

# Weight loss, weight maintenance, and adaptive thermogenesis.

Citation for published version (APA):

Camps, S. G., Verhoef, S., & Westerterp, K. R. (2013). Weight loss, weight maintenance, and adaptive thermogenesis. *American Journal of Clinical Nutrition*, 97(5), 990-994.  
<https://doi.org/10.3945/ajcn.112.050310>

## Document status and date:

Published: 01/05/2013

## DOI:

[10.3945/ajcn.112.050310](https://doi.org/10.3945/ajcn.112.050310)

## Document Version:

Publisher's PDF, also known as Version of record

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# Weight loss, weight maintenance, and adaptive thermogenesis<sup>1–3</sup>

Stefan GJA Camps, Sanne PM Verhoef, and Klaas R Westerterp

## ABSTRACT

**Background:** Diet-induced weight loss is accompanied by adaptive thermogenesis, ie, a disproportional or greater than expected reduction of resting metabolic rate (RMR).

**Objective:** The aim of this study was to investigate whether adaptive thermogenesis is sustained during weight maintenance after weight loss.

**Design:** Subjects were 22 men and 69 women [mean  $\pm$  SD age: 40  $\pm$  9 y; body mass index (BMI; in kg/m<sup>2</sup>): 31.9  $\pm$  3.0]. They followed a very-low-energy diet for 8 wk, followed by a 44-wk period of weight maintenance. Body composition was assessed with a 3-compartment model based on body weight, total body water (deuterium dilution), and body volume. RMR was measured (RMRm) with a ventilated hood. In addition, RMR was predicted (RMRp) on the basis of the measured body composition: RMRp (MJ/d) = 0.024  $\times$  fat mass (kg) + 0.102  $\times$  fat-free mass (kg) + 0.85. Measurements took place before the diet and 8, 20, and 52 wk after the start of the diet.

**Results:** The ratio of RMRm to RMRp decreased from 1.004  $\pm$  0.077 before the diet to 0.963  $\pm$  0.073 after the diet ( $P < 0.001$ ), and the decrease was sustained after 20 wk (0.983  $\pm$  0.063;  $P < 0.01$ ) and 52 wk (0.984  $\pm$  0.068;  $P < 0.01$ ). RMRm/RMRp was correlated with the weight loss after 8 wk ( $P < 0.01$ ), 20 wk ( $P < 0.05$ ), and 52 wk ( $P < 0.05$ ).

**Conclusion:** Weight loss results in adaptive thermogenesis, and there is no indication for a change in adaptive thermogenesis up to 1 y, when weight loss is maintained. This trial was registered at clinicaltrials.gov as NCT01015508. *Am J Clin Nutr* 2013;97:990–4.

## INTRODUCTION

The increasing prevalence of obesity and its comorbidities is one of the major health problems in our modern world (1). Although weight-loss strategies target both sides of energy balance, intake and expenditure, the success of long-term weight-loss maintenance is low (2, 3). Adaptive thermogenesis, which is described as a decrease in energy expenditure beyond what can be predicted by the loss of fat-free mass (FFM)<sup>4</sup> and fat mass (FM), could be an important factor that compromises the maintenance of a reduced body weight. In origin, this metabolic adaptation is a biologically meaningful survival mechanism that conserves energy in the face of starvation and dangerously low energy supplies (4, 5).

Studies performed in lean and obese subjects have shown significant reductions in energy expenditure during and shortly after weight loss, to values below predictions based on weight loss and body-composition changes (6–14). Leibel et al (6) showed that a weight loss of 10% was accompanied by a reduction in resting metabolic rate (RMR) of 0.57 MJ/d below

