Published in final edited form as:

Int J Obes (Lond). 2021 April ; 45(4): 840–849. doi:10.1038/s41366-021-00748-y.

Reduced metabolic efficiency in sedentary eucaloric conditions predicts greater weight regain in adults with obesity following sustained weight loss

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Abstract

Background—Successful long-term weight loss maintenance after caloric restriction (CR) is rarely achieved. Besides known metabolic, behavioral, and cognitive factors, 24-hour energy expenditure (24hEE) relative to body size (i.e., metabolic efficiency) might influence subsequent weight loss maintenance.

Methods—Eleven participants with obesity (BMI=39.0±8.7 kg/m^2, body fat=36.1±6.4%) had 24hEE measured in a whole-room indirect calorimeter during eucaloric conditions and weight stability prior to starting a 6-week inpatient CR study (50% of daily energy needs). Twenty-four-hour energy expenditure was adjusted via regression analysis for fat free mass (FFM) and fat mass

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Author contributions: T.H., S.H., and P.P. wrote the manuscript. T.H., S.H., and P.P. performed data analyses. S.B.V. and J.K. designed the clinical protocol. A.B., J.K., and S.B.V. reviewed the manuscript. P.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest Statement: The authors have nothing to disclose.

Prior presentation: This work has not been presented previously.

Supplementary information: supplemental material can be found at[32]

Clinical Trial: NCT00687115, NCT00523627

(FM) by DXA. Body composition was reassessed at the end of CR and after 1-year follow-up. Free-living weight was assessed by monthly weight measurements during 12 months.

Results—After 6-week CR, participants lost 8.5±2.7% weight (FFM: −6.3±3.6 kg, FM: −3.4±1.2 kg) but regained 5.1±8.0% one year following CR, which was mostly due to FFM regain (+5.7±5.5 kg) and unchanged FM. A relatively higher 24hEE by 100 kcal/day prior to CR was associated with an average greater rate of weight regain by +0.3 kg/month during follow-up and a greater final weight regain by +5.1 kg after 1 year of follow-up.

Conclusion—These results suggest that reduced metabolic efficiency in 24hEE during eucaloric, sedentary conditions may predict greater weight regain after CR-induced weight loss.

Keywords

caloric restriction; weight loss; weight regain; weight maintenance; energy expenditure

Introduction

Successful long-term weight loss maintenance following a prolonged period of caloric restriction (CR) is defined as a sustained weight loss of ~5–10% of baseline body weight[1] but is only achieved and maintained by ~20% individuals[2]. Physiological determinants which subvert weight maintenance after weight loss are not fully elucidated[3, 4] but may include greater "metabolic slowing"[5–8], increased skeletal muscle work efficiency[9, 10], greater loss in lean mass during CR[11–13], a reduced capacity to oxidize fat[14–16], and changes in appetite-related hormones[17].

In previous studies, relatively higher 24-hour energy expenditure (24hEE) than expected by body composition and measured in the confined environment of a whole-room calorimeter during energy balance has been associated with greater *ad libitum* food intake and overeating[18–20], possibly mediated by physiological energy sensing mechanisms[21–24] that might increase weight gain susceptibility[19] by increased drive to (over)eat[25, 26]. Based on these prior findings, we hypothesize that higher eucaloric 24hEE measured before a CR period might additionally identify individuals more prone to weight regain after weight loss.

Therefore, in the present longitudinal study, we measured 24hEE during eucaloric and sedentary conditions at baseline in overweight individuals or in individuals with obesity who then underwent a 6-week inpatient CR period to test whether 24hEE (adjusted for body composition, i.e., energy efficiency) is a determinant of free-living weight regain one year after CR completion.

Methods

Study participants

Between 2008 and 2016, healthy overweight individuals or in healthy individuals with obesity were screened for participation in a carefully controlled inpatient CR study (clinicaltrial.gov identifier: NCT00687115)[27] consisting of three phases: 1) a 3-week baseline period when participants underwent body composition assessment and metabolic tests while receiving daily a weight maintaining diet (WMD) composed of 50%

carbohydrates, 30% fats, and 20% proteins; 2) a 6-week CR period, during which participants consumed daily a balanced, 50%-calorie reduced, liquid diet (Ensure; Abbott Laboratories, Columbus, OH, 58% carbohydrate, 27% fat, and 15% protein); and, 3) a 2-week post-CR period when participants repeated body composition assessment and metabolic tests while receiving a daily WMD based on the new achieved weight. Participants were fully informed of the nature and purpose of the study, and written informed consent was obtained before admission. The study was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases.

Out of 54 screened individuals, a total of 18 healthy overweight individuals or healthy individuals with obesity with a BMI>27 kg/m^2 and without diabetes (determined as per 75-g oral glucose tolerance test)[28] were admitted to our clinical research unit and placed on a daily adjustable WMD (50% carbohydrate, 30% fat, and 20% protein) to keep their body weight within ±1% of admission weight during the 3-week baseline period of the study[29]. On day 2 of the baseline period and during the post-CR period, percentage body fat (PFAT), fat-free mass (FFM), and fat mass (FM) were measured using dual-energy X-ray absorptiometry (DXA; DPX-1, GE Healthcare Lunar, Madison, WI).

