowest for subjects with a BMI less than 22 kg/m² [17]. As BMI increased, the relative risk of T2DM increased; at a BMI of 35, the risk of T2DM relative to BMI of 22 was increased 40-fold. Similar results have also been shown in men [4].

Cardiovascular disease is strongly related to excessive weight. For obese men younger than 65 years, the relative risk of coronary vascular (CV) disease is 2.61 with a BMI of 29.0-32.9, and 3.44 with BMI ≥ 33 compared with lean men with a BMI of 23.0 [18]. The Framingham heart study has shown that obese women are 115% and obese men are 81% more likely to die before the age of 70 years compared with a person within the normal weight range [15]. The study also found an average reduction in life expectancy of 7.1 years in obese women and 5.8 years in obese men compared with men and women of normal weight.

1.2 The benefits of weight loss

Intentional weight loss in overweight and obese individuals has numerous health benefits [6, 19-21]. Weight loss significantly improves cardiovascular disease risk factors including lowering blood pressure [22], the level of LDL cholesterol and serum triglycerides [23], while increasing the proportion of HDL [24]. A modest weight loss of 5kg has been shown to halve the risk of developing T2DM [17]. Other health benefits of weight loss include improved fertility [25] and decreased pain associated with hip and knee osteoarthritis [26]. There are also psychological benefits from weight loss such as improved self-esteem and quality of life [27, 28].
1.3 Body weight regulation

Several hormones have been shown to contribute to regulation of body weight. These hormones are involved in the short-term (ghrelin, cholecystokinin (CCK), peptide YY (PYY), GLP-1, oxyntomodulin, amylin and pancreatic polypeptide (PP)) and long-term regulation of energy balance (leptin and insulin). Only one of these (ghrelin) stimulates food intake; all the others suppress the desire to eat, as do circulating nutrients such as glucose and free fatty acids.

Leptin is a hormone secreted by fat cells; it inhibits food intake [29] and increases energy expenditure [30]. It has been shown that leptin levels fall dramatically following weight loss [31]. A comparison of age and BMI-matched post-obese male and female subjects with never-obese subjects found that plasma leptin levels were lower but respiratory quotient (RQ) higher in post-obese subjects [32]. A higher RQ indicates a lower level of fat oxidation, which may promote weight gain [33]. It has been suggested that leptin has a stimulating effect on fat oxidation in obese subjects [34]. Furthermore, following weight loss levels of circulating ghrelin, are greatly elevated [35], while CCK [36], insulin [37] and free fatty acids [38] (all of which can inhibit food intake) fall, promoting weight regain. In addition, it has been shown that there is a reduction in total energy expenditure of 8±5kcal per/kilogram of fat free mass per day following 10% weight loss [39]. Thus, a formerly obese person needs to consume approximately 15% fewer calories a day to maintain their reduced body weight compared to a person of the same body composition who has never been obese [40]. The mechanisms for this decreased energy expenditure following weight loss have not been fully established; however, as leptin increases energy expenditure, it could be due to the reduction in circulating leptin levels [41], and/or as a result of thyroid hormone thyroxine (T4) being converted to the inactive reverse-triiodothyronine (reverse-T3) instead of triiodothyronine (T3) [42]. It could also be due to a reduction in non-resting energy expenditure, as several studies show skeletal muscle efficacy improves following weight loss [43, 44].

Recently, it was revealed that the changes in levels of appetite regulating hormones that occur following weight loss are sustained with prolonged weight maintenance. This was first shown in a study conducted in the clinical research unit (CRU) at the Heidelberg Repatriation Hospital in Melbourne, Australia [31]. Appetite regulating hormones were measured in 50 obese patients; prior to weight loss, following a ten-week weight-loss dietary intervention (VLED), and one year following the VLED. At the end of the diet, and one year after weight loss, the release of the satiety hormones CCK, PYY and amylin, were reduced, potentially encouraging hyperphagia and weight gain. In addition, levels of circulating ghrelin and hunger (measured via a visual analogue scale) were elevated both immediately and one year following weight loss. Rosenbaum and colleagues reported that reduction in energy expenditure following weight loss persists in adults who have maintained a reduced body weight for at least one year [45].

