The effect of rate of weight loss on long-term weight management: a randomised controlled trial

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Summary

Background Guidelines recommend gradual weight loss for the treatment of obesity, indicative of a widely held opinion that weight lost rapidly is more quickly regained. We aimed to investigate the effect of the rate of weight loss on the rate of regain in obese people.

Methods For this two phase, randomised, non-masked, dietary intervention trial in a Melbourne metropolitan hospital, we enrolled 204 participants (51 men and 153 women) aged 18–70 years with a BMI between 30 and 45 kg/m². During phase 1, we randomly assigned (1:1) participants with a block design (block sizes of 2, 4, and 6) to account for sex, age, and BMI, to either a 12-week rapid weight loss or a 36-week gradual programme, both aimed at 15% weight loss. We placed participants who lost 12.5% or more weight during phase 1 on a weight maintenance diet for 144 weeks (phase 2). The primary outcome was mean weight loss maintained at week 144 of phase 2. We investigated the primary outcome by both completers only and intention-to-treat analyses. This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000190909.

Findings 200 participants were randomly assigned to the gradual weight loss (n=103) or rapid weight loss (n=97) programme between Aug 8, 2008, and March 9, 2010. After phase 1, 51 (50%) participants in the gradual weight loss group and 76 (81%) in the rapid weight loss group achieved 12.5% or more weight loss in the allocated time and started phase 2. At the end of phase 2, both gradual weight loss and rapid weight loss participants who completed the study (n=43 in gradual weight loss and n=61 in rapid weight loss) had regained most of their lost weight (gradual weight loss 71.2% regain, 95% CI 58.1–84.3 vs rapid weight loss 70.5%, 57.8–83.2). Intention-to-treat analysis showed similar results (gradual weight loss 76.3% regain, 95% CI 65.2–87.4 vs rapid weight loss 76.3%, 65.8–86.8). In phase 2, one participant in the rapid weight loss group developed cholecystitis, requiring cholecystectomy. In phase 2, two participants in the rapid weight loss group developed cancer.

Interpretation The rate of weight loss does not affect the proportion of weight regained within 144 weeks. These findings are not consistent with present dietary guidelines which recommend gradual over rapid weight loss, based on the belief that rapid weight loss is more quickly regained.

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Introduction

During the past decade, the prevalence of obesity has increased significantly, and it now represents a major health problem in both low-income and high-income countries.1 Dietary weight loss is generally unsuccessful in the long-term,2,3 and optimum non-invasive methods to achieve and maintain weight loss remain elusive. Guidelines worldwide recommend gradual weight loss for the treatment of obesity,4–6 reflecting a widely-held opinion that rapid weight loss is associated with poorer long-term outcomes than is gradual weight loss. This notion probably stems from the belief that obesity is caused by bad social habits and that gradual weight loss allows more time to change such habits. The widespread belief in the superiority of gradual over rapid weight loss has recently been questioned,7,8 and scientific evidence does not support the superiority of a gradual approach in achieving or maintaining weight loss.9 Findings of a non-randomised study9 showed that participants who lost weight rapidly achieved and maintained greater weight loss than did those who lost weight gradually. However, individuals who chose rapid weight loss might have been more motivated than those who did not.

We aimed to investigate whether the rate of weight loss affects the rate of regain, and whether weight loss-induced changes in circulating appetite-mediating hormones and subjective appetite are affected by the rate of weight loss.

Methods

Study design and participants We did a two-phase, randomised, non-masked, dietary intervention trial between August, 2008, and July, 2013, in a Clinical Research Unit at a Melbourne metropolitan hospital.

We recruited volunteers using radio and newspaper advertisements and by word of mouth. Eligible patients at screening were obese (BMI 30·0–45·0 kg/m²), otherwise healthy, and aged between 18 and 70 years. Key

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exclusion criteria included use of a very low energy diet or weight loss drugs in the previous 3 months, pregnancy or lactation, smoking, current use of drugs known to affect bodyweight, previous weight loss surgery, and the presence of clinically significant disease (including diabetes). The appendix shows full inclusion and exclusion criteria. The trial protocol is available online.

The study was approved and monitored by the Austin Health Human Research Ethics Committee. Each participant provided written informed consent.

