# Effect of Calorie Restriction on Resting Metabolic Rate and Spontaneous Physical Activity

*Corby K. Martin,* Leonie K. Heilbronn,† Lilian de Jonge,‡ James P. DeLany,§ Julia Volaufova,¶ Stephen D. Anton,* Leanne M. Redman,** Steven R. Smith,†† and Eric Ravussin***

**Abstract**

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***Objective:*** It is unclear if resting metabolic rate (RMR) and spontaneous physical activity (SPA) decrease in weight-reduced non-obese participants. Additionally, it is unknown if changes in SPA, measured in a respiratory chamber, reflect changes in free-living physical activity level (PAL).

***Research Methods and Procedures:*** Participants ($N = 48$) were randomized into 4 groups for 6 months: calorie restriction (CR, 25% restriction), CR plus structured exercise (CR+EX, 12.5% restriction plus 12.5% increased energy expenditure via exercise), low-calorie diet (LCD, 890 kcal/d supplement diet until 15% weight loss, then weight maintenance), and control (weight maintenance). Measurements were collected at baseline, Month 3, and Month 6. Body composition and RMR were measured by DXA and indirect calorimetry, respectively. Two measures of SPA were collected in a respiratory chamber (percent of time active and kcal/d). Free-living PAL (PAL = total daily energy expenditure by doubly labeled water/RMR) was also measured. Regression equations at baseline were used to adjust RMR for fat-free mass and SPA (kcal/d) for body weight.

***Results:*** Adjusted RMR decreased at Month 3 in the CR group and at Month 6 in the CR+EX and LCD groups. Neither measure of SPA decreased significantly in any group. PAL decreased at Month 3 in the CR and LCD groups, but not in the CR+EX group, who engaged in structured exercise. Changes in SPA in the chamber and free-living PAL were not related.

***Discussion:*** Body weight is defended in non-obese participants during modest caloric restriction, evidenced by metabolic adaptation of RMR and reduced energy expenditure through physical activity.

**Key words: caloric restriction, metabolic adaptation, physical activity, energy expenditure, metabolism**

## Introduction

Body weight changes are a function of energy balance; weight gain occurs when energy intake exceeds energy expenditure (EE),[1] and weight loss occurs when EE exceeds energy intake (1). Energy is expended through resting metabolic rate (RMR), physical activity, and the thermic effect of food. The largest component of EE is RMR, which accounts for 60% to 70% of total daily EE (2). Physical activity accounts for 20% to 40% and is the most variable component of total daily EE (3). Spontaneous physical activity (SPA) reflects fidgeting and changing posture and the energy costs of this activity (2,4,5). SPA accounts for a modest amount (8% to 15%) of total daily EE (~350 kcal/d on average, varying from 138 to 685 kcal/d) (2).

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Departments of *Health Psychology, ‡Energy Metabolism, **Human Physiology, and ††Endocrinology Laboratory, Pennington Biomedical Research Center, Baton Rouge, Louisiana; †Diabetes Research Group, Garvan Institute, Sydney, Australia; §Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and ¶Public Health and Health Systems Research, Louisiana State University Health Sciences Center, New Orleans, Louisiana.
Address correspondence to Corby K. Martin, Department of Health Psychology, Pennington Biomedical Research Center, 6400 Perkins Rd., Baton Rouge, LA 70808.
E-mail: martinck@pbrc.edu


[1] Nonstandard abbreviations: EE, energy expenditure; RMR, resting metabolic rate; SPA, spontaneous physical activity; FFM, fat-free mass; CR, calorie restriction; FM, fat mass; NEE, non-resting EE; PAL, physical activity level; TEE, total daily EE; DLW, doubly labeled water; CALERIE, Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy; EX, structured exercise; LCD, low-calorie diet; CI, confidence interval.

Although RMR is highly associated with body size and composition, particularly fat-free mass (FFM), considerable variability exists among individuals after controlling for difference in FFM and other variables, such as fat mass, age, and sex (6). There are conflicting reports of whether or not RMR "adapts" or decreases beyond expected values based on changes in body composition in response to calorie restriction (CR) and weight loss. If RMR exhibits metabolic adaptation, this would provide evidence that metabolic changes defend body weight, which might partly explain why people have difficulty maintaining weight loss.

A recent study found that sleeping metabolic rate and 24-hour EE, measured in a respiratory chamber, decreased beyond values predicted by body mass after 6 months of CR in non-obese volunteers (7). Additionally, a recent meta-analysis found that formerly obese participants were more likely to have low RMR values after adjustment for differences in FFM and fat mass (FM) compared with controls (8). After a protein-sparing modified fast (~300 kcal/d) in a sample of obese females, RMR was lower than expected after controlling for loss of FFM (9). This decrease in RMR persisted even after 2 months of energy balance. Similar findings were found by Leibel et al. (10), who reported that RMR, adjusted for body composition, decreased after an 800 kcal/d liquid diet. Many of these studies examined obese participants who were undergoing restrictive diets or modified fasts (~300 and 800 kcal/d), and not all studies have found that RMR decreases during CR. For example, one year after weight loss surgery, no decrease in RMR, adjusted for changes in body composition, was found among obese women (11), and no decrease in RMR was found after accounting for change in FFM and FM among men and women who were tested during weight maintenance before weight loss surgery and 14 months after surgery (12). Similarly, RMR, expressed in terms of FFM, was found to be unchanged after weight loss (13), and weight-reduced people on the National Weight Control Registry had no decrease in RMR after controlling for FFM, FM, age, and sex compared with a weight-matched sample (14).

