

## Long-term changes in energy expenditure and body composition after massive weight loss induced by gastric bypass surgery<sup>1-4</sup>

Sai Krupa Das, Susan B Roberts, Megan A McCrory, LK George Hsu, Scott A Shikora, Joseph J Kehayias, Gerard E Dallal, and Edward Saltzman

### ABSTRACT

**Background:** Little is known about the determinants of individual variability in body weight and fat loss after gastric bypass surgery or about the effects of massive weight loss induced by this surgery on energy requirements.

**Objectives:** The objectives were to determine changes in energy expenditure and body composition with weight loss induced by gastric bypass surgery and to identify presurgery predictors of weight loss.

**Design:** Thirty extremely obese women and men with a mean ( $\pm$ SD) age of  $39.0 \pm 9.6$  y and a body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) of  $50.1 \pm 9.3$  were tested longitudinally under weight-stable conditions before surgery and after weight loss and stabilization ( $14 \pm 2$  mo). Total energy expenditure (TEE), resting energy expenditure (REE), body composition, and fasting leptin were measured.

**Results:** Subjects lost  $53.2 \pm 22.2$  kg body weight and had significant decreases in REE ( $-2.4 \pm 1.0$  MJ/d;  $P < 0.001$ ) and TEE ( $-3.6 \pm 2.5$  MJ/d;  $P < 0.001$ ). Changes in REE were predicted by changes in fat-free mass and fat mass. The average physical activity level (TEE/REE) was 1.61 at both baseline and follow-up ( $P = 0.98$ ). Weight loss was predicted by baseline fat mass and BMI but not by any energy expenditure variable or leptin. Measured REE at follow-up was not significantly different from predicted REE.

**Conclusions:** TEE and REE decreased by 25% on average after massive weight loss induced by gastric bypass surgery. REE changes were predicted by loss of body tissue; thus, there was no significant long-term change in energy efficiency that would independently promote weight regain. *Am J Clin Nutr* 2003;78:22-30.

**KEY WORDS** Obesity, weight loss, energy expenditure, fat mass, fat-free mass, body water, gastric bypass surgery, energy requirements

### INTRODUCTION

The prevalence of extreme obesity has increased 3-fold over the past 4 decades, and as many as 6 million Americans are now classified as being extremely obese, ie, having a body mass index (BMI; in  $\text{kg}/\text{m}^2$ )  $\geq 40$  (1). A more recent report suggests that the prevalence rates of this population continue to rise (2). Persons this severely obese often have a long history of excess weight, of repeated failures with traditional weight-loss methods, or both, and gastric bypass surgery is increasingly being viewed as a

useful treatment option for achieving sustainable weight loss. However, relatively little is known about the long-term effects of weight loss induced by gastric bypass surgery on energy requirements or about the reasons for the observed substantial variability in weight loss between patients.

Studies that examined changes in energy requirements with moderate weight loss showed that active weight loss is associated with decreases in total energy expenditure (TEE) (3-8) and resting energy expenditure (REE) that are disproportionately large relative to the loss of body tissues (3, 7, 9-12). However, the extent to which these changes persist after weight restabilization remains controversial. Some studies have suggested that there is a persistent decrease in energy expenditure after moderate weight loss (9, 13, 14), whereas other studies showed no such changes (15-19). The question of whether there is a persistent decrease in energy expenditure after substantial weight loss is also controversial, primarily because most of the studies of this issue (8, 20-23) have had a very small number of subjects, failed to adequately account for the expected decrease in energy expenditure due to losses of fat, fat-free mass (FFM) (24-28), or both.

There is also a lack of information on why gastric bypass surgery causes some patients to lose much more weight than others (29, 30) and on whether it is possible to identify presurgical predictors of weight loss that could help identify those patients who are likely to obtain the maximum benefit from gastric bypass surgery. The potential predictors of weight loss are TEE, REE, and leptin, which have been suggested to predict weight loss in several (23, 31-36), although not all (17, 37), previous studies.

<sup>1</sup> From the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston (SKD, SBR, MAM, JJK, GED, and ES), and the Tufts-New England Medical Center Hospital, Boston (LKGH, SAS, and ES).

<sup>2</sup> The contents of this publication do not necessarily reflect the views or policies of the US Department of Agriculture.

<sup>3</sup> Supported by NIH grants MH/DK54092-01A3, M01-RR00054 (provided to the New England Medical Center General Clinical Research Center through the National Center for Research Services), by grant P30 DK 46200 (provided to the Boston Obesity Nutrition Research Center), and by the US Department of Agriculture Agricultural Research Service under contract 53-3K06-5-10.

<sup>4</sup> Address reprint requests to SB Roberts, Energy Metabolism Laboratory, Room 608, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, 711 Washington Street, Boston, MA 02111. E-mail: susan.roberts@tufts.edu.

Received February 13, 2002.

Accepted for publication December 3, 2002.

We therefore conducted a study to determine the magnitude of changes in TEE and components of energy expenditure with massive weight loss and subsequent weight restabilization in subjects undergoing gastric bypass surgery. We also examined the utility of several baseline variables—including body composition, energy expenditure (TEE, REE, and substrate oxidation), and fasting leptin concentrations—for predicting body weight and fat loss in individual subjects.

## SUBJECTS AND METHODS

### Subjects

The subjects were 30 adults (24 women and 6 men aged  $39.0 \pm 9.6$  y;  $\bar{x} \pm SD$ ) who underwent gastric bypass surgery for weight reduction at the Tufts–New England Medical Center Hospital and participated in both baseline and follow-up (after weight loss and weight restabilization) investigations. Persons were ineligible for the study if they had diabetes, cancer, coronary heart disease, endocrine disorders, or other acute or chronic diseases or if they were using medication known to influence energy expenditure. The ratio of women to men admitted to the study (5:1) was similar to the ratio of those seeking gastric bypass surgery. Of the 36 subjects studied at baseline, 6 subjects (all women) did not return for follow-up (1 did not undergo gastric bypass surgery, 2 became pregnant, 1 had burn injuries, and 2 relocated), which resulted in a study population of 30. Measurements were conducted at the Clinical Study Unit (CSU) of Tufts–New England Medical Center Hospital and at the Jean Mayer US Department of Agriculture Human Nutrition Research Center at Tufts University. The study was approved by the Human Investigation Review Committee of Tufts University and Tufts–New England Medical Center Hospital. All subjects gave written informed consent before participating.

### Study protocol

All subjects were initially tested before gastric bypass surgery and then were retested after weight loss and weight restabilization. To determine weight stabilization, subjects weighed themselves at home or at other ambulatory sites 3 times/wk in the fasting state in the month before testing. Subjects who were not weight stable (defined as a weight within 2.3 kg of initial weight) during this period (at baseline and  $\approx 12$  mo after gastric bypass surgery) were monitored further until the defined weight stability was achieved. The average time from gastric bypass surgery to weight stability was  $14 \pm 2$  mo.