Randomisation and masking
In phase 1, we randomly allocated (1:1) patients to either a rapid or gradual weight loss programme. Randomisation was done with a computer-generated randomisation sequence with a block design accounting for the potential confounding factors of sex, age (≤40 and >40 years), and BMI (<35 and ≥35 kg/m²). A research assistant not involved with the study held the randomisation list and allocated participants to treatment groups under the supervision of the study statistician. Investigators (other than the study statistician) did not have access to the randomisation list at any time during the trial.

Laboratory staff were masked to treatment assignments (blood tubes were only numbered and had no other identifying information). Participants, dietitians, study investigators, and research staff who did the assessments were not masked to treatment assignments.

Procedures
In the rapid weight loss programme, participants consumed a commercially available very low energy diet preparation (Optifast, Nestlé Nutrition, Vevey, Switzerland) according to the manufacturer’s recommendations, for 12 weeks. This diet contains between 450 and 800 kcal per day. Three meals per day were replaced with Optifast, aiming for 15% weight loss (about 1·5 kg per week) during 12 weeks. In the gradual weight loss programme, participants consumed an energy-reduced diet (400–500 kcal per day deficit), on the basis of recommendations in the Australian Guide to Healthy Eating, with one to two Optifast meal replacements every day, with the aim of 15% weight loss during 36 weeks (roughly 0·5 kg per week).

All participants received meal replacements at no cost, were given similar dietary education materials, and had appointments with the same qualified dietitian every 2 weeks [six appointments for rapid weight loss and 18 for gradual weight loss participants during phase 1]. Personalised projected graphs to track expected and actual weight loss were drawn for every participant. Both groups were prescribed the same overall energy deficit (105000 kcal) during either 12 (rapid weight loss) or 36 (gradual weight loss) weeks. Adherence to the diets was estimated by the rate at which participants were losing weight. Participants who achieved 12·5% weight loss or more in the allocated timeframe were eligible to enter phase 2.

In phase 2, for 144 weeks, participants were instructed to follow an individualised diet for weight maintenance, based on the Australian Guide to Healthy Eating, and had individual sessions with the dietitian at weeks 4 and 12, and then every 12 weeks for 144 weeks. During these appointments, adherence to the diet was assessed with the participants’ self-reported food intake. Participants regaining their lost weight were advised to follow an energy-reduced diet (400–500 kcal per day deficit).

Throughout the study, all participants were instructed to undertake 30 min or longer per day of mild- to moderate-intensity exercise (eg, a brisk walk). The total study duration was 156 weeks (3·0 years) for rapid weight loss and 180 weeks (3·5 years) for gradual weight loss participants.

All measurements were taken after an overnight fast, barefoot, wearing light clothing, and having just emptied the bladder. We used bioelectrical impedance analysis to measure body composition (BIA, Tanita TBF-300, WW Wedderburn Pty, Sydney, Australia) with the standard adult mode of measurement. Waist (at umbilicus) and hip (at greater trochanters) circumferences were measured to the nearest 0·5 cm with a tape measure. We measured blood pressure with a manual sphygmomanometer, after participants were seated for at least 5 min. Subjective ratings of appetite were collected with a validated visual analogue scale.

Blood samples were stored at −80°C until analysis. We measured plasma total ghrelin and leptin concentrations with radioimmunoassay (Millipore, Billerica, MA, USA), and 3,β-hydroxybutyrate with an enzymatic assay (3,β-hydroxybutyrate II reagent for GM7 Series Analysers, Analox Instruments, London, UK). We measured physical activity with a pedometer (Piezoelectric G-Sensor Pedometer 2026, Guangdong, China), which was worn for 7 consecutive days. The appendix shows more details on methods.

Outcomes
The primary outcome was mean weight loss maintained at week 144 of phase 2. The results of this endpoint are reported as the difference between groups of weight regained in phase 2. Key secondary outcomes were mean difference in fasting ghrelin and leptin concentrations, and subjective appetite, all measured at baseline, end of phase 1 (week 12 for rapid weight loss and week 36 for gradual weight loss), and at weeks 48 and 144 of phase 2. Secondary outcomes not reported here were postprandial ghrelin and leptin concentrations; fasting and postprandial insulin, glucose, and cholecystokinin concentrations; and the effect of self-reported psychological factors on the maintenance of weight loss in the two groups. Key exploratory analyses were mean change in physical activity levels between groups at baseline, the end of phase 1 and weeks 48 and 144 of phase 2;
concentration of 3-β-hydroxybutyrate, which is related to ketone concentration in the blood, during phase 1 in a subset of 40 sequential participants at baseline, and after 5%, 10%, and 15% weight loss. To study the physiological changes induced by weight loss irrespective of the rate of weight loss, we combined data from completers of both groups in post-hoc analyses of changes in ghrelin and subjective hunger at the end of phase 1 and at weeks 48 and 144 of phase 2, and changes in leptin and ghrelin stratified according to percentage of lost weight regained at week 144 of phase 2. We recorded and graded adverse events for the duration of the trial.