what was predicted from the relation of energy expenditure to FFM and FM at baseline in the same obese subjects. Doucet et al (7) showed similar results. They used a regression equation relating RMR of control participants to their FFM and FM in a context of weight stability to predict RMR after weight loss. Already after 2 wk of energy restriction, RMR was observed to decrease by 0.47 and 0.64 MJ/d more than predicted, and this difference was 0.96 and 0.61 MJ/d by week 8, respectively, in men and women. Once body weight stability was reached at the end of the program at  $\sim$ 10% weight loss, RMR remained below predicted values in men but not in women. Astrup et al (14) conducted a meta-analysis on a large sample of data on RMR in formerly obese subjects and never-obese control subjects. They showed that, after differences in body size and composition were taken into account, formerly obese subjects had a 3–5% lower RMR than did never-obese control subjects. Moreover, there is proof for a longer-term disproportionate reduction in energy expenditure, even up to 6 y (15, 16). Van Gemert et al (15) followed subjects who underwent vertical gastric banding and found a disproportional reduction in RMR of 0.44 MJ/d after 36 mo at an average weight loss of 40%.

A sustained adaptive thermogenesis favors a positive energy balance during weight maintenance and may predispose to weight regain. The aim of this study was to quantify adaptive thermogenesis after 8 wk of a very-low-energy diet (VLED) and how this adaptation evolved during 1 y of follow-up. Adaptive thermogenesis was assessed from a comparison between measured and predicted RMR, where the RMR prediction equation included FFM and FM as independent variables (17).

## SUBJECTS AND METHODS

### Subjects

Ninety-one healthy subjects (69 women and 22 men) with a mean  $\pm$  SD age of 40  $\pm$  9 y and with a mean  $\pm$  SD BMI (in

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<sup>4</sup> Abbreviations used: FFM, fat-free mass; FM, fat mass; RMR, resting metabolic rate; RMRm, measured resting metabolic rate; RMRp, predicted resting metabolic rate; VLED, very-low-energy diet.

Received August 31, 2012. Accepted for publication January 22, 2013.

First published online March 27, 2013; doi: 10.3945/ajcn.112.050310.

kg/m<sup>2</sup>) of  $31.9 \pm 3.0$  (**Table 1**) were recruited by advertisements in local newspapers and on notice boards at the university. They underwent an initial screening that included measurements of body weight and height and the completion of a questionnaire on general health. All were in good health, not using medication (except for contraception), nonsmokers, and at most moderate alcohol consumers. They were weight stable as defined by a weight change  $<5$  kg for  $\geq 3$  mo before the study. The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and the procedures were approved by the Ethics Committee of the Maastricht University Medical Centre. Written informed consent was obtained from all participants.

### Study design

The study covered a full year, starting with a VLED for 8 wk followed by a 44-wk period of weight maintenance (**Figure 1**). Subjects came to the university for measurements on 4 occasions: the day before the start of the diet (baseline), 8 wk after the start of the diet (end of the diet), 20 wk after the start of the diet, and 52 wk after the start of the diet. On each occasion, measurements included RMR followed by body composition and were performed from 0800 in the morning onward in the fasting state.

### RMR

To reach the university for RMR measurements, subjects were instructed to travel by public transport or by car to avoid physical activity that would increase RMR. After arrival, they rested on a bed for 30 min, which was followed by 30 min of RMR measurements in the supine position with the use of an open-circuit ventilated-hood system (18). Gas analyses were performed with a paramagnetic oxygen analyzer (Servomex type 1158; Crowborough) and an infrared carbon dioxide analyzer (Servomex type 1520), whereas flow was kept at a constant rate of 80 L/min and was additionally measured as described by Schoffelen et al (19). The within individual CV for this system is  $3.3 \pm 2.1\%$  (18). Calculation of RMR from measured oxygen consumption and carbon dioxide production was based on Brouwer's formula (20).

### Body composition

Height was measured at screening to the nearest 0.1 cm with the use of a wall-mounted stadiometer (model 220; Seca). Body composition was determined according to Siri's 3-compartment model based on body weight, body volume, and total body water (21). Body weight was measured by using a calibrated scale (Life Measurement Corporation). Body volume was measured via air-displacement plethysmography with the BodPod System (Life Measurement Corporation) (22, 23). Total body water was determined by using deuterium dilution during the preceding night, according to the Maastricht protocol (24). BMI was calculated by dividing body weight by height squared (kg/m<sup>2</sup>).