The study was conducted over a 15-d period at both time points, ie, at baseline and follow-up. Subjects were free-living, except for 3 overnight inpatient stays for measurements including REE and the thermic effect of food (TEF). The subjects were admitted to the CSU on the day before the start of the study. After the subjects fasted overnight, TEE was measured by using the doubly labeled water method and REE was also measured, which were followed by a 4-h TEF measurement. Body composition was also measured as described below. Subjects then returned home with instructions on how to collect daily urine samples for the measurement of TEE. They were readmitted on days 7–8 for additional body-composition testing and other measurements, after which they returned home for the rest of the week and continued the urine collections at home. Finally, subjects returned to the CSU on the evening of day 14, and a second REE measurement was made on the morning

of day 15. Fasting blood samples were obtained on days 1 and 15, and food-frequency, physical activity, and other questionnaires were also completed as summarized below.

### Total energy expenditure

A 15-d doubly labeled water study was conducted to measure TEE. On day 1, subjects were given a mixed dose of doubly labeled water ( $^2\text{H}_2^{18}\text{O}$ ) containing 0.1 g  $\text{H}_2^{18}\text{O}$  and 0.07 g  $^2\text{H}_2\text{O}$  per kg body weight. The dose was administered orally after the subjects had fasted overnight and collected a baseline urine sample early in the morning. Subjects remained in the CSU while the urine specimens were collected every hour for 5 h after administration of the doubly labeled water. Baseline and 5-h postdose urine samples were used for analysis and calculations.

The subjects were carefully instructed on how to collect and freeze the second void of the day while at home on subsequent days; the urine samples collected on days 1, 8, and 15 at the CSU were supervised. All urine samples were stored at  $-20^\circ\text{C}$  until analyzed.

Urinary isotope enrichment was measured with a Hydra gas isotope ratio mass spectrometer (PDZ Europa Ltd, Cheshire, United Kingdom) according to the method of Prosser and Scrimgeour (38) with a slight modification involving the use of a gas autosampler with a specially designed flushing needle (PDZ Europa Ltd) to introduce the equilibration gas. For the  $^2\text{H}_2\text{O}$  analysis, platinum was used as a catalyst. The tubes were filled with gas (carbon dioxide gas for  $\text{H}_2^{18}\text{O}$  and hydrogen gas for  $^2\text{H}_2\text{O}$ ) by using a flushing needle and were then equilibrated (overnight for  $\text{H}_2^{18}\text{O}$  and 3 d for  $^2\text{H}_2\text{O}$ ). After equilibration, the tubes were loaded on a second autosampler, on which gas from each tube was sequentially allowed to flow into a stream of helium gas (dried by magnesium perchlorate) and analyzed for isotopic abundance.  $^2\text{H}_2\text{O}$  and  $\text{H}_2^{18}\text{O}$  were analyzed in triplicate in urine samples collected at baseline, 5 h postdose, and 2, 4, 6, 8, 10, 14, and 15 d postdose.

TEE was calculated according to standard procedures (39), with a correction for isotopic fractionation in adults (40) and with the use of a constant dilution space ratio as suggested by Racette et al (41). In these calculations, the individual values for food quotient (FQ) used to convert measured carbon dioxide production ( $\dot{V}\text{CO}_2$ ) rates to TEE were obtained from a food-frequency questionnaire (42). It should be noted that, although underreporting of energy intake is a common concern in studies involving obese subjects, inaccurate FQ values introduce only very small errors into the calculation of TEE (43). Non-resting energy expenditure (NREE) was calculated as the difference between TEE and REE (described below). Activity energy expenditure (AEE) was calculated as the difference between TEE and the sum of REE and the group mean TEF (described below). Mean rather than individual TEF values were used to reduce the effect of variability in individual TEF measurements on subsequent calculations.

### Resting energy expenditure and the thermic effect of food

REE was measured on 2 mornings (days 1 and 15) after the subjects had fasted overnight for 12 h at the CSU. Measurements were made by indirect calorimetry (Deltatrac portable metabolic cart; SensorMedics Corp, Yorba Linda, CA) with subjects resting supine in comfortable thermoneutral conditions. The calorimeter was calibrated with a standard gas mixture (96%  $\text{O}_2$  and 4%  $\text{CO}_2$ ) before each test, and standard alcohol burn tests were conducted periodically to ensure the accuracy of the calorimeter ( $\pm 1\%$ ). Subjects were instructed to relax and avoid hyperventilating, fidgeting, and sleeping during measurements, and oxygen consumption

( $\dot{V}O_2$ ) and  $\dot{V}CO_2$  were measured every minute for 30 min. REE was calculated according to Weir's equation (44) with the use of mean  $\dot{V}O_2$  and  $\dot{V}CO_2$  values. After the assessment of REE on day 1, TEF was measured for 4 h after the consumption of 400 mL of a mixed liquid meal (Pediasure, FQ = 0.88; Abbott Laboratories, Abbott Park, IL), which provided 1.67 MJ energy as 43.9 g carbohydrate (44% of energy), 12.0 g protein (12% of energy), and 19.9 g fat (44% of energy) over 20 min. TEF was calculated as the increase in energy expenditure above REE and was expressed as a percentage of the meal ingested. At follow-up, some subjects were not able to consume all 400 mL of the test meal during the allotted time period because of sensations of fullness or gastrointestinal discomfort. In these cases ( $n = 7$ ), the actual amount of the meal that was consumed was used in the calculations. REE at follow-up was also predicted for each subject by using the standard equations adopted by the World Health Organization and US recommended dietary allowances (45, 46).

### Body composition

The Siri 3-compartment model was used to estimate percentage body fat in most of the subjects at baseline and follow-up. The formula for the Siri 3-compartment model (47) incorporates total body water and body density, which was determined by air-displacement plethysmography (48, 49). This method has been validated for use in extremely obese subjects (50). Total body water was determined from  $H_2^{18}O$  dilution, which was measured as part of the determination of TEE. FFM was calculated as the difference between body weight and fat mass. At baseline, air-displacement plethysmography measurements were not obtained in 6 subjects, and in these cases fat mass was predicted from  $H_2^{18}O$ -dilution values [the correlation between air-displacement plethysmography and  $H_2^{18}O$  dilution for fat mass is  $r = 0.997$  ( $P < 0.001$ ) and for FFM is  $r = 0.995$  ( $P < 0.001$ )]. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer, and weight was measured to the nearest 100 g with a calibrated scale (model CN-20, DETECTO; Cardinal Scale Manufacturing Co, Webb City, MO). Waist circumference was measured at the level of the umbilicus, and hip circumference was measured as the maximal circumference at the level of the buttocks.