It is likely that the physiological adaptations that encourage weight gain described above combine to make maintenance of weight loss so difficult.
1.4 Very low energy diets (VLEDs)

VLEDs have been used by obese individuals to achieve substantial weight loss for more than 30 years [46]. VLEDs are nutritionally sound diets containing between 1845 and 3280 KJ (450 and 800 Kcal) per day, and typically consist of meal replacement formulations. In the initial phase, a VLED often consists of a meal replacement three times daily as a substitute for breakfast, lunch and dinner. In addition, the person consumes a bowl of non-starchy vegetables for fibre, with a teaspoon of oil to help contract the gallbladder thus reducing the risk of gallstone formation [47].

Despite the positive literature regarding the benefit and long term success of VLEDs [48, 49] 98.5% of surveyed Australian dietitians do not recommend VLEDs, believing the notion “the faster you lose the weight the faster it is regained” (unpublished data). This is based on a belief that rapid weight loss does not promote the necessary lifestyle changes required to maintain weight loss in the longer term. Such a view is based on several assumptions: 1) overweight is only the result of self-chosen lifestyle; 2) the physiological adaptations that occur following weight loss are different from those that follow slow gradual loss; 3) all weight regain is due to simple return to old habits.

2. STUDY RATIONALE

The evidence that rapidly achieved weight loss is regained faster than weight that is lost slowly is scarce. A review of the literature conducted in 2000 by the National Health and Medical Research Council of Australia as part of its evidence-based guidelines for the management of obesity, compared long-term weight loss with different diet therapies (Table 1). This review demonstrated that 2 years after initiation of weight loss therapy, weight loss maintenance after using a VLED is no worse, and possibly better, than other diet therapies [50].

Whereas the above analysis of the literature found that the long-term weight outcome of people who followed a VLED is no worse than people who followed low energy diets. A large meta-analysis by Anderson et al. found that followers of VLEDs lose significantly more weight initially and maintain significantly greater weight losses than followers of low energy, balanced diets [48].

Toubro and Astrup randomised obese patients to a VLED or a conventional low calorie diet and counselled them to lose approximately 13 kg [49]. The VLED group took 8 weeks to achieve the target weight loss whereas the conventional group took 17 weeks. After 1 year, the VLED group was maintaining

<table>
<thead>
<tr>
<th>Diet</th>
<th>Weight loss 1-2 years</th>
<th>Weight loss &gt; 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad lib low fat</td>
<td>-3.9 kg</td>
<td>-2.7 kg</td>
</tr>
<tr>
<td>Low energy</td>
<td>-6.7 kg</td>
<td>-1.1 kg</td>
</tr>
<tr>
<td>Very low energy</td>
<td>-11.8 kg</td>
<td>-4.1 kg</td>
</tr>
<tr>
<td>Meal replacement</td>
<td>-5.5 kg</td>
<td>-6.5 kg</td>
</tr>
<tr>
<td>‘Popular’ diets</td>
<td>Not known</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Table 1. Long-term weight losses for different diets
an extra 2.4 kg loss compared to the conventional group. After 2 years the difference was 3.0 kg extra. Although the differences were not statistically significant, the study did show that a large and rapid weight loss did not result in poorer maintenance of the loss compared to a conventional diet. So there appears to be little evidence that “the faster you lose weight the quicker you regain it” yet the belief is often touted in the lay-press and by health practitioners.

It would appear therefore that the rate of weight loss may not be important to the long-term maintenance of weight loss. The purpose of this study is to compare the long-term weight outcome and the short-term and long-term physiological adaptations to different rates of weight loss.