Physical activity includes SPA, which is reliably measured in respiratory chambers with radar motion detectors. Data on the percent of time active in a respiratory chamber can be used to calculate the energy costs of movement, expressed as kcal/d (2). Therefore, SPA can be expressed as: 1) percent activity in a respiratory chamber, and 2) the energy costs of this activity (kcal/d). Spontaneous physical activity has been found to be reproducible (15), and physical activity measured in a respiratory chamber has been found to be reflective of free-living physical activity (3,16). Low levels of SPA have been found to predict weight gain in Pima Indian males, and SPA appears to be a biologically regulated phenomenon that is familial (5). It is unclear if physical activity (SPA and free-living) decreases in response to CR, thus demonstrating metabolic adaptation.

Physical activity increases in calorie-restricted rhesus monkeys (17) and rodents (18), but this might reflect an increase in food seeking behavior (17). Conversely, in humans, apathy and reduced activity have been noted during semi-starvation (19). During less severe energy imbalance, researchers have found that activity measured during free-living conditions does not change significantly. For example, Levine et al. found that posture allocation (time spent lying or sitting vs. standing or ambulating) did not change when obese people lost weight (4). Results from respiratory chamber studies indicated that, in humans, percent activity decreased in participants who were prescribed a 50% energy-reduced diet and in a group of participants whose energy intake alternated between 50% and 100% of baseline energy intake (20). Other researchers have failed to detect adaptation of SPA. After an 800 kcal/d diet, percent activity was not found to decrease after a 10% weight loss (10).

One limitation of testing for changes in SPA is the confined quarters of respiratory chambers, which are used to quantify percent activity and the amount of energy expended in fidgeting, changing posture, etc. Measures of EE in respiratory chambers are lower than those during free-living conditions due to lower levels of physical activity (21). Therefore, research is needed that measures energy expended through physical activity both in respiratory chambers and during free-living conditions. Our study is one of the first to measure activity both in a respiratory chamber and during 2-week free-living periods in non-obese humans who undergo weight reduction.

Change in EE associated with weight loss is influenced by the effect of altered skeletal muscle work efficiency on energy expended in physical activity. Maintaining a 10% weight loss has been found to be associated with decreased RMR, total daily EE, and non-resting EE [NEE = total daily EE − (RMR + thermic effect of food)], after controlling for FFM (22). Much of the variance (35%) in the decrease in the energy cost of activity is due to increased skeletal muscle efficiency, which helps defend against weight loss by reducing the energy costs of activity.

Based on previous research, it is unclear if RMR decreases due to CR beyond values expected from the loss of FFM, thus demonstrating metabolic adaptation. It is unclear also if percent activity in a metabolic chamber decreases in response to CR or if the energy cost of this activity (kcal/d) decreases beyond expected values based on body mass. Furthermore, few studies have tested for metabolic adaptation in non-obese volunteers, and few studies have examined adaptation of physical activity measured both in the respiratory chamber and in free-living conditions. In the present study, free-living physical activity was quantified as physical activity level [PAL; PAL = TEE by doubly labeled water (DLW)/RMR].

The purpose of this study was to test for metabolic adaptation of RMR and SPA (percent activity in the chamber and the energy cost of this activity) during 6 months of CR in non-obese adults. Three groups of participants were calorie restricted, and a control group consumed a weight maintenance diet. It was hypothesized that metabolic adaptation would occur for RMR but not SPA, based on the findings of Levine et al. (4), in the 3 groups that were calorie restricted. No adaptation was expected in the control group. To determine if any changes in SPA reflected changes in free-living activity level, changes in PAL were examined over 2-week periods after 3 and 6 months of CR. It was hypothesized that PAL would not change significantly due to CR.

## Research Methods and Procedures

### *Participants*

Volunteers ($N = 48$) for this study were enrolled in Phase I of the CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) study at the Pennington Biomedical Research Center. A complete description of the CALERIE study is available elsewhere (7). Participants were overweight (BMI, 25 to 30 kg/$m^2$), non-smoking adults (age, 25 to 45 years for females; 25 to 50 years for males). Participants were not taking any medications other than oral contraceptives, and they provided written informed consent. The Institutional Review Board of the Pennington Biomedical Research Center and the Data Safety and Monitoring Board of CALERIE approved the protocol and consent form.

### *Intervention/Diets*

Participants were randomly assigned to one of 4 groups for 6 months: control (weight maintenance diet), CR (25% CR based on baseline energy requirements), CR+EX (CR plus structured exercise; 12.5% CR plus 12.5% increase in EE by structured exercise), and low-calorie diet (LCD; 890 kcal/d liquid diet until 15% reduction in body weight, followed by weight maintenance). The randomization procedure was stratified for sex and BMI ($<$27.5 kg/$m^2$ or $\geq$27.5 kg/$m^2$).