Energy expenditure measurements

At baseline, 24hEE was measured in a large, open-circuit indirect whole-room calorimeter (respiratory chamber) for 24 hours when subjects were fed a eucaloric diet (50% carbohydrate, 30% fat, 20% protein), as previously described[27, 30]. Briefly, participants entered the whole-room calorimeter at 08:00AM after having fasted overnight and eating breakfast at 07:00AM. They remained therein for 23h and 15min during which three meals were provided at 11:00AM, 4:00PM, and 7:00PM. While in the whole-room calorimeter, participants were asked to remain sedentary and avoid exercise. The mean ambient temperature while in the whole-room calorimeter was 23.1±1.6°C (mean±SD). Twenty-four-hour energy expenditure (24hEE) and respiratory exchange ratio (RER) were calculated from previously derived equations[31] by extrapolating to 24h the average CO_2 production and O_2 consumption per minute during the 23h and 15min in the whole-room calorimeter.

To closely achieve energy balance during the 24hEE assessment in the whole-room calorimeter, 24hEE was measured twice during eucaloric conditions in the baseline period. The first eucaloric 24hEE assessment was obtained while participants resided for 24h in the whole-room calorimeter with total energy intake calculated using a unit-specific formula to achieve 24h energy balance in the confined environment of the whole-room calorimeter[30]. Participants then had another eucaloric 24hEE assessment inside the whole-room calorimeter in which the total energy intake was equal to the 24hEE value calculated during the first eucaloric 24hEE assessment, for precise determination of 24hEE during energy balance in the setting of whole-room calorimeter. During the post-CR period, 9 out of 11 participants underwent another 24hEE assessment in eucaloric, sedentary conditions with the same macronutrient composition of the baseline 24hEE assessment. Two participants did not undergo the post-CR 24hEE assessment due to technical and logistic issues.

Follow-up outpatient visits following weight loss

Out of 18 admitted participants, 15 completed the inpatient part of the study and 11 returned for monthly follow-up outpatient visits when weight measurements were obtained up to one year following discharge. One year after discharge, participants also underwent another body composition assessment. One participant only returned until the 4-month visit. Due to technical issues, one participant had no valid data for body composition at the 1-year visit.

Statistical analysis

Statistical analysis was performed using the SAS statistical software package (SAS Enterprise Guide Version 7.15; SAS Institute, Cary, NC).

Power calculations were performed prior to analyses to calculate the minimum detectable correlation between metabolic efficiency in 24hEE at baseline prior to diet-induced weight loss and free-living weight regain after 1 year of follow-up. A sample size of 11 participants achieved a statistical power >0.80 (2-sided alpha=0.05) to detect a minimum correlation of 0.74.

Unless otherwise specified, data were expressed as mean±SD or as mean with 95% confidence interval (CI). All reported weight and body composition changes (Δ) were expressed as absolute changes in kg, unless otherwise specified. Anthropometric and metabolic measurements obtained before CR, at the end of CR, and at the 1-year follow-up visit were analyzed using Student's paired t-test.

Multivariate regression analysis was used to calculate the *predicted* values of 24hEE (dependent variable) using FFM and FM at baseline as independent variables. To increase precision of regression estimates, we combined data from all participants (n=11) who returned to follow-up visits during the current study (NCT00687115) with data from another study at our section (NCT00523627) including n=97 participants undergoing the same baseline procedures (Supplemental Figure 1; supplemental material can be found at[32]). The residual values (=measured minus *predicted* values) of 24hEE obtained from the linear regression model calculated in the expanded cohort of 108 participants were derived and considered as the unexplained variability in 24hEE after *adjustment* for body composition[33]{Schlogl, 2013 #120}. *Adjusted* 24hEE was calculated in all n=11 participants by adding the average unadjusted 24hEE in this study group to the residual values obtained by regression analysis. The extent of adaptive thermogenesis (AT) in the post-CR period was calculated as the difference between measured 24hEE in the post-CR period minus the *predicted* value of 24hEE, which was calculated by applying the linear regression equation between 24hEE at baseline (dependent variable) vs. baseline FFM and FM (independent variables) to the FFM and FM values in the post-CR period, as previously described[34].

Weight regain was calculated as the difference between the weight at the 1-year follow-up visit minus the weight at the end of 6-week CR. Similar calculations were done for FFM and FM. Percentage weight regain was calculated as weight regain at 1 year divided by the weight at the end of 6-week CR multiplied by 100. Due to the intra-individual variation in weight during the 1-year follow-up period, for each participant weight regain was also expressed as a monthly *rate* of weight regain by calculating the slope of the linear regression equation of all monthly weight values during the 1-year period vs. time in months (Supplemental Figure 2)[32]. The monthly rate of weight change was further expressed as percentage of the weight measured at the end of 6-week CR.