3. OVERALL HYPOTHESIS

The broad hypothesis is that the rate of weight loss will not influence long-term weight maintenance. In addition, we expect to find that the physiological adaptations encouraging weight regain are no different following rapid or slow weight loss, and that there will be no reversal of these adaptations over a three-year period. We propose that some psychological characteristics could influence the success of weight loss maintenance.

3.1 Specific Hypotheses to be tested:

1. The rate of weight loss will not impact on the capacity to maintain the lost weight.

2. Physiological adaptations will not be different between rapid and slow weight loss groups.

3. Physiological adaptations encouraging weight regain do not reverse with long-term maintenance of weight loss.

4. Behavioural changes will not differ significantly between the slow and rapid weight loss groups throughout the 3 years of follow-up.

4. OVERALL AIM

The overall aim of this study is to compare the long-term weight outcomes achieved by two different rates of weight loss. This aim will be accomplished through three specific experimental aims.

4.1 Specific Aims

Aim 1: To compare the weight outcome at three years following rapid or slow weight loss. Obese subjects will be randomly assigned to either a rapid or a gradual weight loss program. The primary end-point of the study is the weight loss maintained at three years.
**Aim 2:** To compare short and long term physiological adaptations following weight loss at two different rates.

Following weight loss, peripheral hormones and circulating nutrient levels change in a direction that favours weight regain. This research will explore whether circulating nutrients and hormone levels, and ratings of hunger and satiety, both in the fasting state and postprandial state, differ in relation to different rates of weight loss and weight maintenance periods.

**Aim 3:** To determine the impact of personality, social functioning and motivation to the maintenance of weight loss at two different rates.

We will examine if there are any subject characteristics that predict successful weight maintenance. In addition, we will assess if personality and social behaviours enable some subjects to achieve greater success on particular types of weight loss program.

### 5. STUDY DESIGN

The study is a randomised non-blinded dietary intervention trial in two phases. Phase 1 refers to the weight loss phase where all participants will be placed on either a rapid weight loss program (12 weeks in duration) or a gradual weight loss program (36 weeks in duration). Phase 2 refers to the weight maintenance phase where eligible participants will placed on a weight maintaining diet for 3 years following phase 1.

**5.1 Phase 1:**

Following the on-site screening appointment all successfully screened subjects will be randomised to either the rapid or gradual weight loss group.

**Rapid Weight Loss Group:** Participants will consume a commercially available very low energy diet (VLED) preparation (Optifast®) (Nestlé Nutrition, Vevey, Switzerland) for 12 weeks. Up to three meals a day will be replaced with Optifast®, with 2 cups of vegetables per day. The use of one teaspoon of oil daily will be encouraged to stimulate contraction of the gall bladder and reduce the risk of gall stone formation [51]. This diet contains from 1845 and 3280 KJ (450 and 800 Kcal) per day. Subjects will be required to lose at least 15 ± 2% of their body weight (approximately 1.5kg/week) over the 12 week period. Individuals randomised to this group will have a total of 6 consultations with a dietitian.

**Gradual Weight Loss Group:** Participants will be instructed to undergo a weight loss program based on recommendations in the Australian Guide to Healthy Eating (15% protein, 25-30% (or less) fat and 55-60% carbohydrates) [52], with at least one daily meal replaced with an Optifast® VLED preparation. A daily energy deficit of 1700 to 2100kJ (400 to 500kcal) will be recommended, with a minimum intake of 5,000 kilojoules a day. Subjects are required to lose at least 15 ± 2% of their body weight (approximately 0.5kg/week) over a 36-week period. Individuals randomised to this group will have a total of 18 consultations with a dietitian.
Appointments will be at the same interval with similar quality of dietary education materials for all subjects. Projected weight-loss graphs will be personalised to each participant and utilised at each visit to compare expected and actual weight-loss achieved at each time point. Both the rapid and gradual weight loss group will have prescriptions for the same overall energy deficit (430,500 kJ or 105,000 kcal). The rapid weight loss group will be asked to accumulate the deficit over 12 weeks while the gradual weight loss group will accumulate the same deficit over 36 weeks. In both treatment groups, participants will be instructed to undertake at least 30 minutes a day of mild to moderate intensity exercise (e.g. brisk walk).