**Statistical analysis**

On the basis of an expected 50% attrition rate during the trial,13 200 participants were needed at baseline to detect...
a between-group difference in mean weight regain of more than 5 kg with a power of 0.9 and significance level of 0.05.

We did analyses of bodyweight on two datasets: one for completers only, and one for intention to treat, in which missing data from participants who discontinued the study were replaced with baseline measures. We compared success rates between groups on the basis of intervals calculated with the Yates’ continuity correction. Probability of successful weight loss at the end of phase 1 was also modelled with a logistic regression analysis that adjusted for other potential contributing factors. To account for non-completers and other missing values, we did analysis of weight regain with linear mixed effects models, and adjusted for treatment group, age, sex, and weight loss at the end of phase 1. Data were assumed missing at random after adjusting for these covariates. We did sensitivity analyses to the missing data assumption both assuming 100% weight regain for non-completers, and with multiple imputation (20 imputations with chained equations in which linear regression analyses were applied to the imputed data sets at each time point followed by a pooling of results). We found no significant differences in these analyses, therefore we do not report the results here.

For analysis of small samples (ie, 3-β-hydroxybutyrate data and comparisons of data stratified according to percentage weight loss) and visual analogue scale scores, we did analyses of medians with Wilcoxon signed-rank tests or Wilcoxon rank-sum tests (for comparisons between groups). We used linear mixed effects to analyse percentage changes in fasting hormones in individuals who completed phase 1. A sensitivity analysis to missing data assumptions was done as above, with multiple imputation and adjusting for age and sex, and no differences in significance were detected. We analysed data with the free package R (version 2.15.0) and multiple imputation was done with the mice package.

The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000190909. Recruitment for a pilot study originally began on the Aug 8, 2008, when pilot studies did not require registration. Due to a misunderstanding between the first and senior authors, there was a delay in registering the study when funding was obtained to do the full 5 year trial.

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**Table 1: Baseline characteristics of participants entering the weight-loss phase and the subsequent weight-maintenance phase**

<table>
<thead>
<tr>
<th></th>
<th>All (n=200)</th>
<th>Rapid weight loss group (n=97)</th>
<th>Gradual weight loss group (n=103)</th>
<th>All (n=127)</th>
<th>Rapid weight loss group (n=76)</th>
<th>Gradual weight loss group (n=51)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td>49.6 (10.9)</td>
<td>50.1 (11.1)</td>
<td>49.7 (11.4)</td>
<td>49.8 (11.3)</td>
<td>49.6 (11.6)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>25.5%</td>
<td>26.8%</td>
<td>24.3%</td>
<td>28.3%</td>
<td>27.6%</td>
<td>29.4%</td>
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<td>Weight (kg)</td>
<td>96.8 (14.0)</td>
<td>96.4 (13.8)</td>
<td>97.2 (14.2)</td>
<td>97.0 (13.4)</td>
<td>97.0 (13.3)</td>
<td>97.0 (13.7)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>35.3 (3.8)</td>
<td>35.2 (3.7)</td>
<td>35.5 (4.0)</td>
<td>35.3 (3.9)</td>
<td>35.2 (3.7)</td>
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<td>Waist circumference (cm)</td>
<td>108.1 (10.3)</td>
<td>108.2 (10.6)</td>
<td>107.9 (10.0)</td>
<td>107.8 (10.2)</td>
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<td>Hip circumference (cm)</td>
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<td>118.3 (10.4)</td>
<td>118.7 (9.9)</td>
<td>117.8 (11.3)</td>
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<td>Systolic blood pressure (mm Hg)</td>
<td>131.0 (10.2)</td>
<td>130.4 (15.7)</td>
<td>131.5 (13.8)</td>
<td>131.3 (15.4)</td>
<td>130.3 (15.6)</td>
<td>132.8 (15.8)</td>
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<td>Diastolic blood pressure (mm Hg)</td>
<td>82.3 (9.0)</td>
<td>82.6 (9.3)</td>
<td>81.9 (8.8)</td>
<td>82.5 (9.5)</td>
<td>82.9 (8.9)</td>
<td>81.9 (10.4)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>49.7 (12.7)</td>
<td>48.5 (12.2)</td>
<td>50.9 (13.1)</td>
<td>49.1 (12.7)</td>
<td>48.7 (12.7)</td>
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<td>Fat-free mass (kg)</td>
<td>45.0 (12.4)</td>
<td>44.6 (12.6)</td>
<td>45.4 (12.3)</td>
<td>45.6 (12.6)</td>
<td>45.0 (12.9)</td>
<td>46.5 (12.2)</td>
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<tr>
<td>Daily steps</td>
<td>7319 (2819)</td>
<td>7107 (2599)</td>
<td>7530 (3023)</td>
<td>7344 (2550)</td>
<td>7150 (2397)</td>
<td>7643 (2268)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%).