### Fasting biochemical measures

Biochemical measures were determined in fasting blood samples collected at baseline and follow-up. Serum reverse triiodothyronine ( $rT_3$ ) was measured with the  $^{125}I$  radioimmunoassay (RIA kit; BioChem ImmunoSystems, Cortland Manor, NY). Thyroxine and thyroid hormone binding ratio were analyzed with the Cloning Enzyme Donor Immuno Assay with the use of Beckman Synchrony LX Systems (Beckman Instruments Inc, Fullerton, CA). Thyrotropin and free thyroxine were analyzed with the Microparticle Enzyme Immuno Assay by using the AXSYM System (Abbott Laboratories). Fasting plasma leptin concentrations were measured with a sensitive commercial double-antibody RIA (Human leptin specific RIA kit; Linco Research, Inc, St Louis) that detects relatively low leptin concentrations (0.5 ng/mL).

### Self-reported activity questionnaires (leisure and occupational)

The energy expenditure for leisure time activities during the previous 12-mo period was estimated via a structured interview by using the Minnesota Leisure Time Physical Activity (LTPA) questionnaire (51, 52). Occupational activity over the same period

was assessed by using the self-administered Tecumseh Occupational Activity Questionnaire (53–55). Because the occupational activity questionnaire was used in conjunction with the LTPA, we used the modifications suggested by Montoye et al (56), which included eliminating questions on the LTPA that pertain to work-related activity. Self-reported physical activity from both questionnaires (expressed in min/d) was added and classified by METs [the ratio of energy expended to measured or estimated REE (56)] into light ( $\leq 4$  METs), moderate (4.1–5.9 METs), or heavy ( $\geq 6$  METs) categories.

### Statistics

Statistical analyses were performed by using SPSS 10.0.7 and SYSTAT 9.0.1 (SPSS Inc, Chicago) and SAS (version 8; SAS Institute Inc, Cary, NC). Results are expressed as means  $\pm$  SDs unless otherwise specified. Leptin was the only variable that needed log transformation. Changes in variables were calculated as follow-up values minus baseline values. Student's  $t$  test for paired data was used to examine whether there were significant changes over time in body weight, body composition, energy expenditure, activity, and biochemical variables. In addition, the potential confounding effects of several aspects particular to the study sample [including surgical details such as length of the bypassed intestine (roux-limb) and protocol-related aspects such as sex and time until weight stability] were examined by using analysis of covariance. No confounding effects of any of these variables on the relations between energy expenditure and body-composition variables were observed. In addition, analyses were performed with data from men and women combined and from women only. However, the results remained the same with or without the inclusion of the 6 men; thus, data are presented for all subjects combined.

To determine whether the within-subject relation between changes in energy expenditure ( $\Delta TEE$  or  $\Delta REE$  and  $\Delta NREE$ ) and body composition ( $\Delta FFM$  and  $\Delta \text{fat mass}$ ) at follow-up were different from the cross-sectional relations at baseline between energy expenditure and body composition, a mixed-model regression analysis was performed by using SAS's mixed procedure. All models included a baseline intercept, a change in intercept, and FFM (baseline values and changes from baseline); some models additionally included fat mass (baseline values and changes from baseline). The models show energy expenditure at follow-up, with significance terms for  $\Delta \text{intercept}$  and for each of the variables in the model. Details of the models used are given in Appendix A.

In addition, regression analysis was used to determine whether baseline variables [ie, TEE, REE, physical activity level (PAL), AEE, NREE, respiratory quotient (RQ), postprandial RQ (PPRQ), reported physical activity, and fasting leptin] were predictors of change in fat mass. In these analyses, values for TEE, REE, AEE, NREE, and fasting leptin were expressed as a percentage of the value predicted from baseline body composition, and baseline BMI was also used as an independent variable. Baseline BMI was a strong predictor of change in fat mass ( $r = 0.79$ ,  $P < 0.001$ ). Student's  $t$  test for paired data was used to compare the mean measured REE at follow-up with the mean REE predicted at follow up from the WHO equations (45, 46).

## RESULTS

Subject characteristics at baseline are summarized in **Table 1**. The mean duration of weight loss after gastric bypass surgery was



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

	Women (n = 24)	Men (n = 6)
Age (y)	38.9 ± 9.0	39.2 ± 12.7
Height (cm)	163.0 ± 7.0	183.0 ± 5.4
Baseline weight (kg)	127.4 ± 24.7	187.9 ± 29.5
Baseline BMI (kg/m <sup>2</sup> )	48.3 ± 8.2	57.3 ± 10.4
Baseline waist-to-hip ratio	0.92 ± 0.12	0.94 ± 0.05

<sup>1</sup> $\bar{x} \pm SD$ .

14 ± 2 mo. No significant trends in body weight were found during the measurement of energy expenditure at either baseline or follow-up, and mean changes within both study periods were relatively small ( $\Delta$ weight at baseline:  $-4 \pm 144$  g/d;  $\Delta$ weight at follow-up:  $73.4 \pm 13.6$  g/d).

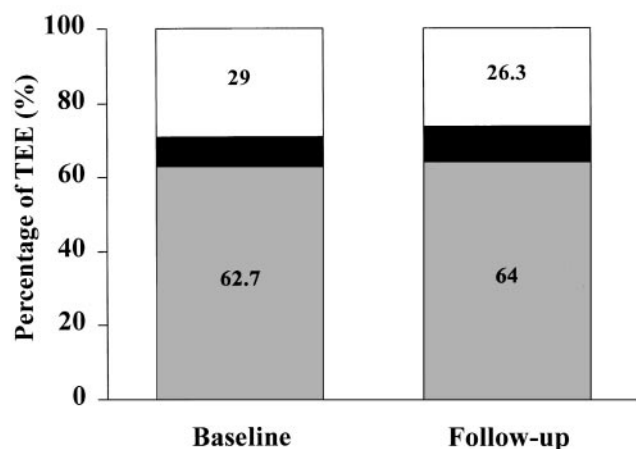
Body composition and energy expenditure data at baseline and follow-up and changes over time, including data on self reported activity, are shown in **Table 2**. Gastric bypass surgery resulted in a substantial mean weight loss of  $38 \pm 19\%$  of initial weight. There were large and significant changes in all body-composition variables and, on average, weight loss was 79% fat and 21% FFM. The proportions of weight lost as fat and FFM were not significantly related to the amount of weight loss. TEE, REE, and NREE were significantly lower at follow-up than at baseline. However, no significant changes in TEF, fasting RQ, or PPRQ (data not shown) were observed. Although there were large reductions in components of TEE, no significant changes in energy expenditure components were found when they were expressed as a fraction of TEE (**Figure 1**). In addition, there were no significant changes