The associations between weight regain at 1 year and 24hEE measured prior to staring CR and CR-induced body composition changes (FFM and FM losses) after 6-week CR was quantified by Pearson's correlation coefficient and confirmed by linear mixed models analysis[35, 36] including all monthly follow-up weights while accounting for repeated measures using a first-order autoregressive covariance structure and adjusting for follow-up time and for the weight at the end of 6-week CR. Sensitivity analyses were also performed using the ANCOVA method (i.e., considering weight after 1 year as dependent variable and baseline weight as predictor) and similar results were obtained.

For graphical purposes and ease of interpretation, the aforementioned analyses using continuous 24hEE data were followed up with confirmatory analyses using two distinct metabolic groups. In these confirmatory analyses, we arbitrarily categorized individuals into two groups with either a lower- or higher-than-median adjusted 24hEE prior to CR (=2446 kcal/day, Table 1). Paired t-test was used to evaluate the within-group changes in body weight and composition over the course of the study while unpaired t-test was used to compare between-group differences at different time points.

Results

The characteristics of study participants are presented in Table 1. At baseline, BMI and body fat were 39.0±8.7 kg/m^2 and 36.1±6.4%, respectively. The mean difference in adjusted 24hEE between individuals with low vs. high eucaloric 24hEE at baseline was 254±73 kcal/day (p=0.0003). There were no differences in anthropometrics between both groups (all p>0.4).

At the end of 6-week CR, participants lost 8.5±2.7% weight (−9.7±3.8 kg, p<0.0001), of which 3.4±1.2 kg were FM and 6.3±3.6 kg were FFM. After 1 year of follow-up, participants regained 5.1±8.0% body weight (+5.7±9.0 kg, p=0.08) which was mostly FFM (+5.6±5.5 kg, p=0.02) whereas no overall regain in FM was observed (p=0.7). Individual weight regain during the monthly follow-up visits is shown in Supplemental Figure 2[32]. A relatively higher adjusted 24hEE at baseline before starting CR was associated with greater weight regain 1 year after CR was completed (r=0.82, p=0.003, Figure 1A), reflecting a greater monthly rate of weight regain over 1 year of follow-up (absolute rate: r=0.62, p=0.04, Figure 1B), such that a 100 kcal/day higher adjusted 24hEE at baseline predicted an average +5.1 kg (CI: +2.2, +7.9) total greater weight gain and +0.3 kg/month greater weight gain (CI: +0.01, +0.60) after 1 year of follow-up. Similar results were obtained when using percentage weight regain after 1 year (r=0.86, p=0.001, Supplemental Figure 3A) and rate of percentage weight regain (r=0.63, p=0.04, Supplemental Figure 3B)[32]. The positive association between adjusted 24hEE at baseline and weight regain at follow-up was confirmed in a mixed model analysis using all follow-up data points for monthly weight (β= +0.5 kg/month per +100 kcal/day difference in adjusted 24hEE at baseline, CI: +0.2, +0.7,

$p<0.0001$). Similar results were obtained when the aforementioned analyses were stratified by sex (females/males) and by ethnicity (Native Americans/Caucasians) (data not shown).

The average extent of AT in the post-CR period was −126 kcal/day (CI: −277 to +24; $p=0.09$). When including the estimate of AT obtained in the post-CR period into the multivariate mixed model analysis along with adjusted 24hEE at baseline, we found that AT in the post-CR period was an independent predictor of weight regain ($\beta=+0.21$ kg/month per −100 kcal/day difference in post-CR AT, 95% CI: +0.02, +0.45, $p=0.04$), although adjusted 24hEE at baseline was still the strongest independent predictor ($\beta=+0.70$ kg/month per +100 kcal/day difference in adjusted 24hEE at baseline, 95% CI: +0.41, +1.00, $p<0.0001$) of weight regain.

Losses in FM and FFM after 6-week inpatient CR were not associated with weight regain at 1 year and the monthly rate of weight regain in univariate models (all $p\geq0.10$, Figure 1, panels C–F) but were in mixed model analyses using monthly follow-up weights (FFM loss: $\beta=+0.14$ kg/month per 10 kg FFM lost, $p=0.05$; FM loss: $\beta=+3.9$ kg/month per 10 kg FM lost, $p=0.02$). However, when adjusted 24hEE was added to the mixed models it was the sole determinant of weight regain ($p=0.009$).

A lower 24-h RER during energy balance prior to CR was associated with greater weight regain at 1 year ($r=-0.72$, $p=0.02$, Supplemental Figure 4A) and a greater monthly rate of weight regain ($r=-0.60$, $p=0.05$, Supplemental Figure 4B)[32]. These results were confirmed in mixed model analyses using monthly follow-up weights ($\beta=+1.3$ kg/month per 0.1 lower RER at baseline); however, when adjusted 24hEE was included in the mixed model analysis, 24-h RER was no longer significant ($p>0.05$) and 24hEE was the sole independent determinant of weight regain ($p=0.04$).