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**Figure 2: Rate of weight loss during phase 1 for successful participants (mean % change, 95% CI)**

Successful participants were those who achieved at least 12.5% weight loss from baseline to end of phase 1.

*p=0.009; †p=0.0001.
Role of the funding source

The funders were not involved in the trial design, patient recruitment; data collection, analysis, interpretation, or presentation; writing or editing of the report; or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

204 participants were randomly assigned to either the rapid weight loss or gradual weight loss group; 200 participants started the diet (figure 1). Table 1 shows baseline characteristics of the two groups.

179 (89.5%) participants completed phase 1. Significantly more participants discontinued the gradual weight loss programme than the rapid weight loss programme (18 [18%] vs three [3%]; p=0.002). The main reason given for withdrawal in both groups was difficulty adhering to the diet.

Figure 2 shows mean rates of weight loss for participants who achieved 12.5% or more weight loss. Of those who completed phase 1, 76 of 94 (81%) rapid weight loss participants achieved 12.5% or more weight loss, compared with 53 of 85 (62%) gradual weight loss participants (p=0.009). Intention-to-treat analysis showed similar results (76 of 97 [78%] vs 53 of 103 [51%], p=0.0001). In those who achieved 12.5% or more weight loss, hip circumference decreased significantly more in the gradual weight loss group than in the rapid weight loss group (table 2; intention-to-treat results shown in appendix). We detected no significant differences between the changes in fat-free mass and fat mass, or other anthropometric measurements between the two groups. When predicting achievement of target weight (≥12.5% weight loss at the end of phase 1) with regression analysis, diet group remained a significant factor when adjusting for age, baseline weight, and sex (none of which were significant; data not shown).

In the gradual weight loss group, two participants achieved the weight loss goal by week 12 (rather than the allocated 36 weeks) and were therefore excluded, leaving 51 participants in the gradual weight loss group and 76 participants in the rapid weight loss group who started phase 2 (table 1). Attrition in phase 2 was not significantly different between groups (figure 1). With the exception of six participants (one in the gradual weight loss group and five in the rapid weight loss group), all participants started to regain their lost weight during phase 2 and were prescribed a 400–500 kcal per day energy deficit diet.

Figure 3 shows weight regain during phase 2. Study completers regained most of their lost weight (table 2). By week 144 of phase 2, average weight regain was 10.4 kg (95% CI 8.4–12.4; 71.2% of lost weight regained, 58.1–84.3) in gradual weight loss participants and 10.3 kg (8.5–12.1; 70.5%, 57.8–83.2) in rapid weight loss participants (difference between groups 0.09 kg, p=0.85).