**TABLE 2**  
Summary of body-composition and energy expenditure data by phase of measurement<sup>1</sup>

	Baseline	Follow-up	Change over time
<b>Body composition</b>			
Body weight (kg)	139.5 ± 35.3	86.1 ± 20.6 <sup>2</sup>	-53.4 ± 22.2
BMI (kg/m <sup>2</sup> )	50.1 ± 9.3	30.8 ± 5.7 <sup>2</sup>	-19.3 ± 6.7
Body fat (% of wt)	51.3 ± 4.6	33.9 ± 8.6 <sup>2</sup>	-17.4 ± 7.7
Fat mass (kg)	72.2 ± 23.0	30.1 ± 13.1 <sup>2</sup>	-42.1 ± 18.3
<b>Energy expenditure</b>			
TEE (MJ/d)	14.8 ± 2.6	11.2 ± 3.1 <sup>2</sup>	-3.6 ± 2.5
REE (MJ/d)	9.3 ± 1.8	6.9 ± 1.1 <sup>2</sup>	-2.4 ± 1.0
NREE (MJ/d)	5.5 ± 1.3	4.3 ± 2.3 <sup>3</sup>	-1.2 ± 2.4
TEF (% of meal)	8.3 ± 4.1	9.9 ± 3.2	1.6 ± 6.0
Fasting RQ	0.77 ± 0.02	0.76 ± 0.04	-0.01 ± 0.05
PAL	1.61 ± 0.15	1.61 ± 0.28	0.002 ± 0.3
FQ	0.84 ± 0.02	0.85 ± 0.02	0.004 ± 0.005
<b>Reported activity, leisure + occupational</b>			
Light (min/d)	290 ± 205	230 ± 139	-60 ± 177
Moderate (min/d)	14 ± 31	22 ± 24	8 ± 40
Heavy (min/d)	11 ± 14	15 ± 12	4 ± 16
Total (min/d)	315 ± 220	267 ± 13.1	-48 ± 180

<sup>1</sup> $\bar{x} \pm SD$ ; n = 24 F, 6 M. FFM, fat free mass; TEE, total energy expenditure; REE, resting energy expenditure; NREE, nonresting energy expenditure; TEF, thermic effect of food; RQ, respiratory quotient, FQ, food quotient, PAL, physical activity level.

<sup>2,3</sup>Significantly different from baseline (paired *t* tests): <sup>2</sup>*P* < 0.001, <sup>3</sup>*P* < 0.01.

**FIGURE 1.** Activity energy expenditure (AEE; □), thermic effect of food (TEF; ■), and resting energy expenditure (REE; ■) as a percentage of total energy expenditure (TEE) at baseline ( $\bar{x} \pm SD$ : 29 ± 6.2% for AEE, 8.3 ± 2.8% for TEF, and 62.7 ± 5.7% for REE) and after weight reduction and weight reestablishment (follow-up) after gastric bypass surgery (26.3 ± 14.1% for AEE, 9.7 ± 3.5% for TEF, and 64 ± 11.7% for REE). n = 24 F and 6 M. There were no significant differences by paired *t* test.

between baseline and follow-up in the reported time spent in all categories of activity.

Fasting biochemical measures are shown in **Table 3**. There were significant decreases in free serum thyroxine, rT<sub>3</sub>, and thyrotropin after weight loss, but mean values were within the normal range at both time points. Decreases in the thyroid hormone binding ratio and free thyroxine index were also found, but these decreases were not significant. The decrease in leptin concentration with weight loss was significant.

Different models for predicting energy expenditure at follow-up from baseline body composition and changes in body composition over time are shown in **Table 4**. As shown, models predicting follow-up REE, NREE, and TEE from intercepts and FFM variables consistently showed a decrease in energy expenditure at follow-up that was not fully accounted for after the decrease in FFM was included in the model, ie, the intercept term was significant in the model predicting REE from FFM alone. However, when fat mass variables (baseline fat mass and  $\Delta$ fat mass) were added

**TABLE 3**  
Summary of biochemical variables by phase of measurement<sup>1</sup>

	Baseline	Follow-up (after weight loss)	Change over time
Thyroxine (μ/dL)	7.8 ± 1.3	6.7 ± 1.4 <sup>2</sup>	-1.1 ± 1.59
FT <sub>4</sub> index (μIU/mL)	6.8 ± 1.1	6.6 ± 1.0	-0.2 ± 1.4
rT <sub>3</sub> (ng/mL)	0.20 ± 0.01	0.17 ± 0.01 <sup>3</sup>	-0.03 ± 0.01
Thyrotropin (μIU/mL)	2.6 ± 1.5	1.6 ± 0.9 <sup>4</sup>	-1.0 ± 0.9
THBR	0.9 ± 0.1	1.2 ± 1.4	0.3 ± 1.5
Leptin (ng/mL)	52.6 ± 17.1	12.3 ± 7.6 <sup>3</sup>	-40.3 ± 15.2

<sup>1</sup> $\bar{x} \pm SD$ ; n = 24 F, 6 M. THBR, thyroid hormone binding ratio; rT<sub>3</sub>, reverse triiodothyronine; FT<sub>4</sub>, free thyroxine.

<sup>2-4</sup>Significantly different from baseline (paired *t* tests): <sup>2</sup>*P* < 0.05, <sup>3</sup>*P* < 0.01, <sup>4</sup>*P* < 0.001.

**TABLE 4**Results of mixed-model regression analysis showing the changes in energy expenditure in relation to body composition<sup>1</sup>