To promote adherence to the diets, participants were provided with all of their food for a 2-week baseline period, the first 12 weeks after randomization, and the last 2 weeks of the intervention (Weeks 22 to 24). Participants consumed a self-selected diet during Weeks 13 to 22, although they were provided with a meal plan and a calorie target, and they received extensive training in adhering to their meal plan through weekly group sessions. All diets (except the liquid supplement phase of the LCD) were based on the American Heart Association Step 1 recommendations ($\leq$30% fat). Participants in the CR+EX group engaged in structured exercise (walking/running or bicycling on a stationary bike) 5 days per week to increase their EE by 12.5% of baseline energy requirements. Individual exercise prescriptions were calculated by measuring the oxygen cost (V-Max 29 Series; SensorMedics, Yorba Linda, CA) at 3 levels of their chosen exercise, either walking/running on a treadmill or bicycling on a stationary bike, and an equation for estimating EE was generated. At each exercise session, participants selected the exercise intensity at which they wished to work. Participants were required to conduct 3 of 5 exercise sessions per week under supervision at the Center and wore portable heart rate monitors (Polar S-610; Polar Beat, Port Washington, NY) to assess compliance during unsupervised sessions.

### *Measures*

Participants completed metabolic testing at baseline, at which time they were in energy balance, at Month 3, and at Month 6.

*RMR.* RMR was measured over a 60-minute period by indirect calorimetry using a Deltatrac II Metabolic cart (Datex-Ohmeda, Helsinki, Finland). After the subject rested quietly for 20 minutes, a transparent plastic hood connected to the device was placed over the head of the participant. To determine RMR, calculations of $O_2$ consumption and $CO_2$ production were made from continuous measurements of $O_2$ and $CO_2$ concentrations in inspired and expired air diluted with a constant air flow (40 L/min) generated by the metabolic cart. Participants remained motionless and awake during the test, and the last 30 minutes of the measurement were used to calculate RMR.

*SPA.* SPA was measured in a whole room indirect calorimeter and was represented as the percent of time that the participant was active and the energy cost of this activity (kcal/d) (2). Volunteers entered the chamber before breakfast at 8:00 AM and left the chamber at 7:30 AM the next morning. The chamber is equipped with radar motion detectors (Model D9/30, Ann Arbor, MI) that detect and record the movement of participants in the chamber.

The percent of time that the participant was active was quantified using previously described methods (23). Briefly, the percent of time that participants were active was recorded by radar motion detectors and averaged over 15-minute blocks of time. Each unit represents the percent of the day that the participant was active; e.g., 7% means that the participant was active for 101 minutes of the one-day chamber stay.

The energy cost of SPA (kcal/d) was calculated using previously described methods (2). The percent of time that the participant was active was regressed against EE data for the corresponding time periods. The slope of this regression represents the cost of physical activity per activity unit and is used to calculate the energy cost of SPA over 24 hours (one day).

*TEE and PAL.* TEE over 2 weeks was measured by DLW at baseline, Month 3, and Month 6. The baseline measurement included two 2-week DLW periods. During the first

DLW period, participants followed their usual diet at home. During the second period, participants were provided with a weight maintenance diet by the metabolic kitchen. Briefly, subjects provided 2 urine samples before being dosed (2.0 g of 10% enriched $H_2{}^{18}O$ and 0.12 g of 99.9% enriched $^2H_2O$ per kg of estimated total body water) and 1 sample at 3, 4.5, and 6 hours after dosing. The first post-dose urine (3 hours) was discarded. On Days 7 and 14 after dosing, subjects provided 2 more timed urine samples under supervision. Each sample was analyzed for $^{18}O$ and $^2H$ abundance by isotope ratio mass spectrometry using automated devices for deuterium (H/Device, Finnigan) and $^{18}O$ (GasBench, Finnigan), as previously reported (24). The isotopic enrichments of the post-dose urines compared with the pre-dose samples were used to calculate elimination rates ($k_H$ and $k_O$) using linear regression. $CO_2$ production was calculated using the equations of Schoeller (25), later modified by Racette et al. (26). TEE was calculated by multiplying $CO_2$ by the energy equivalent of $CO_2$ based on the estimated food quotient of the diet at each time-point (0.86).

The PAL was calculated as follows: PAL = TEE/RMR.

*Body Weight and Composition.* Weight was measured weekly with the participant in a hospital gown after a 12-hour fast and after the participant had voided. Body composition was measured with DXA (QDA 4500A; Hologics, Bedford, MA).

### Statistical Analyses

Mean values (± standard error) are presented in text and tables. Mixed linear models were used to evaluate changes from baseline in the outcome variables. Group and time were fixed effects, with an interaction term included, and the repeated factor was time (Months 0, 3, and 6). The significance level was set at 0.05.

Change in RMR was evaluated with a 3-step process. First, RMR was regressed against FFM or FFM and FM at baseline ($N = 48$) to generate linear equations that were then used to calculate expected values of RMR at 3 and 6 months from observed values of FFM or FFM and FM. Differences between expected and observed RMR were analyzed at Months 3 and 6, and 95% confidence intervals (CIs) for these values are provided. Second, data from the three groups who were dieting (CR, CR+EX, and LCD) were collapsed. Differences between expected and observed RMR were examined between this combined group and the control group. Third, RMR was assessed without adjusting RMR for FFM.