<table>
<thead>
<tr>
<th>End of phase 1 for successful weight loss participants</th>
<th>End of phase 2 for all study completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=76)</td>
<td>(n=61)</td>
</tr>
<tr>
<td>Weight change from baseline (kg)</td>
<td>Rapid weight loss group</td>
</tr>
<tr>
<td></td>
<td>Gradual weight loss group</td>
</tr>
<tr>
<td></td>
<td>p value</td>
</tr>
<tr>
<td>-14.6 (-15.1 to -14.0)</td>
<td>-14.3 (-15.1 to -13.5)</td>
</tr>
<tr>
<td>BMI change from baseline (kg/m²)</td>
<td>Rapid weight loss group</td>
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<tr>
<td></td>
<td>Gradual weight loss group</td>
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<tr>
<td></td>
<td>p value</td>
</tr>
<tr>
<td>-5.3 (-5.5 to -5.1)</td>
<td>-5.2 (-5.5 to -5.0)</td>
</tr>
<tr>
<td>Change in waist circumference from baseline (cm)</td>
<td>Rapid weight loss group</td>
</tr>
<tr>
<td></td>
<td>Gradual weight loss group</td>
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<tr>
<td></td>
<td>p value</td>
</tr>
<tr>
<td>-15.5 (-16.7 to -14.3)</td>
<td>-16.2 (-17.6 to -15.0)</td>
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<tr>
<td>Change in hip circumference from baseline (cm)</td>
<td>Rapid weight loss group</td>
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<td></td>
<td>Gradual weight loss group</td>
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<tr>
<td></td>
<td>p value</td>
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<tr>
<td>-13.1 (-14.2 to -12.0)</td>
<td>-15.0 (-16.4 to -13.6)</td>
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<tr>
<td>Change in fat mass from baseline (kg)</td>
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<td></td>
<td>p value</td>
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<tr>
<td>-12.7 (-13.8 to -11.6)</td>
<td>-14.1 (-15.7 to -12.6)</td>
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</tbody>
</table>
| Change in fat free mass from baseline (kg)           | Rap...
95% CI –2.8 to 2.6; 0.72%; 95% CI -18.7–17.3). Weight was not significantly different between groups after week 48 of phase 2. When we assumed a return to baseline weight in those who discontinued the study during phase 2, there were no significant differences between groups in mean rate of regain or percentage of lost weight regained (mean regain at week 144 in gradual weight loss group 76.3%, 95% CI 65.2–87.4; rapid weight loss group 76.3%, 65.8–86.8; appendix). Adjustment for age and sex did not affect this outcome (data not shown). In phase 1, we detected no significant differences in body composition and anthropometric measurements between the rapid weight loss and gradual weight loss groups at the end of phase 2 (table 2; intention-to-treat results shown in appendix).

In a subgroup of 40 patients (20 in the gradual weight loss group and 20 in the rapid weight loss group) in whom 3-β-hydroxybutyrate was measured at 5% and 10% weight loss during phase 1, concentrations of this metabolite were significantly higher in the rapid weight loss group compared with the gradual weight loss group (figure 4). We detected no significant differences in 3-β-hydroxybutyrate at the end of phase 1 (mean 15% weight loss) between treatment groups.

Figure 5 shows changes in fasting hormone concentrations throughout the study, and table 2 shows changes from baseline. Leptin decreased during phase 1 in both groups, and the reduction in leptin at the end of phase 1 was more pronounced with rapid weight loss than gradual weight loss (p=0.03). Leptin concentrations rose in both groups during phase 2, and there was no difference in leptin between groups at weeks 48 and 144 of phase 2. A repeated measures analysis showed that leptin was not significantly different from baseline in either group at week 48 of phase 2 (gradual weight loss 18%, 95% CI –1.6 to 37.8, p=0.07 vs baseline; rapid weight loss –5.5%, 95% CI –21.5 to 10.5, p=0.50), although it was significantly increased at week 144 of phase 2 in both groups (gradual weight loss 23.2%, 95% CI 2.5–43.8, p=0.0280; rapid weight loss 43.6%, 26.7–60.5, p<0.0001). The groups were not significantly different in percentage change at either timepoint (week 48, –23.6%, 95% CI –49.0 to 1.9, p=0.06; week 144, 20.5%, –6.3 to 47.2, p=0.13). Irrespective of initial rate of weight loss, individuals who regained 75% or more of lost weight by week 144 (n=45) had large increases in leptin above baseline concentrations (median 43.4%, 95% CI 23.4–60.4), whereas in those who regained less than 25% of lost weight (n=15), leptin remained below baseline at week 144 (table 3).

Table 2 shows absolute changes in ghrelin. At all measured timepoints, mean fasting ghrelin values were not significantly different between groups. However, repeated measures analysis showed that ghrelin increased after weight loss and remained high during phase 2 (figure 5). Compared with baseline, in the rapid weight loss group, ghrelin concentrations were 40.0% (95% CI 26.7–53.4) higher at the end of phase 1, 21.7% (8.6–34.8) higher at week 48, and 15.5% (2.4–28.6) higher at week 144 of phase 2. Similarly, in the gradual weight loss group, we noted a 29.1% (13.2–45.1) increase after weight loss, and concentrations were 22.1% (6.1–38.0) higher at week 48 of phase 2. The increase in ghrelin from baseline at week 144 of phase 2 was not significant (10.1%, –5.8 to 26.0%) in the gradual weight loss group. When we combined data from both groups, ghrelin increased at the end of phase 1 (35% increase vs baseline, 95% CI 25.5–45.7), and decreased during phase 2, but still remained significantly higher than
baseline at weeks 48 (mean 21.9% higher, 95% CI 11.8–31.9, p=0.0001) and 144 weeks (mean 13.3% higher, 3.3–23.4, p=0.009). We recorded no significant differences in the change in ghrelin concentrations during phase 2 between participants with the most (>75%) and least (<25%) weight regain.