	Coefficient ± SEE (kg)	<i>P</i> for coefficient	<i>P</i> for between- vs within-subject difference <sup>2</sup>	<i>P</i> for cross-sectional vs longitudinal <sup>3</sup>
<b>REE, with FFM only</b>				
Intercept	2.4210 ± 0.65	0.0009		0.0007
ΔIntercept	-1.0397 ± 0.30	0.0017		
Baseline FFM	0.1020 ± 0.01	<0.0001	0.54	
ΔFFM	0.1177 ± 0.03	0.0001		
<b>REE, with FFM and fat mass</b>				
Intercept	2.4041 ± 0.59	<0.0004		0.1594
ΔIntercept	-0.5652 ± 0.30	0.0700		
Baseline FFM	0.0757 ± 0.01	<0.0001	0.80	
ΔFFM	0.0823 ± 0.03	0.0038		
Baseline fat mass	0.0246 ± 0.01	0.0017	0.62	
ΔFat	0.0205 ± 0.01	0.0044		
<b>TEE, with FFM only</b>				
Intercept	3.6946 ± 1.59	0.0272		0.0084
ΔIntercept	-2.7148 ± 0.99	0.0107		
Baseline FFM	0.1661 ± 0.02	<0.0001	0.24	
ΔFFM	0.0698 ± 0.09	0.4258		
<b>TEE, with FFM and fat mass</b>				
Intercept	4.5925 ± 1.63	0.0092		0.0033
ΔIntercept	-3.9490 ± 1.09	0.0014		
Baseline FFM	0.1512 ± 0.03	<0.0001	0.92	
ΔFFM	0.1599 ± 0.09	0.0897		
Baseline fat mass	0.0013 ± 0.02	0.9479	0.03	
ΔFat mass	-0.0525 ± 0.02	0.0356		
<b>NREE, with FFM only</b>				
Intercept	1.1981 ± 1.31	0.3694		0.1104
ΔIntercept	-1.5953 ± 0.97	0.1104		
Baseline FFM	0.0653 ± 0.02	0.0022	0.17	
ΔFFM	-0.0415 ± 0.08	0.6199		
<b>NREE, with FFM and fat mass</b>				
Intercept	2.1226 ± 1.37	0.1333		0.0097
ΔIntercept	-3.3136 ± 1.04	0.0040		
Baseline FFM	0.0756 ± 0.03	0.0098	0.89	
ΔFFM	0.0648 ± 0.08	0.4460		
Baseline fat mass	-0.0225 ± 0.02	0.1708	0.04	
ΔFat Mass	-0.0684 ± 0.02	0.0051		

<sup>1</sup>*n* = 24 F, 6 M. REE, resting energy expenditure, TEE, total energy expenditure; FFM, fat-free mass; NREE, nonresting energy expenditure; Δ, change (follow-up - baseline).

<sup>2</sup>Comparison of the coefficients at baseline with the coefficients for change.

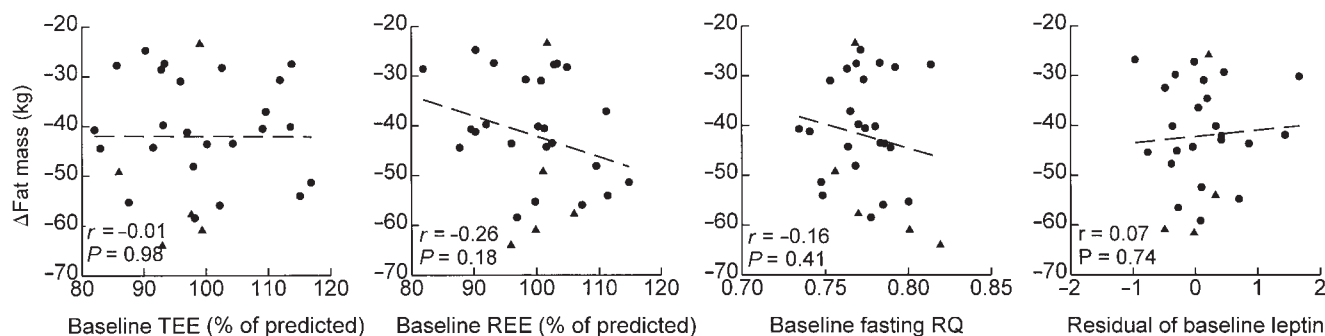
<sup>3</sup>*P* value for the global hypothesis that the coefficient for the Δintercept is 0 and the coefficients for baseline values are equal to the corresponding coefficients for change.

to the model predicting REE, there was no longer any significant decrease in REE that was independent of changes in body composition (the Δintercept coefficient was nearly significant, *P* = 0.07, but was quantitatively modest at -0.56 MJ/d ≈ 5% of TEE at follow-up). Models predicting NREE and TEE both had significant negative coefficients for the Δintercept, which were partially counterbalanced by significant positive Δfat coefficients (note that the negative value for Δfat had a positive effect on energy expenditure when multiplied by the negative fat mass change term). Unlike REE, models for TEE and NREE incorporating changes in FFM, fat mass, and the Δintercept suggested that the decreases in TEE and NREE were not completely predicted by changes in body composition. (There was a general decrease in ΔTEE and ΔNREE seen in the negative Δintercept term that was partially counterbalanced by some of the positive coefficients for body composition.)

Concerning the use of baseline indexes to predict weight loss and body-composition changes, baseline BMI was the best predictor of the change in BMI, change in body weight was best predicted by baseline body weight, and fat mass change was best predicted by baseline fat mass (as anticipated by regression to the mean effects). The results from an analysis of predictors of weight loss in models that adjusted for baseline BMI or body fat content showed that none of the examined energy expenditure variables (ie, baseline TEE, REE, PAL, AEE, NREE, PPRQ, RQ, reported physical activity, and fasting leptin) were significant predictors of weight or fat loss. Some of the relations between change in fat mass and baseline TEE, REE, RQ, and fasting leptin—adjusted for baseline BMI—are shown in **Figure 2**.

A comparison of mean follow-up REEs with mean values for REE predicted from standard equations (45, 46) is shown in **Table 5**. No significant difference between mean measured REE





**FIGURE 2.** Partial regression plots of the change ( $\Delta$ ) in fat mass against baseline total energy expenditure (TEE), baseline resting energy expenditure (REE), baseline fasting respiratory quotient (RQ), and baseline leptin concentrations in women ( $\bullet$ ;  $n = 24$ ) and men ( $\blacktriangle$ ;  $n = 6$ ). Baseline TEE was predicted from fat-free mass (FFM), and baseline REE was predicted from FFM and fat mass. The residual for baseline leptin (from the regression of log leptin on percentage body fat) was expressed as a percentage of that predicted from percentage body fat. The regression coefficients were adjusted for baseline BMI.

and mean predicted REE values were observed for men and women separately or for all subjects combined.

## DISCUSSION

This study showed that both TEE and REE decreased by 25% on average after massive weight loss and weight restabilization after gastric bypass surgery. We also found, in contrast with several previous reports (8, 20–23, 31, 33, 37), that the change in REE was explained by losses of both FFM and fat mass. In addition, we observed that mean REE after weight loss was not significantly different from REE predicted with the use of standard equations developed in nonobese persons (45, 46). Combined, these results suggest no energetic adaptation of REE toward increased efficiency after massive weight loss induced by gastric bypass surgery.