Data from four participants were eliminated from the SPA analyses because of the motion detectors recording constant movement in the chamber that was not associated with the participant (e.g., a loose piece of paper was continuously moving due to air circulation). Change in SPA was assessed with a 4-step process. First, percent activity was analyzed without adjusting for body mass, although baseline percent activity values were entered as covariates. Second, change in the energy cost of activity in the chamber (kcal/d) was evaluated without adjustment for body mass (kg). Third, the energy cost of activity was regressed against body weight at baseline ($N = 48$) to generate linear equations that were then used to calculate expected values of the energy cost of SPA at 3 and 6 months from measured or observed body weight. Differences between expected and observed energy cost of SPA were analyzed at Months 3 and 6 by group. Fourth, data from the 3 groups who were dieting (CR, CR+EX, and LCD) were collapsed, and changes in SPA were compared between this combined group and the control group.

Changes in PAL at Months 3 and 6 were analyzed without adjusting for body mass because the ratio of TEE by RMR normalizes for body size. Baseline values were entered as covariates. Because of the large amount of variability in the relationship between TEE and RMR when the intercept is not zero (27), an additional analysis was conducted. TEE values were regressed against RMR at baseline ($N = 48$) to generate linear equations that were then used to calculate expected values of TEE at Month 6 from observed or measured RMR values. Differences between expected and measured TEE were analyzed by group.

Weight change over the 2-week DLW periods preceding metabolic testing was used as a measure of energy balance. Weight change was calculated for each participant by instructing them to weigh themselves in the morning in a fasting state after the first void and in the same clothing (e.g., pajamas) or without clothing. These daily body weights were plotted, and a regression equation was used to quantify the amount of weight change over the 2-week period. ANOVA was used to test for differences in energy balance among the groups at Month 3 and 6. The results were examined to explore if differences in energy balance appeared to systematically affect the results.

*Correlation Analyses.* Correlation analyses were conducted to measure associations among the outcome variables, i.e., RMR, SPA (percent of time active and the energy costs of activity), and PAL at baseline, with all participants included in the analysis and collapsed across group. Additional correlation analyses were conducted to determine if changes in the outcome variables at Months 3 and 6 were associated with each other, or with change in body weight, for the dieting groups combined and the control group. The significance level was set at 0.01 for these analyses to help control for the probability of type I error inflation.

## Results

### Baseline Characteristics and Weight Loss

A complete description of the study sample and weight loss data are reported elsewhere (7). The majority of the sample identified themselves as white ($n = 30$, 63%),

**Table 1.** Participant characteristics

| | Men ($n$ = 21) | Women ($n$ = 27) |
|---|---|---|
| Age (yrs) | 37 (2.0) | 37 (1.0) |
| Body weight (kg) | 89.2 (1.9) | 76.2 (1.3) |
| BMI (kg/m$^2$) | 27.9 (0.4) | 27.7 (0.3) |
| Fat mass (kg) | 22.0 (0.9) | 28.8 (1.0) |
| Fat-free mass (kg) | 67.1 (1.5) | 47.4 (0.7) |
| Baseline (Week 0) RMR (kcal/d) | 1737 (33) | 1407 (27) |
| Baseline (Week 0) energy requirements (kcal/d) | 3248 (72) | 2449 (55) |

RMR, resting metabolic rate. Data are mean (standard error). The age, body weight, and BMI data are reported elsewhere (7).

followed by African-American ($n$ = 16, 33%), and Asian or Latino ($n$ = 2, 4%). The descriptive characteristics of the 48 participants who enrolled are provided in Table 1. Forty-six (20 males and 26 females) participants completed the 6-month study. One control participant dropped out for personal reasons, and one LCD participant was lost to follow-up. Mean weight loss as a percent of initial body weight by group was: −1.0% (1.1) for the control group, −10.4% (0.9) for the CR group, −10.0% (0.8) for the CR+EX group, and −13.9% (0.7) for the LCD group. On average, the LCD group was in energy balance and consuming a diet to maintain their lower body weight by Week 10.

### Metabolic Adaptation

*RMR.* RMR data are summarized in Table 2. At baseline, FFM accounted for 77% of the variance in RMR (RMR = 584 ± 17 × FFM, $R^2$ = 0.77, $p < 0.0001$), where RMR is expressed in kcal/d and FFM in kg (Figure 1). FM, age, and gender did not account for a statistically significant amount of variance in RMR. At follow-up, compared with predicted RMR values, observed values were significantly lower for the CR group at Month 3, and for the CR+EX and LCD groups at Month 6 (Figure 1; Table 2). An analysis that adjusted RMR for FFM and FM found similar results.