Although participants received the same exercise advice, mean daily steps increased significantly more during phase 1 in rapid weight loss participants than in gradual weight loss participants when all participants who completed phase 1 were included (rapid weight loss mean increase 2279 steps, 95% CI 1696–2861 vs gradual weight loss mean increase 1132, 279–1986; difference between groups 1147, 123–2170, p=0.02). We recorded no significant differences in average daily steps between rapid weight loss and gradual weight loss participants who lost 12.5% weight or more during phase 1 (table 2), or between successful and unsuccessful participants in either group at the end of phase 1 (data not shown). During phase 2, daily steps were not significantly different between the groups (table 2).

The appendix shows appetite ratings. The only significant difference in median appetite ratings between rapid weight loss and gradual weight loss participants was increased prospective consumption at the end of phase 1 in gradual weight loss participants. However, in view of the many tests, this finding might have arisen by chance. When we compared within-group changes from baseline, hunger ratings did not rise significantly during phase 1 in either group, and during phase 2, increased significantly at weeks 48 and 144 in rapid weight loss participants only. When data from both groups were combined, median hunger levels were significantly increased at the end of phase 1 compared with baseline (Hodges-Lehmann estimate 5, 95% CI 0.5–10.0, p=0.04), and at weeks 48 (10, 5.0–15.5, p=0.0002), and 144 (5.0, 1.0–11.0, p=0.02) of phase 2 (appendix).

During phase 1, one participant in the rapid weight loss group developed acute cholecystitis, and required cholecystectomy. After the procedure, she continued to spontaneously increase their activity compared with those in the gradual group. The clear-cut, prescriptive nature of the very low energy diet is simple because fewer choices have to be made than for a hypocaloric diet consisting of regular foods. A meal-replacement diet improves compliance and weight loss compared with an isonenergetic conventional diet. Moreover, as shown in a subgroup of participants, individuals who undertook the rapid diet had higher concentrations of 3-β-hydroxybutyrate during the weight loss phase than did those following the gradual diet. However, by the end of phase 1, this difference was not significant. Ketosis suppresses appetite, increases the satiety hormone cholecystokinin, and mitigates the rise in the orexigenic hormone ghrelin reported after weight loss, which raises the possibility that the rapid weight loss participants might have been less hungry during the weight loss phase than were those following the gradual diet.

Results of numerous studies have shown that after weight loss, concentrations of appetite-mediating hormones change, hunger increases, and energy

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**Discussion**

By contrast with the widely-held belief that weight lost rapidly is more quickly regained, our findings show that regain is similar after gradual or rapid weight loss. Moreover, achievement of a weight loss target was more likely and attrition was lower when weight loss was undertaken rapidly rather than gradually in phase 1. Several possible reasons exist for this finding. Rapid weight loss might motivate participants, which could explain why participants in the rapid group spontaneously increased their activity compared with those in the gradual group. The clear-cut, prescriptive nature of the very low energy diet is simple because fewer choices have to be made than for a hypocaloric diet consisting of regular foods. A meal-replacement diet improves compliance and weight loss compared with an isonenergetic conventional diet. Moreover, as shown in a subgroup of participants, individuals who undertook the rapid diet had higher concentrations of 3-β-hydroxybutyrate during the weight loss phase than did those following the gradual diet. However, by the end of phase 1, this difference was not significant. Ketosis suppresses appetite, increases the satiety hormone cholecystokinin, and mitigates the rise in the orexigenic hormone ghrelin reported after weight loss, which raises the possibility that the rapid weight loss participants might have been less hungry during the weight loss phase than were those following the gradual diet.
long-term use of appetite suppressants rather than on the amount of weight loss above that physiological adaptations to weight loss are long lasting. Our data should guide the option does not affect the rate of weight regain. Third, in individuals maintaining some weight loss without the use of pharmacotherapy. Additionally, for the first time, we show that this finding shows that a 15% weight loss can be achieved in about 80% of individuals only be registered if it can show 5% weight loss above placebo.