Participants will attend fortnightly for individual consultations with the same qualified dietitian. During these visits, anthropometry measurements will be taken and dietary counselling given based on their individual needs in order to remain on their projected curve and achieve their target weight of 15 ± 2% weight loss (See Table 2 for detailed schedule of procedures).

**Note:** Successful participants in phase 1 will be defined as participants who achieve greater than 13% weight loss in the allocated time. Participants who do not achieve at least 15± 2% weight loss on phase 1 will be excluded from the second phase of the study. These participants will be regarded as exclusions rather than withdrawals or dropouts. These patients will be offered on-going group assistance and support at the Austin Health Obesity Clinic.

Excluded participants will be contacted by telephone 3 years post completion of phase 1 (39 or 45 months following commencement of rapid or gradual weight loss diet respectively) and asked to return to the clinic for a follow-up appointment. During this follow-up appointment weight, blood pressure and other anthropometric measurements will be recorded as shown in Table 2.

### 5.2 Phase 2:

All participants who successfully achieved 15 ± 2% weight loss in phase 1 will be eligible to enter into phase 2 of the trial. During phase 2, participants will follow a weight maintenance diet which has been individualised for each participant and similar to the Australian Guidelines for Healthy Eating [52]. Individual sessions will be conducted with the study dietitian quarterly for three years following phase I. Shown in Table 2 are the procedures performed at each visit during phase 2.

### 6. VISITS

#### 6.1 Baseline/Long Visits

At the baseline visit (long visit 1, LV1), measurements of anthropometry will be taken, visual analogue scale (VAS) completed and blood sampling taken (following an overnight fast from 10pm the night before). Participants will then have a standardised breakfast meal followed by blood samples for measurements of glucose, insulin, CCK, ghrelin and leptin at 15, 30, 60, 120, 180, and 240 minutes. Hunger, satiety, and desire to eat will be assessed by a validated visual analogue scale questionnaire (VAS) [53] at the same time points. During the baseline visit, participants will also complete the psychological and food frequency questionnaires. LV2 will occur at the completion of the weight loss phase (month 3 or 9 depending...
on the diet allocated). LV3-5 will occur during phase 2 (weight maintenance period) annually for 3 years.

6.2 Short visits

During short visits, the subjects will be weighed using the bioelectrical impedance analysis (BIA), waist to hip ratio will be measured and they will be given dietary advice, encouragement and support. The short visits will be a one on one session with the dietitian.

7. SUBJECTS

Participants will be assessed at the clinical research unit (CRU) in the Department of Medicine at the Heidelberg Repatriation Hospital. Recruitment may also involve advertisement in local community newspapers. Potentially eligible participants will be invited to attend a screening visit. Once the patient has understood the plain language statement and agrees to participate in the trial, they will be asked to sign the consent form approved by Austin Health Human Research Ethics Committee. Subsequently, a detailed screening examination will be performed (visit 0), where a medical history taken by the a study investigator with weight and height recorded. Blood will also be drawn for thyroid function test (TSH,T3,T4), blood glucose, and a dietitian review will be conducted. Participants will be contacted by telephone within two weeks to confirm their eligibility for the trial.