### Diet

The weight-loss diet (Modifast; Nutrition et Santé Benelux) was followed for 8 wk. The diet was a protein-enriched formula

**TABLE 1**  
Subject characteristics<sup>1</sup>

	Women (n = 69)	Men (n = 22)
Age (y)	39 ± 10	44 ± 7
Weight (kg)	89.0 ± 10.0	103.6 ± 13.0
Height (m)	1.67 ± 0.05	1.81 ± 0.08
BMI (kg/m <sup>2</sup> )	32.1 ± 3.1	31.0 ± 2.5

<sup>1</sup>All values are means ± SDs.

that provided 2.1 MJ/d (51.9 g protein, 50.2 g carbohydrates, and 6.9 g lipids) and a micronutrient content that met the Dutch recommended daily allowance. The VLED was provided to the subjects as sachets with powder. Each sachet represented 1 meal, and 3 sachets were consumed every day. Besides the provided meal replacements, subjects were allowed to eat vegetables when feeling hungry. Subjects were instructed to mix the powder with the amount of water indicated on the packages and were advised to drink water sufficiently throughout the diet period.

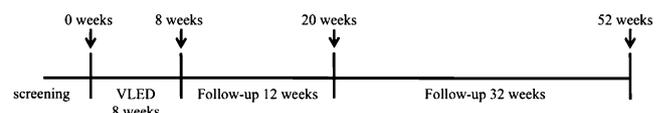
### Calculations and statistical analysis

In addition to the measurement of RMR (RMR<sub>m</sub>) with the ventilated-hood system, RMR was predicted (RMR<sub>p</sub>) with the following equation:  $\text{RMR}_p (\text{MJ/d}) = 0.024 \times \text{FM} (\text{kg}) + 0.102 \times \text{FFM} \times (\text{kg}) + 0.85$  (17). Because FM and FFM are used to calculate RMR<sub>p</sub>, the equation can be used independently for sex. Adaptive thermogenesis was calculated as RMR<sub>m</sub> divided by RMR<sub>p</sub>. The obtained ratio was then compared between the different time points. A value  $>1$  indicates that measured RMR is higher than what is expected based on body composition, and a value  $<1$  indicates that measured RMR is lower than what is expected based on body composition. One-factor repeated-measures ANOVA with Bonferroni adjustment for multiple comparisons and a 1-factor between-group ANCOVA with weight-loss percentage as covariate were used to compare the ratios across 0, 8, 20, and 52 wk. The data were analyzed by using SPSS 20.0 (SPSS Inc). All data are presented as means ± SDs.

## RESULTS

### Body composition

After the 8-wk VLED, weight loss averaged  $9.6 \pm 4.1$  kg ( $P < 0.001$ ; **Table 2**). After 20 and 52 wk, there still was a significant average weight loss compared with baseline:  $8.5 \pm 5.3$  kg ( $P < 0.001$ ) and  $6.0 \pm 5.7$  kg ( $P < 0.001$ ), respectively (**Figure 2**). As a percentage of the starting weight, subjects had lost an average of  $10.3 \pm 4.4\%$  ( $P < 0.001$ ) after the 8-wk VLED. Weight loss was  $9.1 \pm 5.7\%$  ( $P < 0.001$ ) after 20 wk and was  $6.5 \pm 6.1\%$  ( $P < 0.001$ ) after 52 wk. There was large



**FIGURE 1.** Flow chart of the 1-y program the subjects followed; the measurement points are indicated. VLED, very-low-energy diet.