CIs (95%) for the difference between observed and expected RMR values, based on FFM, for each of the four groups are provided in Table 2. The CIs indicate that it was difficult to detect significant differences between the groups who were dieting, e.g., CR compared with CR+EX. Therefore, the RMR values adjusted for FFM of participants in the three groups who were calorie restricted were collapsed into one group and compared with controls. At Month 6, the pooled RMR adjusted value for the dieting group was significantly lower (91 ± 44 kcal/d) than that of the control group ($p < 0.05$). The dieting groups had significantly decreased RMR values at months 3 ($p < 0.01$) and 6 ($p < 0.01$) compared with adjusted values.

Without adjusting RMR for body mass, but adjusting for baseline values, RMR decreased from baseline to Month 3 for the CR ($p < 0.01$) and LCD ($p < 0.05$) groups, and from baseline to Month 6 for the CR+EX ($p < 0.05$) and LCD ($p < 0.01$) groups. No significant change from baseline was detected in the control.

*SPA.* The first measure of SPA, percent activity, was analyzed at 3 and 6 months adjusted for baseline. Percent activity did not decrease for any of the groups from baseline to Months 3 and 6 (all $p$ values > 0.25; Table 3). When the dieting groups were combined and compared with control, no significant differences were found on change scores at Month 3 or 6 ($p$ values > 0.99).

At baseline, body weight (kg) accounted for 14% of variance in the energy costs of SPA ($p$ = 0.001, SPA = −54 + 2.9 × kg, $R^2$ = 0.14). After adjusting for change in body weight (kg), the energy cost of SPA did not decrease for any of the groups at Month 3 or 6 ($p$ values > 0.18; Table 2; Figure 1, bottom panel). Without adjustment for body weight, but controlling for baseline values, the energy costs of SPA (kcal/d) decreased significantly for the LCD group at Month 3 ($p < 0.01$).

The adjusted values for the energy costs of SPA of participants in the three groups who were calorie restricted were collapsed into one group and compared with controls. The change in the energy costs of SPA for the combined dieting groups did not differ significantly from the change in the control group ($p$ values > 0.79). At Months 3 and 6, neither the combined dieting groups nor the control group experienced a significant decrease in the energy costs of SPA beyond expected values ($p$ values > 0.64).

*PAL in Free-living Conditions.* Since PAL is already adjusted for metabolic body size (RMR), PAL was adjusted only for baseline values, but not for changes in body mass. At Month 3, PAL decreased significantly in the CR and LCD groups, but, as expected, did not change significantly in the CR+EX or control groups (Table 3). CIs for change from baseline for each of the 4 groups are provided in Table

**Table 2.** Fat-free mass (kg) and fat mass (kg) values at months 0 (M0), 3 (M3), and 6 (M6) for each group

| | Fat-free mass (kg) | Fat mass (kg) | Observed RMR | Expected RMR | *p* | Confidence interval | | Observed SPA | Expected SPA | *p* | Confidence interval | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper | | | | Lower | Upper |
| Control | | | | | | | | | | | | |
| M0 | 55.6 ± 2.9 | 26.1 ± 1.4 | 1606 ± 64 | — | — | | | 169 ± 16 | — | — | | |
| M3 | 57.0 ± 3.1 | 24.9 ± 1.5 | 1566 ± 60 | 1568 ± 54 | 0.96 | −79 | 76 | 175 ± 16 | 183 ± 9 | 0.70 | −45 | 31 |
| M6 | 56.7 ± 3.1 | 25.1 ± 1.7 | 1588 ± 71 | 1563 ± 54 | 0.52 | −53 | 102 | 188 ± 19 | 183 ± 9 | 0.65 | −31 | 49 |
| CR | | | | | | | | | | | | |
| M0 | 56.4 ± 3.5 | 24.8 ± 1.8 | 1543 ± 71 | — | — | | | 227 ± 32 | — | — | | |
| M3 | 54.4 ± 3.4 | 21.0 ± 1.7 | 1437 ± 72 | 1523 ± 59 | 0.03* | −160 | −11 | 188 ± 22 | 164 ± 9 | 0.19 | −13 | 63 |
| M6 | 53.9 ± 3.3 | 19.2 ± 1.7 | 1484 ± 83 | 1514 ± 57 | 0.41 | −105 | 44 | 178 ± 18 | 157 ± 9 | 0.27 | −16 | 57 |
| CR + EX | | | | | | | | | | | | |
| M0 | 55.8 ± 3.5 | 26.4 ± 1.7 | 1525 ± 64 | — | — | | | 167 ± 20 | — | — | | |
| M3 | 54.8 ± 3.3 | 22.9 ± 1.6 | 1478 ± 65 | 1529 ± 57 | 0.17 | −126 | 23 | 156 ± 18 | 171 ± 9 | 0.43 | −51 | 22 |
| M6 | 53.9 ± 3.2 | 20.2 ± 1.7 | 1425 ± 71 | 1514 ± 55 | 0.02* | −163 | −14 | 145 ± 26 | 160 ± 8 | 0.48 | −51 | 25 |
| LCD | | | | | | | | | | | | |
| M0 | 56.2 ± 3.5 | 26.1 ± 1.8 | 1532 ± 60 | — | — | | | 168 ± 16 | — | — | | |
| M3 | 51.3 ± 3.1 | 19.0 ± 1.9 | 1429 ± 65 | 1469 ± 53 | 0.31 | −118 | 38 | 129 ± 11 | 149 ± 8 | 0.33 | −59 | 20 |
| M6 | 51.8 ± 3.3 | 18.5 ± 1.9 | 1399 ± 55 | 1478 ± 56 | 0.047* | −156 | −1 | 150 ± 25 | 149 ± 9 | 0.97 | −39 | 41 |