Previous studies that examined changes in REE with moderate weight loss resulting from conventional interventions (7, 9, 11, 57, 58) or massive weight loss in smaller groups of subjects (8, 20, 23) generally reported that REE was lower than expected on the basis of the changes in body composition. However, those studies only took into account changes in FFM, and indeed we found a similar result if changes in REE were predicted from FFM alone. Fat tissue is metabolically active and is a significant contributor to REE (24–28); therefore, it needs to be accounted for. Our data show that fat mass contributed significantly to the variability in REE, both in the extremely obese state and after weight loss and restabilization, and that failure to account for the changes in fat mass would have falsely indicated a relative decrease in energy expenditure that did not occur. An additional important

feature of our study was that we measured body composition accurately with the use of a 3-compartment model, which accounts for shifts in body water compartments, whereas most other studies—with the exception of that by Westerterp et al (20)—used 2 compartment models only.

A substantial decrease in TEE with weight loss was also found, averaging 3.6 MJ/d on average. However,  $\approx 66\%$  of this amount was accounted for by the change in REE (2.4 MJ/d) and was therefore predicted by body-composition change, leaving the calculated decrease in the NREE component of energy expenditure at only 1.2 MJ/d (which incorporates both the decrease in energy expenditure for physical activity and arousal and the change in TEF). Mean PAL values (TEE/REE) at follow-up were not significantly different from baseline, as were self-reported amounts of physical activity, which indicated that there was no decrease in NREE over and above that explained by the reduced energy costs of moving a smaller body. However, because energy expenditure ratios can be influenced by body weight as well as by physical activity (59, 60), we also conducted regression analyses to examine this issue. The analyses involved fitting a complex model to widely varying data and suggested both a decrease in NREE independent of body composition and an increase in NREE associated with loss of fat mass; the changes tended to counterbalance each other. One previous study reported no relative decrease in TEE with weight loss (16) and another reported a significant decrease in TEE that was greater than expected from body-composition change (7). The fact that we found only a small mean change in NREE despite massive weight loss and no change in mean PAL supports the suggestion of Amatruda et al (16) that energy expenditure is not abnormally low after weight loss.

With regard to identifying characteristics that might differentiate persons who are more successful at losing weight than are others, we found that baseline weight, fat mass, and BMI all significantly predicted changes in weight and body composition; initially more obese subjects had the greatest changes. This finding is consistent with the findings of several previous studies (17, 23, 31–37). However, caution must be used in the interpretation of this result because there is a regression to the mean effect in such analyses (61) that might obscure the quantitative role of biology. The biological mechanism by which initially larger subjects lose more weight has been suggested to be that they have initially higher energy intakes and thus have a relatively greater absolute restriction of energy intake with gastric bypass surgery [a similar-sized

**TABLE 5**

Measured and predicted resting energy expenditure (REE) at follow-up (after weight loss)<sup>1</sup>

	Men ( $n = 6$ )	Women ( $n = 24$ )	Total ( $n = 30$ )
	<i>MJ/d</i>		
Measured REE	8.67 $\pm$ 0.5	6.52 $\pm$ 0.7	6.97 $\pm$ 1.1
Predicted REE <sup>2</sup>	9.08 $\pm$ 0.8	6.52 $\pm$ 0.6	7.15 $\pm$ 1.4


<sup>1</sup> $\bar{x} \pm$  SEM.

<sup>2</sup>Predicted by using the equations of the World Health Organization (45).

gastric pouch is created in all surgical patients, which restricts the total quantity of food that can be consumed (62)]. However, if this were the case, TEE should predict weight loss better than does initial body weight because TEE is equivalent to energy intake during weight stability. The fact that baseline TEE did not predict weight loss as strongly as did baseline body weight in our study argues against initial energy intake being the primary determinant of weight loss and suggests that other factors may be important. Baseline variables—including TEE, REE, and PAL—were also unrelated to changes in body weight or fat mass in our study when adjusted for body composition and when included in models with baseline body weight or fat mass. Our finding that PAL did not predict weight loss conflicts with the findings of Westerterp et al (20), who unexpectedly reported greater fat loss in more sedentary subjects. However, that study had only a small group of subjects ( $n = 6$ ) and did not account for the potential confounding effect of initial body fat.

A further result from this study is that measured REE after weight reduction was comparable with REE values predicted from standard equations developed from data obtained from normal-weight subjects (45, 46). This finding suggests that standard REE prediction equations are suitable for use in persons after weight loss and are consistent with the results from our study, suggesting that there is no disproportionate long-term decrease in REE with weight loss that would favor weight regain.

Our data suggest that fasting leptin at baseline (relative to body fatness) does not predict weight loss. This observation is contrary to the findings of previous studies in obese subjects, which examined the role of leptin as a predictor of weight-loss success (35, 36). The results of these studies suggest that persons with low leptin concentrations relative to fat mass (ie, greater leptin sensitivity) have greater weight losses. However, these studies examined diet-induced weight loss and smaller reductions in fat mass, which may explain some of the contrasting findings. A further finding related to leptin in the present study was that the leptin concentration was lower after weight reduction than it was at baseline, even after adjustment for changes in body fat. Although this relative decrease in leptin was not associated with measurable changes in energy expenditure, it might potentially help to explain the weight regain observed in some gastric bypass patients; further follow-up studies in this area are needed.

In summary, our results show that energy requirements and REE are significantly reduced after weight loss and weight stabilization after gastric bypass surgery but that the decreases appear to be largely or completely predicted by decreases in body FFM and fat mass. Further studies are needed to examine other potential explanations for the variability in weight loss between patients after gastric bypass surgery, including psychological or behavioral factors that may affect food intake. An appropriate and permanent reduction in energy intake appears to be critical for long-term weight management in patients who have undergone gastric bypass surgery. 

We thank all the patients who participated in the study, Marshall Otter and Irene Ellis for their assistance in the doubly labeled water analysis, the Nutrition Evaluation Laboratory for the leptin analysis, and the nursing staff at the General Clinical Research Center, New England Medical Center, for their expert patient care and support.

SKD contributed to the experimental design, data collection and analysis, and writing of the manuscript. SBR and ES contributed to the experimental design and provided expertise and advice during the process of data collection and manuscript writing. GED assisted with the data analysis and statistical

modeling. MAM and JJK provided advice on the use of body-composition techniques. LKGH contributed to the experimental design, and SAS provided advice on the surgical and clinical aspects of the gastric bypass surgery patients. None of the authors had any affiliation with or personal or financial interest in the funding source.