**TABLE 2**  
Subject characteristics at baseline after 8 wk of a VLED and after 20 and 52 wk of weight maintenance<sup>1</sup>

	Baseline (n = 91)	8 wk (n = 91)	20 wk (n = 91)	52 wk (n = 91)
Weight (kg) <sup>2</sup>	92.9 ± 12.6	83.3 ± 11.4***	84.5 ± 12.4***	87.5 ± 13.4***
FM (kg) <sup>2</sup>	38.7 ± 7.2	30.9 ± 6.9***	31.2 ± 7.2***	33.7 ± 7.8***
FFM (kg) <sup>2</sup>	54.2 ± 10.1	52.4 ± 9.8***	53.3 ± 10.3*	53.8 ± 9.9*
RMRm (MJ/d) <sup>2</sup>	7.31 ± 1.04	6.64 ± 0.88***	6.92 ± 1.05***	6.97 ± 1.00***
RMRp (MJ/d) <sup>2</sup>	7.29 ± 1.03	6.91 ± 0.97***	7.04 ± 1.04***	7.12 ± 1.01***
RMRm/RMRp <sup>2</sup>	1.004 ± 0.077	0.963 ± 0.073**	0.983 ± 0.063*	0.984 ± 0.068*
RMRm/RMRp adjusted <sup>3</sup>		0.967 ± 0.007*	0.985 ± 0.007*	0.979 ± 0.007*

<sup>1</sup> One-factor repeated-measures ANOVA with Bonferroni adjustment was used for multiple comparisons, and a 1-factor between-group ANCOVA with weight-loss percentage as covariate was used to compare the ratios across 0, 8, 20, and 52 wk. \**P* < 0.05 compared with baseline. \*\**P* < 0.01 compared with baseline. \*\*\**P* < 0.001 compared with baseline. FFM, fat-free mass; FM, fat mass; RMRm, measured resting metabolic rate; RMRp, predicted resting metabolic rate; VLED, very-low-energy diet.

<sup>2</sup> Values are means ± SDs.

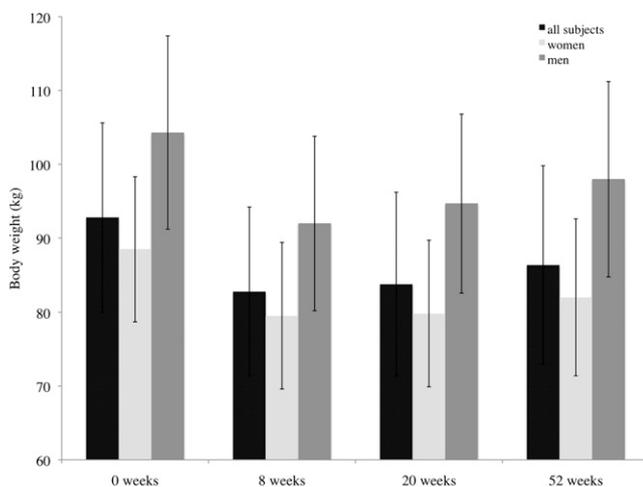
<sup>3</sup> Values are means ± SEs and were adjusted for the percentage weight loss.

interindividual variation in weight loss, which indicated a difference in the success of weight loss and of maintaining the lost weight.

## RMR

RMRm decreased significantly from  $7.31 \pm 1.04$  MJ/d at baseline to  $6.64 \pm 0.88$  MJ/d after the VLED ( $P < 0.001$ ; Table 2). The decrease in RMRm compared with baseline was also observed after 20 wk ( $6.92 \pm 1.05$  MJ/d;  $P < 0.001$ ) and after 52 wk ( $6.97 \pm 1.00$  MJ/d;  $P < 0.001$ ). The decrease in RMRm was expected, because body weight was reduced at all time points compared with baseline. Thus, the expected decrease in energy expenditure was observed in the predicted RMR as well. RMRp decreased significantly ( $P < 0.001$ ) from baseline ( $7.29 \pm 1.03$  MJ/d) to after the VLED ( $6.91 \pm 0.97$  MJ/d). After 20 wk ( $7.04 \pm 1.04$  MJ/d;  $P < 0.001$ ) and 52 wk ( $7.12 \pm 1.01$  MJ/d;  $P < 0.001$ ), the RMRp was also lower than at baseline. A comparison of RMRm with RMRp at baseline showed that the ratio of RMRm to RMRp was  $1.004 \pm 0.077$  on average. Values were highly correlated ( $R^2 = 0.72$ ,  $P < 0.001$ ) and confirmed the validity of the prediction equation for the subject group under