A higher adjusted 24hEE prior to CR was associated with both greater regain of FM ($r=0.81$, $p=0.009$, Figure 2A) and FFM ($r=0.70$, $p=0.03$, Figure 2B) after 1 year of follow-up, e.g., a 100 kcal/day higher 24hEE at baseline predicted +2.9 kg (CI: +1.0, +4.8) greater FM regain and +2.8 kg (CI: +0.3, +5.4) greater FFM regain. Greater FM loss after 6-week CR predicted greater FM regain ($r=-0.72$, $p=0.03$, Supplemental Figure 5A), and greater FFM loss after 6-week CR predicted greater FFM regain ($r=-0.75$, $p=0.02$, Supplemental Figure 5B)[32]. In partial correlation analyses controlling for either FM or FFM loss respectively, adjusted eucaloric 24hEE prior to CR was still associated with 1-year regain of FM (*partial* $r=0.76$, $p=0.03$) and tended to be associated with 1-year regain of FFM (*partial* $r=0.63$, $p=0.09$). A lower 24-h RER during energy balance prior to CR was associated with greater FM gain at 1 year ($r=-0.74$, $p=0.02$, Supplemental Figure 4C) but not with changes in FFM ($p=0.13$, Supplemental Figure 4D)[32]. In *partial* correlation analyses controlling for RER, the associations between adjusted eucaloric 24hEE prior to CR and FM and FFM gain at 1 year became insignificant (both $p>0.13$).

For illustrative purposes and to confirm our results obtained using continuous 24hEE data, we performed a group-wise comparison of individuals with *low* versus *high* eucaloric 24hEE as arbitrarily defined by the median (2446 kcal/day) value of adjusted 24hEE prior to CR (Table 1). The monthly weight regain trajectories between both groups are shown in Figure

3A. One year after CR completion, individuals with *high* eucaloric 24hEE regained 0.3 kg (CI: −2.4, +3.0) or 3.7% of their lost weight, while individuals with *low* eucaloric 24hEE regained 13.8 kg (CI: −1.1, +28.8) or 123.2% of their lost weight. Individuals with *high* eucaloric 24hEE regained 13.5±4.4 kg (CI: +4.1, +11.7) more weight after 1-year follow-up than individuals with *low* eucaloric 24hEE (p=0.009, Figure 3B). Individuals with *high* eucaloric 24hEE regained 7.4 kg (CI: +2.2, +6.9) more FM than those with *low* eucaloric 24hEE (p=0.01, Figure 3C) while FFM regain was similar between both groups (p=0.09, Figure 3D).

Discussion

In healthy individuals with obesity, we provide evidence that 24hEE during eucaloric conditions at low energy turnover prior to CR – as accurately measured for 24-h in the confined environment of a whole-room calorimeter and adjusted for body composition (e.g., energy efficiency per kg of FFM) – is a determinant of long-term, free-living weight regain following sustained (6-week) diet-induced weight loss, such that a relatively higher 24hEE by 100 kcal/day predicted greater weight regain by an average of 0.5 kg/month over one year of follow-up. Importantly, relatively higher 24hEE also predicted both greater FM and FFM regain one year after CR.

By separating study participants into two metabolic groups with either a lower- or higher-than-median adjusted eucaloric 24hEE in sedentary conditions prior to CR, we found that those participants classified as “metabolically efficient” (*low* 24hEE) were able to keep their weight stable after weight loss (8.2 kg weight lost versus 0.3 kg weight regained), while “metabolically inefficient” participants (*high* 24hEE) regained more than they had lost (11.2 kg weight lost versus 13.8 kg weight regained).

Metabolic characteristics determining the individual susceptibility to weight regain after a period of weight loss have been intensively studied over the past decades[4, 6, 8, 14–17, 37, 38]. Two major concepts emerged as plausible predictors of weight regain susceptibility: the hypothesis of “metabolic slowing” due to increased energy efficiency by Keys, Rosenbaum, Leibel, Müller, Pasman *et al*[6, 9, 37, 39, 40], and the “collateral fattening” hypothesis by Dullo *et al*[11–13]. Both concepts will be discussed with regard to the findings of the present study.