Our findings show that physiological adaptations encouraging weight loss, such as a rise in ghrelin concentration and hunger, persist for at least 3 years, even after most of the lost weight has been regained. Additionally, participants maintaining a substantial weight loss (eg, weight regain of <25% at the end of the trial) had a persistent reduction in fasting leptin concentration. By contrast, in individuals who regained most or all of their lost weight, mean leptin concentrations were higher at the end of phase 2 than at baseline. These data suggest that either leptin concentration rises to discourage an increase above baseline weight, or that more fat is regained than muscle. More research is needed to investigate this.

It would be impossible to obtain adequate obligatory micronutrients such as vitamins, minerals, and essential amino acids while achieving the caloric restriction needed for rapid weight loss if only normal food were ingested. Therefore, individuals undergoing rapid weight loss need to take properly formulated supplements. The safety of very low energy diets has been questioned; those used in the 1970s were dangerous and even led to fatalities. In the 1970s, more than 60 deaths were associated with a popular liquid protein diet that consisted entirely of solutions of collagen or gelatine hydrolysates. Post-mortem findings were consistent with the cardiac effects of protein-calorie malnutrition (which include myocardial atrophy, QT prolongation, and ventricular arrhythmias). However, increasing evidence suggests that modern very low energy diets, which are formulated with high quality protein and supplemented with micronutrients, are safe if used under supervision. In the present study, the only serious adverse event probably related to the dietary intervention was acute cholecystitis during phase 1 in a participant in the rapid weight loss group.

Although we did not do a cost-effectiveness analysis, a rapid weight loss programme is probably more economical than a gradual weight loss programme. The average cost of a dietitian consultation in Australia is roughly AUD$90. During the weight loss period of our study, the rapid group had six dietitian consultations ($540) and the gradual group had 18 ($1620). Because participants in both treatment groups received roughly 250 meal replacements (during 12 or 36 weeks), rapid weight loss was not only more successful, but also a more cost-effective approach.

A strength of our study was low attrition (22% compared with about 40% in studies of free-living participants with comparable durations). Of note, the health-care professionals involved in the trial were experienced in obesity treatment; therefore, the weight outcomes and participant retention might have been greater than those reported in other settings. The main weakness of our study was the exclusion of people who smoked, had diabetes, took weight-altering drugs, or were severely obese, which made our results difficult to generalise to the average patients seeking medical assistance with weight loss.

To achieve weight loss similar to what could be achieved with bariatric surgery, medical treatment will need to combine methods to reliably achieve, and maintain, substantial weight loss. Our findings show 12.5% or more weight loss is more achievable if undertaken rapidly. A strategy to suppress hunger after weight loss and therefore prevent weight regain, such as pharmacotherapy that has long-term safety and efficacy, is still awaited (panel).

Panel: Research in context

Systematic review
We searched PubMed on July 7, 2014, for randomised clinical trials published in English assessing the rate of weight loss on weight maintenance. We used the following search terms: “rate of weight loss”, “rapid or fast weight loss”, “gradual or slow weight loss”, “weight regain”, with no publication date parameter. We found no randomised clinical trials.

Interpretation
The standard way to achieve weight loss, as practised by dietitians and commercial weight loss companies, is to advise people to undertake lifestyle modification to reduce calorie intake and increase physical activity. Further, the general consensus is that weight loss should be gradual, with 0.5 kg per week as the rate generally advised. Additionally, pharmaceutical companies are focused on developing drugs that are designed to achieve weight loss. This situation shows both current practice and the FDA decree that a drug will only be registered if it can show 5% weight loss above placebo.

Our findings show that a 15% weight loss can be achieved in about 80% of individuals without the use of pharmacotherapy. Additionally, for the first time, we show that this option does not affect the rate of weight regain. Third, in individuals maintaining some weight loss, at 3 years ghrelin remains high and leptin remains low. This finding confirms that physiological adaptations to weight loss are long lasting. Our data should guide committees that develop clinical guidelines for the management of obesity to change their advice. Our data should also prompt regulatory authorities to focus on the safety of long-term use of appetite suppressants rather than on the amount of weight loss above placebo a drug can achieve.

Contributors
JP, PS, LAP, and KP designed the study. Data was collected by PS, CJB, JP, ED and KP, and analysed by LP and KP. KP, PS, LAP, and JP wrote the report (first draft written by KP). All authors vouch for the data and analysis, and agree with the decision to publish the report.