study. One-factor repeated-measures ANOVA and ANCOVA with control for percentage weight loss were used to compare the average ratios across 8, 20, and 52 wk to baseline. The ratio decreased significantly to  $0.963 \pm 0.073$  after the VLED ( $P < 0.01$ ). In addition, after 20 wk ( $0.983 \pm 0.063$ ;  $P < 0.05$ ) and 52 wk ( $0.984 \pm 0.068$ ;  $P < 0.05$ ), the ratio was still lower in comparison with the ratio at baseline. No significant difference ( $P = 0.206$ ) was found between the ratios after 8, 20, and 52 wk after control for percentage weight loss. In addition, adjusted means delivered by ANCOVA with control for percentage weight loss, differences across 8, 20, and 52 wk confirmed these results (Table 2). RMRm/RMRp showed a large interindividual variation, and individual values were related to percentage weight loss (Figure 3). No sex differences in the change of RMRm/RMRp were observed over time. A correlation was observed between the ratio and percentage weight loss after 8 wk ( $R^2 = 0.47$ ,  $P < 0.05$ ), 20 wk ( $R^2 = 0.52$ ,  $P < 0.05$ ), and 52 wk ( $R^2 = 0.60$ ,  $P < 0.05$ ), which indicated that subjects with a larger percentage weight loss had a proportionally larger reduction in RMR. In addition, the reduction in RMR, as indicated by the slope and intercept of the regression lines, was similar after 8, 20, and 52 wk.

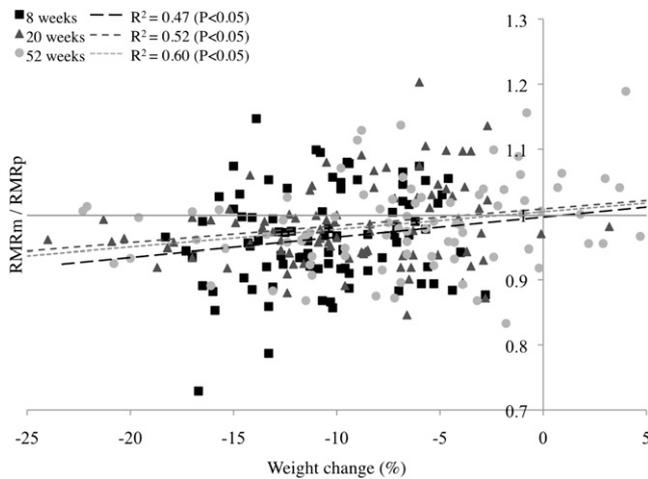


**FIGURE 2.** Mean ( $\pm$ SD) body weight at 0, 8, 20, and 52 wk of the 1-y study. The black bars represent the average body weight of all subjects, the light-gray bars of women ( $n = 69$ ), and the dark-gray bars of men ( $n = 22$ ).

## DISCUSSION

Measurement of energy expenditure and body composition before and after an 8-wk VLED and during and after a 44-wk period of follow-up showed that adaptive thermogenesis develops during weight loss and that it is sustained up to 44 wk when body weight is maintained below the initial prediet weight. In addition, a significant correlation was found between the adaptive thermogenesis and percentage weight loss after 8, 20, and 52 wk, which indicated that subjects with a larger weight loss showed a greater reduction in RMR and that, in the case of unsuccessful maintenance of the lost weight and a return to or beyond the starting weight, adaptive thermogenesis is no longer observed.