RMR, resting metabolic rate; SPA, spontaneous physical activity; CR, calorie restriction; EX, structured exercise; LCD, low-calorie diet. Data are mean ± standard error. Mean observed values of RMR and the energy costs of activity in the respiratory chamber (SPA; kcal/d) at months 0, 3, and 6 for each group. Corresponding expected values and the confidence intervals (95%) for the difference between observed and expected values are also represented. Expected RMR was calculated at 3 and 6 months from RMR = 584 ± 17 × FFM, $R^2 = 0.77$, $p < 0.0001$ and Expected SPA from SPA = −54 + 2.9 × kg, $R^2 = 0.14$, $p < 0.01$. Both equations were generated from the 48 participants measured at baseline. The *p* values represent the comparison between observed and expected values.

* Significant *p* value.

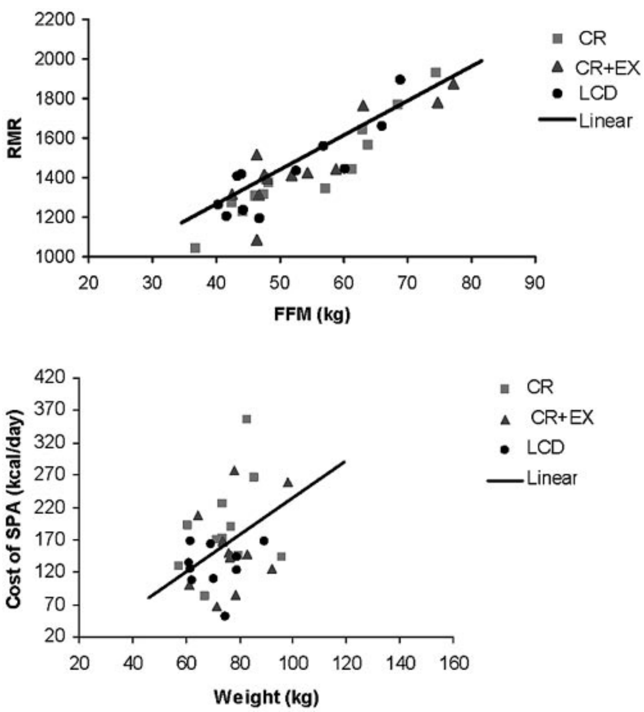


*Figure 1:* Top panel: linear regression at baseline between RMR [RMR = 584 ± 17 × FFM (kg), $R^2 = 0.77$, $p < 0.0001$] and FFM and the corresponding observed values at Month 3. Bottom panel: linear regression at baseline between SPA [SPA = −54 + 2.9 × weight (kg), $R^2 = 0.14$, $p < 0.01$] and body mass (kg) and the corresponding observed values at Month 3.

3. The CIs indicate that it is possible to detect significant differences on change from baseline among the 4 groups, possibly because one group, CR+EX, should have experienced either no decrease or an increase in PAL. Indeed, a marginally significant difference ($p = 0.065$) was found between the CR and CR+EX groups on change from baseline at Month 6, and the mean difference scores indicate that the CR group decreased PAL and the CR+EX group increased PAL. In addition, the LCD group differed significantly from the CR+EX ($p < 0.05$) and control ($p < 0.05$) groups on change from baseline at Month 3. The LCD group experienced larger decreases compared with the CR+EX and control groups.

The PAL data of participants in the 3 groups who were calorie restricted were also collapsed into one group and compared with controls. The dieting groups did not differ significantly from the control group on change scores at Months 3 and 6 ($p$ values $> 0.32$). Nevertheless, the dieting groups experienced a significant decrease in PAL at Month 3 ($p < 0.0001$) but not at Month 6.

Due to the large amount of variability in the relationship between TEE and RMR when the intercept is not 0 (27), TEE was regressed against RMR at baseline, and RMR accounted for 73% of variance in TEE ($p < 0.0001$, TEE = −231 + 1.9 × RMR, $R^2 = 0.73$). At Month 6, the observed TEE values were not significantly different from the TEE values that were expected based on RMR values and the regression equation from baseline ($p$ values $> 0.20$).

*Energy Balance.* The CR and CR+EX groups had significantly different energy balance during the DLW phase compared with the LCD group at Month 3. Examination of the means indicated that the LCD group was in energy balance and the CR and CR+EX groups were in negative energy balance (−0.84 kg and −1.17 kg, respectively, during the 2-week DLW period). However, only the CR group showed a difference between observed and expected levels of RMR at this time-point. At Month 6, there were no significant differences in energy balance among the CR and CR+EX groups and the LCD group, but only the CR+EX and LCD groups experienced significant metabolic adaptation. Hence, there is no consistent pattern in these data suggesting that energy balance systematically affected the results.