## REFERENCES

1. Flegal KM, Carroll RJ, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Relat Metab Disord* 1998;22:39–47.
2. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002;288:1723–7.
3. Ravussin E, Burnand B, Schutz Y, Jequier E. Energy expenditure before and during energy restriction in obese patients. *Am J Clin Nutr* 1985;41:753–9.
4. Heyman M, Young VR, Fuss P, Tsay R, Joseph L, Roberts SB. Underfeeding and body weight regulation in normal weight young men. *Am J Physiol* 1992;263:R250–7.
5. Racette SB, Schoeller DA, Kushner RF, Neil KM, Herling-Jaffaldano K. Effects of aerobic exercise and dietary carbohydrate on energy expenditure and body composition during weight reduction in obese women. *Am J Clin Nutr* 1995;61:486–94.
6. Kempen KPG, Saris WHM, Westerterp KR. Energy balance during an 8-wk energy restricted diet with and without exercise in obese women. *Am J Clin Nutr* 1995;62:722–9.
7. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med* 1995;332:621–8.
8. van Gemert WG, Westerterp KR, Van Acker BAC, et al. Energy substrate and protein metabolism in morbid obesity before, during and after massive weight loss. *Int J Obes Relat Metab Disord* 2000;24:711–8.
9. Elliot D, Goldberg L, Kuehl KS, Bennett WM. Sustained depression of the resting metabolic rate after massive weight loss. *Am J Clin Nutr* 1989;49:93–6.
10. Heshka S, Yang M-U, Wang J, Burt P, Pi-Sunyer FX. Weight loss and change in resting metabolic rate. *Am J Clin Nutr* 1990;52:981–6.
11. Valtuena S, Blanch S, Barenys M, Sola R, Salas-Salvado J. Changes in body composition and resting energy expenditure after rapid weight loss: is there an energy-metabolism adaptation in obese patients? *Int J Obes Relat Metab Disord* 1995;19:119–25.
12. Doucet E, St Pierre S, Almeras N, Mauriege P, Richard D, Tremblay A. Changes in energy expenditure and substrate oxidation resulting from weight loss in obese men and women: is there an important contribution from leptin. *J Clin Endocrinol Metab* 2000;8:1550–6.
13. Leibel RL, Hirsch J. Diminished energy requirements in reduced-obese patients. *Metabolism* 1984;33:164–70.
14. Weyer C, Pratley R, Salbe A, Bogardus C, Ravussin E, Tataranni P. Energy expenditure, fat oxidation, and body weight regulation: a study of metabolic adaptation to long-term weight change. *J Clin Endocrinol Metab* 2000;85:1087–94.
15. Wadden TA, Foster GD, Letizia KA, Mullen JL. Long-term effects of dieting on resting metabolic rate in obese outpatients. *JAMA* 1990;264:707–11.
16. Amatruda JM, Statt MC, Welle SL. Total and resting energy expenditure in obese women reduced to ideal body weight. *J Clin Invest* 1993;92:1236–42.
17. Weinsier RL, Nelson KM, Hensrud DD, Darnel BE, Hunter GR, Schutz Y. Metabolic predictors of obesity. Contribution of resting energy expenditure, thermic effect of food, and fuel utilization to four-year weight gain of post-obese and never-obese women. *J Clin Invest* 1995;95:980–5.
18. Wyatt HR, Grunwald GK, Seagle HM, et al. Resting energy expenditure in reduced-obese subjects in the National Weight Control Registry. *Am J Clin Nutr* 1999;69:1189–93.
19. Weinsier RL, Nagy TR, Hunter GR, Darnell BE, Hensrud DD, Weiss HL. Do adaptive changes in metabolic rate favor weight regain