Consequent to the changes in body composition, RMRp and RMRm decreased after the diet. However, the observed reduction of RMRm was 0.27 MJ/d beyond the calculated reduction of RMRp, which indicated that moderate weight loss is accompanied by adaptive thermogenesis. This agrees with the results that have been described before in the literature (6–14). Furthermore, the



**FIGURE 3.** Correlation of RMRm/RMRp against weight loss at 8 wk (black squares), 20 wk (dark-gray triangles), and 52 wk (light-gray circles) after the start of the very-low-energy diet. RMRm/RMRp is correlated with weight loss after 8 wk ( $R^2 = 0.47$ ,  $P < 0.05$ ), 20 wk ( $R^2 = 0.52$ ,  $P < 0.05$ ), and 52 wk ( $R^2 = 0.60$ ,  $P < 0.05$ ). One-factor repeated-measures ANOVA with Bonferroni adjustment for multiple comparisons and 1-factor between-groups ANCOVA were used to compare the ratios across 0, 8, 20, and 52 wk ( $n = 91$ ). RMRm, measured resting metabolic rate; RMRp, predicted resting metabolic rate.

observed disproportional decrease of RMRm after the VLED was correlated with the percentage weight loss, which showed that subjects with greater weight loss had more adaptive thermogenesis. Although adaptive thermogenesis acts in response to energy restriction to slow weight loss, subjects with the greatest adaptation had the greatest weight loss. This supports the suggestion that compliance with and the energy restriction itself play a role in the amount of weight loss and that the amount of weight loss determines the degree of adaptive thermogenesis (25). In 1995, Leibel et al (6) suggested that the maximal adaptation to the maintenance of a reduced body weight was already attained at a 10% weight loss. This could not be confirmed by our data, in which adaptive thermogenesis correlated with weight loss up to 25% in a linear way.

During and after 44 wk of follow-up after 8 wk of a VLED, RMRm was still disproportional decreased, extending the knowledge about sustained adaptive thermogenesis shown previously by Van Gemert et al up to 6 y but after severe weight loss (>50 kg) by means of gastric banding (15) and by Rosenbaum et al up to just 7 wk of follow-up after 10% weight loss (26). Contrary to Doucet et al (7), who showed a sustained adaptive thermogenesis only in men and not in women up to 4 wk after weight loss, we found a sustained disproportional reduction of RMRm independent of sex. Moreover, the same correlation between the lost weight and adaptive thermogenesis that was obtained after the VLED was found up to 44 wk after weight loss, which indicated that when weight is still below the initial weight from before the diet, adaptive thermogenesis is sustained. At the same time, this indicates that, in the case of unsuccessful maintenance of the lost weight and a return to the starting weight, the adaptive thermogenesis is no longer observed. The disproportionate reduction in energy expenditure favors a positive energy balance during weight maintenance and may predispose to weight regain and could be one of the factors contributing to the high recidivism to obesity (2, 3).

A limitation of this study was that diet and physical activity were not standardized during the 44 wk of follow-up. On the other hand, because of the absence of advice on diet and physical activity, this study reflects achievements in free-living conditions. Another limitation of this study was generated by the large interindividual variation in the results. However, the observed variation allowed adaptive thermogenesis to be correlated to a wide range from unsuccessful to successful weight maintenance during follow-up. One of the major advantages with regard to other studies was the 44 wk of follow-up to investigate sustained thermogenesis after moderate weight loss.

For future research, it is important to elucidate metabolic, neuroendocrine, autonomic, and behavioral changes involved in the adaptive responses, distinct from changes in body weight per se (27). Changes in leptin (26, 28), insulin (29), and thyroid hormones (10, 26, 30, 31), as well as changes in sympathetic tone (30–32), have been shown to be associated with a disproportional reduction in energy expenditure induced by weight loss.

In conclusion, our study showed that moderate weight loss induced by energy restriction leads to a disproportional reduction in RMR. In addition, adaptive thermogenesis was not only observed after the diet, but it was sustained up to 44 wk of follow-up and was positively correlated with the amount of lost weight. As a consequence, adaptive thermogenesis favors a positive energy balance during weight maintenance and may increase the risk of weight regain.

The authors' responsibilities were as follows—KRW and SPMV: designed the study; SGJAC and SPMV: collected the data; SGJAC: analyzed the data and wrote the manuscript; and KRW: supervised the study, contributed to the interpretation of the data, and reviewed the manuscript. All authors read and approved the final manuscript. None of the authors had any conflicts of interest.

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