7.1 Inclusion criteria

The criteria for inclusion in the trial are:
- Healthy men and women aged 18-70 years with a desire to lose weight
- Weight stable for 3 months
- BMI \( \geq 30 \text{kg/m}^2 \) and \( \leq 45 \text{kg/m}^2 \)

7.2 Exclusion criteria

- Pregnancy or breast-feeding
- History of surgical procedures or laxative abuse for weight loss
- The use of any VLCD or weight lowering drugs in the past three months
- Inability to attend scheduled examinations and visits
- For females taking an oral contraceptive pill or hormone replacement: dose must have been stable for the past three months
- For participants receiving thyroid hormone replacement: dose must have been stable for the past three months
- Surgical intervention planned during the study
- Any recent (less than six months) cessation of smoking and current smokers
- Participation in another study, or administration of any investigational drug in the past three months
- Uncontrolled and clinically significant disease or known malignancy that could interfere with the study conduct
• Presence of any clinically significant renal or endocrine disease (including diabetes) according the Investigator or as revealed by screening blood tests
• Use of anti-depressant and antiepileptic medications known to have weight gaining effect (refer to Appendix 1)
• Subjects with known history of alcoholism or drug abuse or dependence within 1 year prior to screening
• Subjects who were obese in early childhood will be excluded to avoid monogenetic obesity

8. DATA COLLECTION

The data collected at each visit are presented in Table 2.

8.1 Anthropometry

At each visit, bioelectrical impedance analysis (BIA) will be used to measure body composition (BIA; Tanita TBF-300, W.W. Wedderburn Pty. Ltd, Sydney, Australia) using the standard adult mode of measurement. The BIA method measures body weight, total body water and estimates fat mass and fat-free mass (the sum of muscle, bone, tissue, water and other fat free mass) in the body. The method uses a foot-foot pressure contact to measure electric current conductance and impedance to derive total body water. From this measure an algorithm incorporating sex, age height and total body mass is used to calculate fat mass (FM) and fat-free mass (FFM).

All measurements will be taken after an overnight fast, barefoot, wearing light clothing and having just emptied the bladder. Waist (at umbilicus) and hip (at greater trochanters) circumferences will be measured to the nearest 0.5 cm using a spring-loaded tape measure. Blood pressure will be measured with a manual sphygmomanometer, after participants are seated for at least 5 min. Height, waist and hip circumference, and blood pressure will be measured in duplicate and recorded as the mean of the two values.

8.2 Blood analyses

Thyroid function: A blood sample will be collected at screening for thyroid-stimulating hormone (TSH, thyrotropin), free thyroxine (FT4), and free triiodothyronine (FT3). Screened participants with abnormal thyroid function will be excluded.

Clinical Chemistry: A total of 7 bloods samples (8ml of blood x 7 samples, totalling 56ml of blood) will be drawn at baseline, at the end of the weight loss period (12 or 36 weeks) and at years 1 and 3 during phase 2 (shown in Table 2). Fasting bloods will be collected to measure insulin, ghrelin, leptin, 3-β-hydroxybutrate (3HB) and glucose at approximately 15 minutes before the start of a standardised breakfast meal. Breakfast will be consumed within 20 minutes and blood samples will be collected at 15, 30, 60, 120, 180, 240 minutes after the completion of the meal for the measurement of insulin, ghrelin and glucose.
At each time point, the 8ml of blood will be divided over three tubes: 4ml was transferred into an Ethylenediaminetetraacetic acid (EDTA), plasma tube (VACUETTE® K3E K3EDTA, 6ml, Greiner Bio-One GmbH, Austria); another 2ml will be transferred into a lithium heparin plasma tube (VACUETTE®LH Lithium Heparin, 4ml, Greiner Bio-One GmbH, Austria); and the remaining 2ml will be transferred into a plasma tube with an inhibitor (pefabloc; described in detail below) added into the tube in advance (VACUETTE®K3E K3EDTA, with inhibitor, 3ml, Greiner Bio-One GmbH, Austria).

All samples will be processed to obtain blood plasma by centrifugation (4°C, 3,500 rpm, 15min), and will be frozen and stored at -80°C until further analysis. These samples will be batched for analyses to maximise the capacity of diagnostic kits, and to minimise inter-assay error.