Declaration of interests
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study was not commercially sponsored, and there were no agreements regarding confidentiality of the data between the sponsor and the authors or their institutions.

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3 Ayyad C, Andersen T. Long-term efficacy of dietary treatment of obese participants on diet and exercise, and Nestlé Healthcare Nutrition Australia technical assistance, and dietitian Jodie Prendergast for counselling regarding confidentiality of the data between the sponsor and the study was not commercially sponsored, and there were no agreements.


Weight loss: slow and steady does not win the race

In *The Lancet Diabetes & Endocrinology*, Katrina Purcell and colleagues report the results of a trial showing that weight regain is similar after gradual or rapid weight loss. Their study has implications for people seeking weight loss treatment and professionals who provide such treatment. In this two-part trial done in Australia, 200 obese individuals were randomly assigned to one of two diets in phase 1. The rapid weight loss group used a very low calorie diet (total 450–800 kcal/day) for 12 weeks. The gradual weight loss group used a low calorie diet (reduction in food intake by 400–500 kcal/day) for 36 weeks. Both diets targeted 15% weight loss. At the end of phase 1, participants who achieved a target of ≥12.5% bodyweight loss continued into a 144 week weight maintenance phase (phase 2).

Findings of the study showed that the initial rate of weight loss in phase 1 did not affect the amount or rate of weight regain in phase 2: completers in both groups regained about 71% of lost weight by week 144 of phase 2. The results of this study provide additional information about very low and low calorie diets that should be considered when establishing the best diet for a patient. First, in both phases of the trial, fewer participants dropped out early in the rapid weight loss group than in the gradual weight loss group. Second, during phase 1, more participants in the rapid weight loss group achieved the target weight loss of 12.5% or more than in the gradual weight loss group (81% vs 62%). Thus, despite having far less time to achieve the same energy deficit, more participants in the rapid weight loss group achieved the desired goal. Third, serum ghrelin concentrations increased during weight loss in both groups and remained increased 144 weeks later, perhaps indicative of the physiological adaptations believed to hinder long-term weight loss success for most individuals making efforts to overcome obesity. After weight loss, hunger increased in the entire cohort, and remained high at 144 weeks, although investigators recorded no consistent evidence that one group had larger changes in subjective appetite ratings than the other.

Although both groups had similar weight regain, patients in the rapid weight loss group, who used a very low calorie diet in phase 1, had a better outcome (albeit in the short-term) compared with those in the gradual weight loss group, who used a low calorie diet.

As the researchers point out, very low calorie diets can encourage adherence, weight loss, and retention. Very low calorie diets restrict food variety, which promotes greater satiety and less food intake compared with diets that have more food variety. Additionally, rapid weight loss on very low calorie diets is presumably intrinsically rewarding and builds self-efficacy because behaviour change is proximally associated with a large and meaningful reward. Finally, very low calorie diets are not complex to follow, have simple rules, limit choice, and essentially eliminate the need for participants to measure or estimate portion size, an endeavour associated with error.

Very low calorie diets are formulated better now to provide adequate protein and essential micronutrients than they were when first introduced decades ago, and are regarded as safe when given under expert supervision. However, these diets are still associated with some risks—eg, fatigue, constipation, and gallstones—and are not appropriate for all patients. 2013 guidelines for the management of overweight and obesity in adults from the American Heart Association, the American College of Cardiology, and the Obesity Society recommend that very low calorie diets be used sparingly and for short durations when medical supervision and an intensive lifestyle modification programme can be provided. The risks of very low calorie diets should be considered and weighed against potential benefits to assess the best course of treatment for a patient.

The weight maintenance intervention provided in the trial by Purcell and colleagues, in the form of sporadic individual sessions with a dietician and additional counselling for individuals who started to regain weight, was clearly ineffective. This finding is consistent with most low-key weight maintenance interventions. As results of the Look AHEAD trial showed, even with very intensive lifestyle interventions that combine diet, exercise, and behaviour therapy, all provided at no-cost to participants, weight regain is inevitable. Pharmacotherapy could be a consideration when weight regain is recorded after initial weight loss with a dietary intervention.

In conclusion, the study by Purcell and colleagues suggests that for weight loss, a slow and steady...
approach does not win the race, and the myth that rapid weight loss is associated with rapid weight regain is no more true than Aesop’s fable. Clinicians should bear in mind that different weight loss approaches might be suitable for different patients in the management of clinical obesity, and that efforts to curb the speed of initial weight loss might hinder their ultimate weight loss success.

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