- in weight reduced individuals? An examination of the set point theory. *Am J Clin Nutr* 2000;72:1088–94.
20. Westerterp KR, Saris WHM, Soeters PB, ten Hoor F. Determinants of weight loss after vertical banded gastroplasty. *Int J Obes Relat Metab Disord* 1991;15:529–34.
  21. Busetto L, Perini P, Giantin V, et al. Relationship between energy expenditure and visceral fat accumulation in obese women submitted to adjustable silicone gastric banding. *Int J Obes Relat Metab Disord* 1995;19:227–33.
  22. Busecemi S, Caimi G, Verga S. Resting metabolic rate and postabsorptive substrate oxidation in morbidly obese subjects before and after massive weight loss. *Int J Obes Relat Metab Disord* 1996;20:41–6.
  23. Harsch-Bobbioni E, Morel P, Huber A, et al. Energy economy hampers body weight loss after gastric bypass. *J Clin Endocrinol Metab* 2000;85:4695–700.
  24. Cunningham JJ. A reanalysis of the factors influencing basal metabolic rate in normal adults. *Am J Clin Nutr* 1980;33:2372–4.
  25. Bernstein RS, Thornton JC, Yang MU, et al. Prediction of the resting metabolic rate in obese patients. *Am J Clin Nutr* 1983;37:595–602.
  26. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man, methods and results using a respiratory chamber. *J Clin Invest* 1986;78:1568–78.
  27. Garby L, Garrow JS, Jorgensen B, et al. Relation between energy expenditure and body composition in man: specific energy expenditure in vivo of fat and fat free tissue. *Eur J Clin Nutr* 1988;42:301–5.
  28. Nelson KM, Weinsier RL, Long CL, Schutz Y. Prediction of resting energy expenditure from fat-free mass and fat mass. *Am J Clin Nutr* 1992;56:848–56.
  29. Brolin RE. Critical analysis of results: weight loss and quality of data. *Am J Clin Nutr* 1992;55(suppl):S77S–81S.
  30. Sugeran HJ, Kellum JM, Engle KM, et al. Gastric bypass for treating severe obesity. *Am J Clin Nutr* 1992;55(suppl):S60S–6S.
  31. Ott MT, Ott L, Haack D, Colacchio TA, Lewis J. The MEE/PEE ratio as a predictor of excess weight loss for up to 1 year after vertical banded gastroplasty. *Arch Surg* 1992;127:1089–93.
  32. Bryson JM, King SE, Burns CM, Baur LA, Swaraj S, Caterson ID. Changes in glucose and lipid metabolism following weight loss produced by a very low calorie diet in obese subjects. *Int J Obes Relat Metab Disord* 1996;20:338–45.
  33. Su W, Jones PJH, Cleator IGM, Phang PT, Birmingham CL. Determinants of weight loss following ileogastroplasty. *Int J Obes Relat Metab Disord* 1996;20:481–7.
  34. Notarius CF, Rhode B, MacLean LD, Magder S. Exercise capacity and energy expenditure of morbidly obese and previously obese subjects. *Clin Invest Med* 1998;21:79–87.
  35. Torgerson JS, Carlsson B, Stenlof K, Carlsson LMS, Bringman E, Sjostrom L. A low serum leptin level at baseline and a large early decline in leptin predict a large 1-year reduction in energy restricted obese humans. *J Clin Endocrinol Metab* 1999;84:4197–203.
  36. Verdich C, Toubro S, Buemann B, et al. Leptin levels are associated with fat oxidation and dietary-induced weight loss in obesity. *Obes Res* 2001;9:452–61.
  37. Camerini G, Adami GF, Marinari GM, Campostano A, Ravera G, Scopirano N. Failure of preoperative resting energy expenditure in predicting weight loss after gastroplasty. *Obes Res* 2001;9:589–91.
  38. Prosser SJ, Scrimgeour CM. High-precision determination of  $^2\text{H}/^1\text{H}$  in  $\text{H}_2$  and  $\text{H}_2\text{O}$  by continuous-flow isotope ratio mass spectrometry. *Anal Chem* 1995;67:1992–7.
  39. Dallal GE, Roberts SB. DLW: a computer program for the calculation of total energy expenditure in doubly labeled water ( $^2\text{H}_2^{18}\text{O}$ ) studies. *Comp Biomed Res* 1991;24:143–51.
  40. Schoeller DA, Ravussin E, Schutz Y, Acheson KJ, Baertschi P, Jequier E. Energy expenditure by doubly labeled water: validation in humans and proposed calculation. *Am J Physiol* 1986;250:R823–30.
  41. Racette SB, Schoeller DA, Luke AH, Shay K, Hnilicka J, Kushner RF. Relative dilution spaces of  $^2\text{H}$  and  $^{18}\text{O}$ -labeled water in humans. *Am J Physiol* 1994;267:E585–90.
  42. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol* 1990;43:1327–35.
  43. Surrao J, Sawaya AL, Dallal GE, Tsay R, Roberts SB. Use of food quotients in human doubly labeled water studies: comparable results obtained with 4 widely used food intake methods. *J Am Diet Assoc* 1998;98:1015–20.
  44. Weir JBV. New method for calculating metabolic rate with special reference to protein metabolism. *J Physiol* 1949;109:1–9.
  45. WHO. World Health Organization: energy and protein requirements. Report of a joint FAO/WHO/UNU expert consultation. Geneva: WHO, 1985:206.
  46. National Research Council. Recommended dietary allowances. 10th ed. Washington, DC: National Academy Press, 1989.
  47. Siri WE. Body composition from fluid spaces and density: analysis of methods. In: Brozek J, Henschel A, eds. *Techniques for measuring body composition*. Washington, DC: National Academy of Sciences, 1961:223–44.
  48. Dempster P, Aitkens S. A new air displacement method for the determination of human body composition. *Med Sci Sports Exerc* 1995;27:1692–7.
  49. McCrory MA, Gomez TD, Bernauer EM, Mole PA. Evaluation of a new air displacement plethysmograph for measuring human body composition. *Med Sci Sports Exerc* 1995;27:1686–91.
  50. Das SK, Saltzman E, Hsu GLK, Wang J, Roberts SB, McCrory MA. Characterization of body composition and validation of methods in extremely obese women. *Obes Res* 2001;9:155S (abstr).
  51. Taylor HL, Jacobs DR, Schucker B, Knudsen J, Leon AS, DeBacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978;31:741–55.
  52. Folsom AR, Jacobs DR Jr, Caspersen CJ, Gomez-Martin O, Knudsen J. Test-retest reliability of the Minnesota Leisure Time Physical Activity Questionnaire. *J Chronic Dis* 1986;39:505–11.
  53. Ainsworth BA, Haskell WL, Leon A, et al. Compendium of physical activities: classification of the energy costs of human physical activities. *Med Sci Sports Exerc* 1993;25:71–80.
  54. Ainsworth BE, Jacobs DRJ, Leon AS, Richardson MT, Montoye HJ. Assessment of the accuracy of physical activity questionnaire occupational data. *J Occup Med* 1993;35:1017–27.
  55. Ainsworth BE, Montoye HJ, Leon AS. Methods of assessing physical activity during leisure and work. In: Bouchard C, Shephard RJ, Stephens T, eds. *Physical activity, fitness, and health*. Champaign, IL: Human Kinetics, 1994:146–59.
  56. Montoye HJ, Kemper HCG, Saris WHM, Washburn RA. *Measuring physical activity and energy expenditure*. Champaign, IL: Human Kinetics, 1996.
  57. Geissler CA, Miller DS, Shah M. The daily metabolic rate of the post-obese and the lean. *Am J Clin Nutr* 1987;45:14–20.
  58. Doucet E, St Pierre S, Almeras N, Despres JP, Bouchard C, Tremblay A. Evidence for the existence of adaptive thermogenesis during weight loss. *Br J Nutr* 2001;85:715–23.
  59. Allison DB, Goran MI, Poehlman ET, Heymsfield SB. Mathematical considerations for using ratios to express biological data. *Int J Obes Relat Metab Disord* 1995;19:644–52.
  60. Goran MI, Allison DB, Poehlman ET. Issues relating to normalization of body fat content in men and women. *Int J Obes Relat Metab Disord* 1995;19:638–43.
  61. Campbell DT, Kenny DA. *A primer on regression artifacts*. New York: The Guilford Press, 1999.
  62. Feurer ID, Crosby LO, Buzby GP, Rosato EF, Mullen JL. Resting energy expenditure in morbid obesity. *Ann Surg* 1983;197:17–21.

## APPENDIX A

According to the model [resting energy expenditure (REE) and fat-free mass (FFM) for the k-th subject]

$$REE_i = c + b_0 + b_1 FFM_1 + b_2 \Delta FFM_i \quad (A1)$$

where  $b_0$  is multiplied by an indicator variable, which is 0 at baseline and 1 at follow-up, and  $REE_i$  is the REE at time  $i$  (1 at baseline and 2 at the follow-up visit),  $FFM_1$  is FFM at baseline,  $\Delta FFM_i$  is the change in FFM from baseline (time 1) to time  $i$ , and  $c$  is a constant.

At baseline (time 1), because  $\Delta FFM_1$  always = 0 and  $b_0 = 0$ , the model reduces to

$$REE_1 = c + b_1 FFM_1 \quad (A2)$$

Thus,  $b_1$  represents the between-subject regression coefficient of FFM at baseline. The difference between  $REE_2$  and  $REE_1$  is as follows:

$$REE_2 - REE_1 = b_0 + b_2 (\Delta FFM_2 - \Delta FFM_1) \quad (A3)$$

However, because  $\Delta FFM_1$  is always 0

$$REE_2 - REE_1 = b_0 + b_2 \Delta FFM_2 \quad (A4)$$

where  $b_2$  is the expected change in REE per unit change in FFM. This model allows  $b_1$  and  $b_2$  to be compared directly. When fat mass is added as a second independent variable, the coefficients for fat mass and FFM at baseline and the coefficients for  $\Delta$ fat mass and  $\Delta$ FFM at the follow-up visit can be compared.