Circulating nutrients and hormones: Hormones investigated for this study are ghrelin, leptin, and insulin. The first plasma EDTA tube will be used to analyse for leptin and the second lithium heparin plasma tube is to be used to analyse for plasma glucose and insulin. The inhibitor added into the third plasma tube outlined above will be Roche Pefabloc (Pefabloc SC, AEBSF, 4-2-Aminoethyl-(benzenesulfonyl fluoride hydrochloride, Roche Applied Science, Indianapolis, USA) to detect ghrelin.

Biochemical Assays: Fasting and postprandial plasma active ghrelin concentrations will be measured using the Ghrelin (Active) Radioimmunoassay (RIA) Kit (Millipore, Billerica, MA). The sensitivity of this assay is 7.8-2000pg/ml. Intra-assay and inter-assay variation is 6.7-9.5% and 9.6-13.7% respectively. Plasma insulin will be measured by commercial radioimmunoassay (Millipore, Billerica, MA). The sensitivity of the plasma insulin assay is 2–200 µU/mL. Intra-assay and inter-assay variation of this assay are 2.2-4.4% and 2.0-6.0% respectively. Plasma leptin will also be measured by commercial radioimmunoassay (Millipore, Billerica, MA). The sensitivity of this assay is 0.5–100 ng/mL. Intra-assay and inter-assay variation of this assay are 3.4-8.3% and 3.6-6.2% respectively. Glucose will be measured using the glucose oxidase method (Analox Glucose Reagent for Analox Analysers, Analox Instruments Ltd, London). 3-β-hydroxybutrate (3HB) will be measured using an enzymatic assay (3-β-hydroxybutrate II reagent for GM7 Series Analysers, Analox Instruments Ltd, London).

Additional testing: A subset of approximately 40 of the 200 patients randomised onto the trial will have fasting blood collected when they reach 5% and 10% weight loss in either the rapid or gradual weight loss group. These extra samples are to measure fasting insulin, 3HB, glucose, FFA, ghrelin, leptin, CCK, PYY and other gut hormones.

8.3 Breakfast Meal Testing

The breakfast meal will consist of a boiled egg (60g), 2 x white toast (tip top Sunblest sandwich loaf) with margarine (10g Flora, original), orange juice (200g Daily Juice, no added sugar), 2 weetbix (Sanitarium) with milk (120g Full cream), The energy and
macronutrient content of the breakfast meal, determined by Food Works Professional is shown below:

<table>
<thead>
<tr>
<th>High Fat Breakfast Meal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Content (kJ)</td>
<td>2000</td>
</tr>
<tr>
<td>Protein (percentage energy)</td>
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</tr>
<tr>
<td>Total Fat (percentage energy)</td>
<td>25</td>
</tr>
<tr>
<td>Carbohydrate (percentage energy)</td>
<td>53</td>
</tr>
</tbody>
</table>

The breakfast meal will be prepared on the morning of testing, consumed within 20 min. No other food or beverage (except water) is to be offered throughout the testing period.

8.4 Food Frequency Questionnaire (FFQ)

The Cancer Council Victoria Food Frequency Questionnaire (CCVFFQ) will be used to assess usual dietary intake. The CCVFFQ is an optically scannable, semi-quantitative questionnaire designed for a culturally diverse Australian population [54] and will be given to subjects both before and after their allocated weight loss program as well as at 1, 2, and 3 years follow up (shown in Table 2). The subjects will be given verbal and written instructions on how to complete the CCVFFQ. Nutrient intake values, glycaemic index and glycaemic load will be calculated using the Australian NUTTAB95 nutrient composition database.

8.5 Psychological Questionnaires

At long visits (LV), participants will complete the following validated questionnaires: The Big Five Inventory (to assess personality type); Social Provisions Scale (to assess social supports); The Ways of Coping Checklist- Revised WCCL-R (to assess coping skills); The Weight Locus of Control Scale (to assess perceived locus of control) and the Three Factor Eating Questionnaire (to assess eating behaviours). These tests will be repeated at yearly intervals for the duration of the study (as shown in Table 2).