Metabolic slowing during and following CR is defined as the decrease in energy expenditure (EE) below that predicted by changes in body composition after weight loss[6–8, 39–41], a phenomenon also termed “adaptive thermogenesis”[41]. The concept of metabolic slowing, which was first introduced by Ancel Keys in his Minnesota starvation experiment[37], is hypothesized as one of the major causal factors for weight regain, especially as it has been shown to persist for up to 7 years after CR[6, 41–43]. In their seminal studies, Rosenbaum, Leibel *et al* reported that metabolic slowing after CR mostly affects nonresting energy expenditure (NREE) with less impact on resting energy expenditure (REE)[6]. They further showed that metabolic slowing after weight loss is partly mediated by increased skeletal muscle work efficiency[9, 10], which can be reversed by leptin and triiodothyronine supplementation as well as resistance training[44, 45]. These previous results indicate that increased energy efficiency in skeletal muscle work following weight loss may predispose to weight regain which appears contradictory to our present findings showing “decreased” energy efficiency during eucaloric conditions at baseline predicts weight regain. However, major differences in the conditions under which the metabolic measurements were made might explain theses seemingly divergent findings: Rosenbaum, Leibel et al. preformed their measurements of skeletal muscle efficiency following controlled weight loss and, while hypothesizing that improvement in skeletal muscle efficiency would predispose to weight regain, they did not test this with free-living follow-up. In the present study, we measured 24hEE in the confined environment of a whole-room calorimeter during energy balance, prior to any intervention. Our EE measurement mostly reflects resting EE components (REE and TEF) while we have no reliable data about NREE (where skeletal muscle work efficiency plays the major role) as physical activity was very limited in the whole-room calorimeter room and no volatile exercise was permitted as per protocol. Therefore, the metabolic efficiency in our study does not reflect “muscle efficiency” but rather “digestive” and/or “basal” efficiency per kg of body mass. We are also interested in the inter-individual differences in this measure as a driver (perhaps appetitive pathways driven by higher EE) of weight regain, rather than group differences following caloric restriction. We believe that our current results do not contradict the previous findings by Rosenbaum, Leibel et al. regarding skeletal muscle work efficiency but, rather, propose an additional opposing metabolic mechanism for REE components, which might further determine the susceptibility to weight regain after weight loss. Indeed, the results of the multivariate analysis showed that the extent of AT (or “metabolic slowing”) after 6-week CR and related weight loss and adjusted 24hEE at baseline (or “eucaloric metabolic efficiency”) were independently associated with weight regain, suggesting that they may constitute independent metabolic mechanisms contributing to weight regain after substantial, CR-induced weight loss. It remains to be elucidated in future studies whether both increased muscle work efficiency following weight loss and reduced “digestive” and/or “basal” efficiency are interrelated and characterize the metabolic phenotype of an individual.

Besides the concept of “metabolic slowing”, Dulloo *et al* developed the hypothesis of “collateral fattening”[11–13] which states that a greater loss in lean mass during CR would drive hyperphagia following CR to restore lean mass leading also to excess fat deposition, which was proposed as an explanation for weight regain and “post-starvation obesity” observed in the Minnesota starvation experiment[37].

In mixed models analyses, we found that greater CR-induced losses in FM and FFM predicted greater weight regain which is in accordance with the collateral fattening hypothesis from Dulloo *et al*[11]. However, in multivariate analyses including all three predictors (24hEE, loss in FM, loss in FFM), only adjusted 24hEE, but not CR-induced changes in body composition, remained an independent predictor of follow-up weight regain.

We therefore propose that a relatively higher metabolic rate might constitute a risk factor for weight regain to recover lean tissue after CR as proposed by Dulloo *et al*[11]. These results suggesting a potential role for EE, rather than body composition, for weight regain are in line with two previous independent studies showing that higher EE, rather than FFM, determines excess energy intake[20, 46]. In accordance with the concept of energy sensing[21–23], we hypothesize that individuals with relatively higher 24hEE might ultimately experience a greater orexigenic drive due to higher energy demands. This is supported by multiple independent studies[18, 47, 48] showing that relatively higher EE is associated with increased food intake in humans. Accordingly, we might speculate that individuals with relatively higher EE at low energy turnover have greater propensity to regain weight due to increased drive to eat. Yet, as a major limitation of the current study, we cannot provide evidence whether weight regain over 1-year follow-up is a result of increased hyperphagia. Future studies should include measurements of appetite-related hormones to elucidate the biological mechanisms underlying weight regain after sustained weight loss[49].

In prior studies, we have demonstrated that greater decrease in 24hEE from energy balance to fasting conditions predicts less weight loss during 6-week CR[27] and greater weight gain during 6-week low-protein overfeeding[50]. Remarkably, this greater decrease in 24hEE is due to a relatively higher 24hEE during energy balance rather than to a lower 24hEE during fasting[51], indicating that *thriftier* individuals have relatively higher 24hEE during energy balance[51]; however, we emphasize that this *thrifty* phenotype characterized by higher energy demands relative to body size is strictly identified under eucaloric conditions but at *low* energy turnover, namely, participants are primarily sedentary within the confined environment of whole-room calorimeter and energy intake is reduced to compensate for the decreased physical activity. On the basis of recent results for diet-induced weight loss/gain in *thrifty* individuals[27, 52], we postulate that the results of this present analysis might extend the bounds of the *thrifty* phenotype to include greater susceptibility to weight regain after clinically meaningful weight loss.