The PAL data also did not reveal a consistent pattern indicating that energy balance affected the results. Both the CR and LCD groups demonstrated a reduction in PAL at Month 3, even though the LCD group was in energy balance and the CR group was in negative energy balance.

***Correlation Analyses***

At baseline, correlation coefficients were calculated among the outcome variables for all participants collapsed across groups. The energy cost of activity in the chamber was significantly correlated with body weight ($r = 0.38$, $p = 0.01$). Importantly, percent activity was positively correlated with PAL ($r = 0.43$, $p < 0.01$), supporting previous findings of an association between activity in a respiratory chamber and free-living activity (3,16). At Months 3 and 6, none of the changes in SPA was correlated with changes in PAL for the dieting groups combined or the control group. Similarly, change in PAL and SPA was not associated with change in body weight.

## Discussion

The results of this study indicate that RMR adapted or decreased beyond values expected from changes in weight and body composition as a result of energy deficit that was achieved through a food-based diet (25% CR) after 3 months and a food-based diet plus structured exercise (25% total CR) after 6 months. Additionally, RMR decreased beyond expected values at Month 6 among participants who lost weight through a supplement-based diet and subsequently maintained their weight loss. The control group did not experience a decrease in RMR. Importantly, at Month 6 the combined data from the dieting groups demonstrated that RMR was lower than expected, resulting in 91 kcal/d less EE compared with control participants, even after dif-

**Table 3.** Mean observed values of percent activity in the respiratory chamber (Activity) and PAL at months 0 (M0), 3 (M3), and 6 (M6) for each group

| | Activity (%) | *p* | Confidence interval | | PAL | *p* | Confidence interval | |
|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | | | Lower | Upper |
| Control | | | | | | | | |
| M0 | 15.9 ± 3.4 | — | | | 1.76 ± 0.04 | | | |
| M3 | 13.1 ± 1.6 | 0.59 | −10.3 | 5.9 | 1.74 ± 0.05 | 0.39 | −0.18 | 0.07 |
| M6 | 10.6 ± 0.9 | 0.30 | −11.3 | 3.6 | 1.82 ± 0.1 | 0.83 | −0.14 | 0.17 |
| CR | | | | | | | | |
| M0 | 13.9 ± 2.3 | — | | | 1.84 ± 0.05 | | | |
| M3 | 14.1 ± 3.5 | 0.80 | −9.1 | 7.1 | 1.62 ± 0.05 | <0.01* | −0.30 | −0.08 |
| M6 | 14.8 ± 3.0 | 0.68 | −8.5 | 5.6 | 1.71 ± 0.05 | 0.17 | −0.26 | 0.05 |
| CR + EX | | | | | | | | |
| M0 | 24.7 ± 3.4 | — | | | 1.73 ± 0.04 | | | |
| M3 | 23.1 ± 6.0 | 0.70 | −6.4 | 9.5 | 1.71 ± 0.06 | 0.25 | −0.18 | 0.05 |
| M6 | 17.1 ± 4.8 | 0.39 | −10.3 | 4.1 | 1.87 ± 0.06 | 0.20 | −0.05 | 0.24 |
| LCD | | | | | | | | |
| M0 | 20.3 ± 4.4 | — | | | 1.87 ± 0.06 | | | |
| M3 | 11.6 ± 2.3 | 0.26 | −13.1 | 3.6 | 1.49 ± 0.08 | <0.0001* | −0.46 | −0.22 |
| M6 | 15.8 ± 4.7 | 0.27 | −10.9 | 3.2 | 1.75 ± 0.07 | 0.27 | −0.25 | 0.07 |

PAL, physical activity level; CR, calorie restriction; EX, structured exercise; LCD, low-calorie diet. Confidence intervals (95%) for change from baseline are also provided. The *p* values indicate if values at months 3 and 6 differed significantly from baseline.
* Significant *p* value.

ferences in FFM were taken into consideration. Physical activity, measured as percent of time active in a respiratory chamber and the energy cost of this activity, did not change significantly with CR. Free-living PAL, however, decreased at Month 3 for the CR and LCD groups, although these changes were not significant at Month 6. The lack of a significant decrease in PAL in the CR+EX group is not surprising because the CR+EX group engaged in a structured exercise regimen during the trial. This is one of the first studies to measure activity both in a respiratory chamber and during 2-week free-living periods in non-obese humans who lost weight. This aspect of the study is important because measures of EE in respiratory chambers are lower than those during free-living conditions due to lower levels of physical activity (21).

The finding that RMR exhibited metabolic adaptation supports previous research conducted with obese participants and extends these findings to overweight adults (BMI 25 to 30 kg/m$^2$) whose CR did not involve a modified fast. Elliot et al. reported metabolic adaptation of RMR after a modified fast (~300 kcal/d) in obese females, and this decrease persisted for 2 months of energy balance (9). Leibel et al. (10) noted that RMR adapted after obese participants consumed an 800 kcal/d diet and maintained body weight for 14 days. The present study fails to support studies that found no decrease in RMR, adjusted for body composition, after weight loss (11–14). Importantly, the participants in this study were non-obese and were randomly assigned to one of three groups with different strategies for caloric restriction compared with one control group.