8.6 Physical Activity Record

A pedometer will be given to all participants. The pedometer will be covered so the subject is blinded to how many steps they have done. The pedometer will be worn by the subject for a week at a time, one week prior to commencing the weight loss program, at the completion of the weight loss program, and at 1, 2, and 3 years follow up. Energy expenditure will also be assessed using a well-established Stanford 7-day physical activity recall [55]. This survey will be given to subjects at the same time points as the pedometer (shown in Table 2).

8.7 Visual Analogue Scale (VAS)

At all long visits (LV), participants will complete the VAS at baseline and at 15, 30, 60, 120, 180, 240 minutes in order to measure appetite ratings.
9. STATISTICAL ANALYSES:

Our experience and the literature indicates a 50% attrition rate for each group is a realistic outcome, along with a weight regain standard deviation of 7kg. Based on these figures, we have calculated that, 200 individuals are required at baseline for a “completers only” equivalence test comparing mean weight regain between the two groups to achieve a power of approximately 0.9 with a significance level of 0.05. The power is based on the assumption of normal data, equivalence between the two groups and where non-equivalence is rejected when the two-sided 95% t-interval for the difference in mean weight regain falls completely within the bounds ± 5kg.

Subjects will be randomized to the rapid and gradual weight loss groups using a randomized block design with random block sizes of 2, 4 and 6 that accounts for potential confounding factors gender (Male or Female), age (≤ 40, > 40 years) and BMI (< 35, ≥ 35kg/m²).

A research assistant located away from the clinic and not involved with the study will hold the randomisation list and under the supervision of the study statistician allocated participants to treatment groups. The research assistant will keep the randomisation sequence private, only revealing a treatment allocation after receiving information demonstrating that the participant is eligible and had consented to the trial. Investigators (other than the study statistician) will not have access to the randomisation list at any time during the duration of the trial.

Statistical analysis will include completers only analysis and primary intention to treat analysis using the return to baseline approach and last observation carried forward approach.

End point comparisons will be carried out using two-sample and paired t-tests or, when necessary, the non-parametric Wilcoxon signed-rank and Mann-Whitney tests. Equivalence tests with a null hypothesis of non-equivalence with suitably chosen equivalence margin will be employed when equivalence is expected. Bonferroni correction will be utilized when making multiple comparisons. In the presence of confounding factors unable to be accounted for in the randomized block design, analysis of covariance will be used for endpoint comparisons between the two groups to account for these factors.

Successful weight maintenance will be defined as an individual not regaining more than 50% of weight lost at the end of the dietary phase. Logistic regression will be used to model successful weight maintenance based on diet group, gender, age, weight loss at the end of the diet phase and appropriate baseline measurements such as BMI.

Generalized linear models will be used to test the effects of personality and social activity on weight maintenance where dietary group and sex are included as fixed effects and baseline measurements such as weight and age and weight loss at the end of the diet phase may be included as covariates. Chi-square tests of independence will also be considered to test independence between successful weight maintenance and personality and social factors.
10. OUTCOMES AND SIGNIFICANCE:

If the study shows that the rate of weight loss is not important to the long-term success of weight maintenance and that the physiological adaptations are the same, it may change the way we approach treatment of obesity. For example, the Austin Health Obesity Weight Control Clinic’s protocol is based on a rapid and large weight loss using a VLED, followed by behaviour modification and (if needed) pharmacotherapy to control hunger. If indeed slow weight loss were superior for long-term weight maintenance, the protocol would need to be changed. If not, VLEDs could be used more widely to rapidly achieve significant weight loss. In addition, this three-year study will determine if the physiological adaptations that occur with weight loss are maintained, or if in fact they reverse over time. Evidence of persistent adaptations (over a three-year period) will provide the empirical evidence required to justify long-term pharmacotherapy to promote weight loss maintenance.
## Table 2 Schedule of Procedures