We also found that lower 24-h RER prior to weight loss was associated with greater weight regain, which is in contrast to previous studies showing that higher RER is associated with greater weight regain after weight loss[14–16] and greater *ad libitum* overeating[20, 53]. As the macronutrient composition of prescribed diets was the same for the eucaloric diet given during the 24hEE assessment at baseline and for the WMD in the prior days, the results for 24hEE are not influenced by any changes in 24-h RER due to changes in food quotient. Yet, in multivariate mixed model analyses including both 24-h RER and 24hEE during eucaloric conditions prior to CR, only 24hEE remained an independent predictor of weight regain at follow-up, suggesting that EE rather than RER may represent the causal metabolic risk factor for weight regain.

Limitations

Our study has limitations. The sample size is relatively small with n=11 participants (with n=6 and n=5 in the respective groups with *low* and *high* 24hEE) and, therefore, our results merit replication in a larger cohort. Our 24hEE measurements were obtained in sedentary conditions and low levels of spontaneous physical activity (e.g., low energy turnover), which may not reflect those in free-living conditions where we did not directly measure physical activity levels. Therefore, we cannot rule out that physical activity may constitute an independent predictor of weight regain as previously shown[54, 55], considering that higher levels of physical activity (e.g., high energy turnover) are beneficial for weight maintenance through better appetite control[56]. The variability in weight regain between individuals with *low* and *high* eucaloric 24hEE was substantial, thus we speculate that other physiological mechanisms in addition to greater energy sensing might explain the differences in weight regain between both metabolic groups, e.g., we hypothesize that differences in the free-living physical activity level might add up to these differences.

We also did not assess dietary intake after weight loss, which might also be associated with the degree of weight regain after weight loss. Importantly, we did not assess skeletal muscle work efficiency, which has been shown to be causal for metabolic slowing and might be involved in weight regain susceptibility[9, 10]. Furthermore, we did not measure changes in appetite-related hormones during and after weight loss, which might also be implicated in weight regain susceptibility after weight loss[17]. We also did not collect data about behavioral markers (e.g., healthy dieting) and cognitive features (e.g., dietary disinhibition)[57] which constitute additional determinants of weight maintenance.

Conclusion

Relatively higher EE at low energy turnover, reflecting reduced efficiency of energy utilization during isocaloric conditions, is associated with greater free-living weight regain after a period of diet-induced weight loss, which might be possibly driven by compensatory overeating relative to energy requirements (altered energy sensing) to restore body mass (mainly, FFM) after weight loss. The clinical characterization of differences in energy metabolism among individuals may lead to new strategies to prevent weight regain in overweight individuals or in individuals with obesity who undergo caloric restriction through dieting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the participants and the clinical staff of the Phoenix Epidemiology and Clinical Research Branch for conducting the examinations. The technical and logistic support of Susan Bonfiglio, PA, in performing procedures and collecting data is gratefully acknowledged.

Funding source: This study was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. P.P. was supported by the program “Rita Levi Montalcini for young researchers” from the Italian Minister of Education and Research (Ministero dell’Istruzione, dell’Università e della Ricerca).

Abbreviations:

24hEE
24-h energy expenditure

AT
adaptive thermogenesis

BMI
body mass index

CI

confidence interval

CR

caloric restriction

dual-energy X-ray absorptiometry

EE

energy expenditure

FFM

fat free mass

FM

fat mass

OGTT

oral glucose tolerance test

SPA

spontaneous physical activity

WMD

weight-maintaining diet

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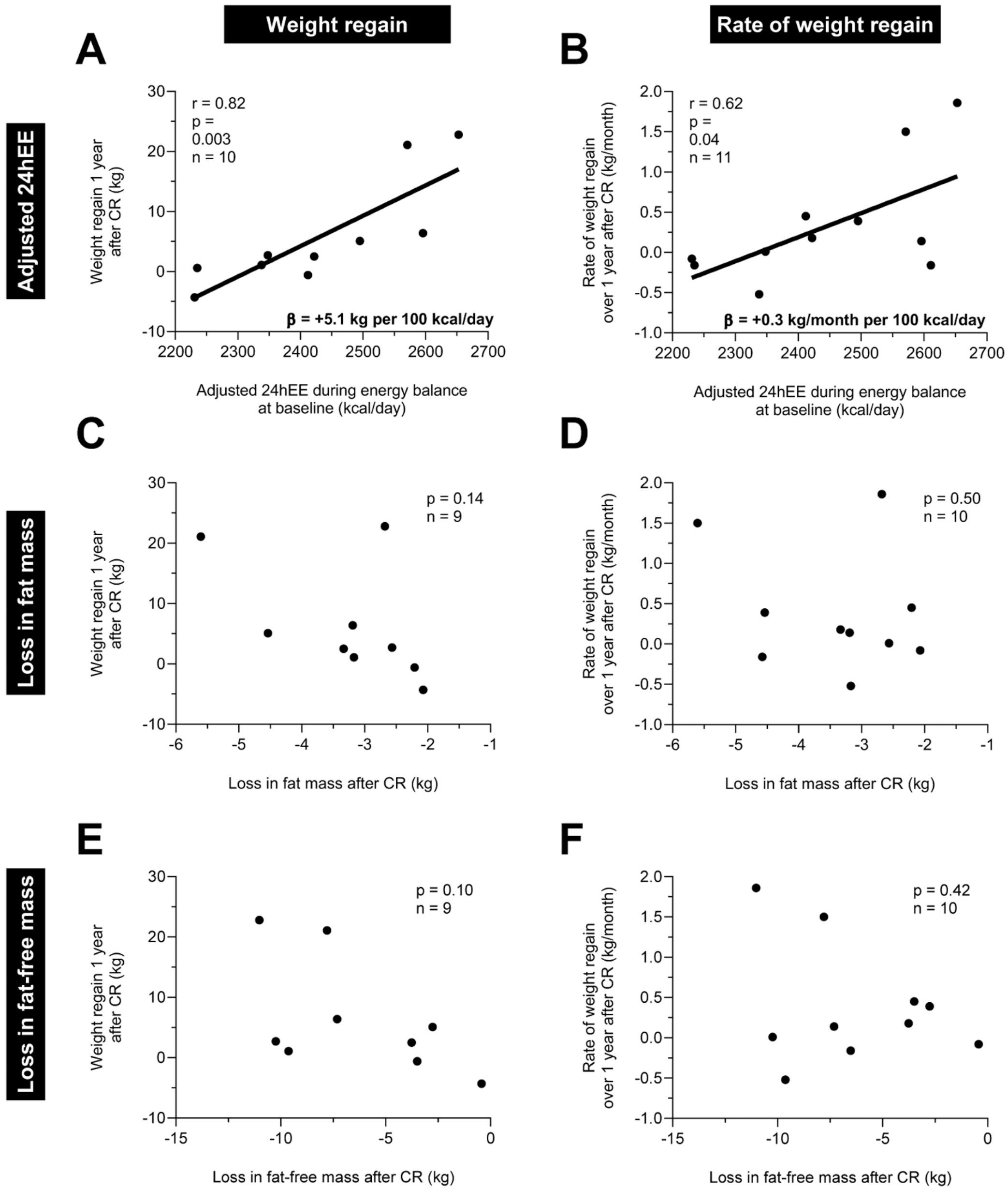

Figure 1. Higher adjusted 24hEE prior to CR, but not CR-induced losses in FFM and FM, predicted greater weight regain one year after 6-week inpatient CR.

Positive associations between adjusted 24hEE during energy balance and weight stability prior to 6-week inpatient CR with 50% of weight-maintaining energy needs and subsequent weight regain (panel A), and monthly rate of weight regain after one year of follow-up in free-living conditions (panel B).

Lack of associations between loss in fat mass after 6-week inpatient CR and 1-year weight regain (panel C), and monthly rate of weight regain after one year of follow-up (panel D).

Lack of associations between loss in fat-free mass after 6-week inpatient CR and 1-year weight regain (panel E), and monthly rate of weight regain after one year of follow-up (panel F).

24hEE, 24-hour energy expenditure; CR, caloric restriction.

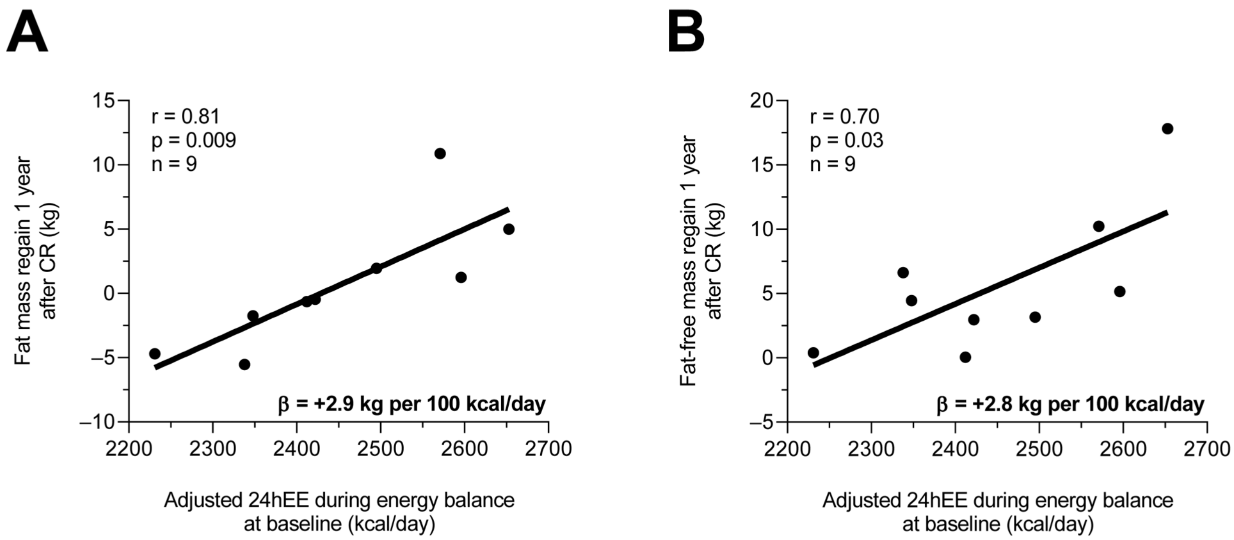

Figure 2. Higher adjusted 24hEE prior to CR predicted greater fat mass and fat-free mass regain one year after 6-week inpatient CR.