When weight is lost, RMR is expected to decrease based on the loss of body mass, and metabolic adaptation occurs when RMR decreases beyond values expected from loss of body mass, namely, FFM and FM. Based on data from this study, metabolic adaptation occurred in the dieting groups, and RMR was 91 kcal/d less than in the control group. This finding has significant implications for overweight individuals who have lost weight. First, their food intake must be tightly controlled to prevent weight regain. Second, if food intake returns to pre-weight loss levels, weight regain is imminent unless EE is increased through exercise. An increase in exercise would need to occur under volitional control, however. In this study, physical activity in the chamber was stable, and free-living PAL decreased at Month 3 in the LCD and CR groups. This finding was not expected; PAL levels were hypothesized to remain stable in the dieting groups. These results support the hypothesis that volitional control is needed to maintain or increase physical activity level during CR. This study is among the first to report decreased PAL during a period of nutritionally adequate CR.

As expected, percent activity in a respiratory chamber and the energy costs of this activity (kcal/d, corrected for change in body mass or kg) did not decrease significantly. These results add to the existing literature on SPA and support the findings of Leibel et al. (10), who did not find a decrease in percent activity after an 800 kcal/d diet and a 10% weight loss, and Levine et al., who demonstrated that SPA or non-exercise activity thermogenesis is stable even when weight is gained or lost (4). Other authors have found decreases in percent activity, however. de Groot et al. (20) found that percent activity decreased during CR, although these data were not corrected for change in body mass. Based on the results of this study, it appears that the energy cost of SPA might decrease transiently when a large energy deficit is created by dieting; however, when these data are corrected for change in body mass, these differences disappear.

It was expected that free-living PAL would reflect changes, or lack of change, in physical activity measured in a respiratory chamber because physical activity measured in a respiratory chamber has been found to reflect free-living physical activity (3,16). In this study, PAL decreased significantly in the LCD and CR groups at Month 3, whereas there was no decrease in SPA expressed in percent activity. These data suggest that a large energy deficit might be associated with a transient decrease in free-living physical activity in humans. During semistarvation, human participants become apathetic and less active (19), and this "adaptation" of physical activity levels could provide a survival advantage because energy is being conserved. However, studies from the animal literature do not consistently support this hypothesis. After initiation of CR, adult rhesus monkeys had decreased activity compared with controls (28), although this difference was not present after 30 months of CR (29). Alternatively, CR was found to increase activity in rhesus monkeys who were calorie restricted (17), and this effect is also noted in rodents (18). In animals, CR might increase physical activity by increasing food-related or food-seeking behavior (17). This scenario does not necessarily apply to modern humans who live in an environment with an ample food supply that is easily available. Indeed, modern humans would not necessarily be susceptible to a drive to increase activity to find food; rather, calorie-restricted humans must resist an obesogenic environment that fosters calorie intake. Additional research is needed to help clarify whether physical activity levels adapt to different levels of CR; however, this research requires well-designed and sufficiently powered studies because the energy expended in SPA is variable among individuals (138 to 685 kcal/d) (2), and this variability might make it difficult to detect consistent responses of SPA to CR.

The correlation analysis of baseline data indicated that percent activity in the chamber was significantly correlated with free-living PAL. This finding supports previous reports that physical activity levels in a respiratory chamber reflect free-living PALs (3,16). However, no significant relationship was found among changes in RMR, SPA (percent of time active and the energy costs of activity), and PAL. Similarly, change in these variables was not significantly associated with change in body weight. The lack of significant findings is not surprising because this study was only 6 months in duration, and longer periods of time are likely needed to detect an association between metabolic adaptation and change in body weight. Nevertheless, the lack of relationship between adaptation of RMR and change in spontaneous physical activity is noteworthy. It appears that any change in RMR, adjusted for levels of FFM, is not associated with adaptation of energy expended in physical activity. This is supported by evidence of metabolic adaptation of RMR, but a lack of a significant decrease in percent activity in the chamber and the energy cost of this activity.

The results of the study must be interpreted in the context of its limitations. First, statistical power was limited due to the number of participants per group. Nevertheless, significant differences between observed and expected RMR values were found, and PAL was found to decrease during the trial. Moreover, differences in change in PAL from baseline to Months 3 and 6 were detected between groups. Second, skeletal muscle work efficiency, which influences change in non-resting EE after weight loss, was not measured. Therefore, reduced PAL in the CR and LCD groups could be due, in part, to increased skeletal muscle work efficiency. Third, energy balance was not tightly controlled during this study, and the groups differed on energy balance at Month 3. Nevertheless, there is no consistent pattern in these data that suggests that energy balance systematically affected the results.

In summary, the results of this study indicate that RMR decreased after CR beyond expected values based on FFM. The percent of time active in a respiratory chamber did not decrease significantly, nor did the energy cost of this activity, after adjustment for changes in body mass (kg). Free-living physical activity level decreased in the 2 groups that followed CR without exercise (CR and LCD), but PAL did not decrease in the group that engaged in structured exercise (CR+EX) or in the control group. Adaptation of RMR was not associated with change in activity levels or weight loss during this relatively short 6-month study. Further research is needed to determine the extent to which metabolic adaptation of RMR affects body weight change over the long term.

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