### Rapid Weight Loss Group

<table>
<thead>
<tr>
<th>Visit</th>
<th>0</th>
<th>1</th>
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<tr>
<td>Visit Length (L=long, S=short)</td>
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<td>L</td>
<td>S</td>
<td>S</td>
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<td>S</td>
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<td>S</td>
<td>S</td>
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### Gradual Weight Loss Group

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<td>0</td>
<td>0.5</td>
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<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Visit Length (L=long, S=short)</td>
<td>S</td>
<td>L</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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### Informed Consent

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### Medical and Weight History

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### Blood Collection

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### Sampling for hormone assays

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### Food Frequency Questionnaire

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### Physical activity record

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### Dietitian Review

|          | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

### Weight and waist/hip circumference

|          | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

### Vital Signs

|          | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

### Dispensing of Optifast

|          | X | X | X | X | X | X | X | X | X | X | X | X |

### Visual Analogue Scale

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<th>X</th>
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</thead>
</table>

### Bioelectrical Impedance Surveys

|          | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

### Adverse Event Monitoring

|          | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

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Version 5, Date 13th of July 2013
Footnotes

1 Informed consent to be obtained prior to performing any study-related assessments;
2 Only fasting measurements to be collected;
3 Fasting and postprandial measurements to be collected after a standard breakfast meal;
4 TSH, T₃, T₄ and blood glucose only collected at this visit;
5 This includes administration of the Stanford 7-day physical activity record as well as pedometers to give to participants 1 week prior to these visits and total steps to be recorded for the 7 days prior to appointment;
6 Includes: heart rate and blood pressure;
7 5 x Psychological Questionnaires;
8 Recording and grading of adverse events to commence following signing of the consent;
9 Excluded participants will be asked to return to the clinic to collect these measurements at 3 years post phase 1.
11. REFERENCES


Appendix 1

Exclusionary Concomitant Medications

<table>
<thead>
<tr>
<th>Antidepressants known to have weight gain effect</th>
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</thead>
<tbody>
<tr>
<td>1. Selective serotonin reuptake inhibitors (SSRIs)</td>
</tr>
<tr>
<td>• Paroxetine</td>
</tr>
<tr>
<td>• Fluoxetine hydrochloride</td>
</tr>
<tr>
<td>• Fluvoxamine maleate</td>
</tr>
<tr>
<td>2. Monamine Oxidase Inhibitors</td>
</tr>
<tr>
<td>3. Mirtazapine</td>
</tr>
<tr>
<td>4. Tricyclic Antidepressants:</td>
</tr>
<tr>
<td>• Clomipramine</td>
</tr>
<tr>
<td>• Imipramine</td>
</tr>
<tr>
<td>• Amitriptyline</td>
</tr>
<tr>
<td>• Doxepin Hydrochloride</td>
</tr>
<tr>
<td>• Dothiepin Hydrochloride</td>
</tr>
<tr>
<td>• Nortiptyline Hydrochloride</td>
</tr>
<tr>
<td>5. Buspirone Hydrochloride</td>
</tr>
<tr>
<td>6. Venlafaxine hydrochloride</td>
</tr>
<tr>
<td>7. Mianserin hydrochloride</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Antiepileptic drugs causing change in weight</th>
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</thead>
<tbody>
<tr>
<td>1. Topiramate</td>
</tr>
<tr>
<td>2. Sodium valproate</td>
</tr>
<tr>
<td>3. Zonisamide</td>
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Author/s: 
Purcell, Katrina

Title: 
A randomised controlled trial investigating the impact of the rate of weight loss on long term weight maintenance

Date: 
2014

Publication Status:

Persistent Link: 
http://hdl.handle.net/11343/41262

File Description: 
Supplementary material - Protocol