Positive associations between adjusted 24hEE during energy balance and weight stability prior to 6-week inpatient CR with 50% of weight-maintaining energy needs and fat mass regain (panel A) and fat-free mass regain (panel B) after one year of follow-up in free-living conditions.

24hEE, 24-hour energy expenditure; CR, caloric restriction.

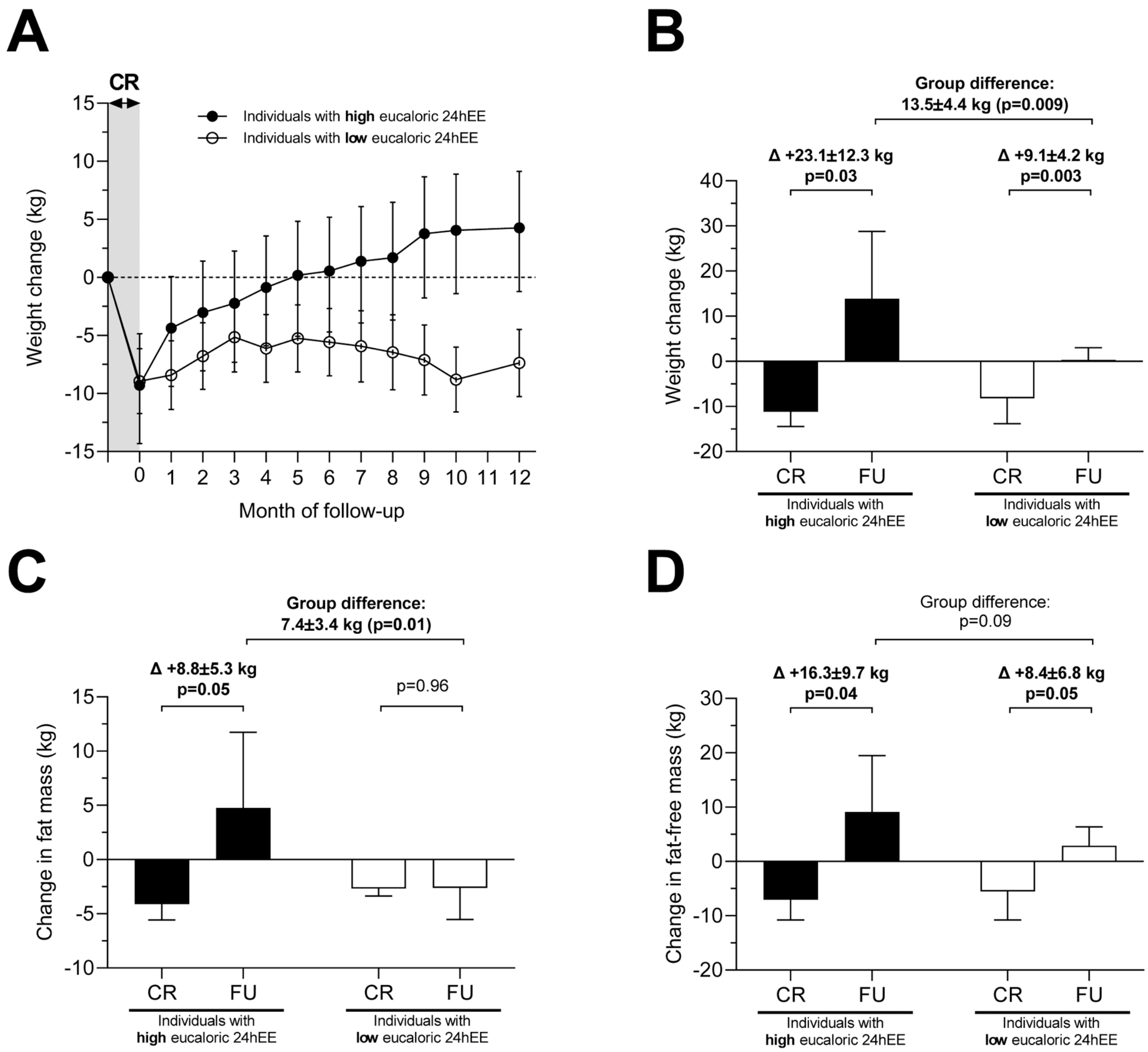

Figure 3. Individuals with higher adjusted 24hEE prior to CR showed greater regain of body weight, fat mass, and fat-free mass one year after 6-week CR.

Comparison of weight regain trajectories during 1-year follow-up period (panel A) and weight changes (panel B), fat mass changes (panel C), and fat-free mass changes (panel D) after 1 year of follow-up between participants with *high* vs. *low* adjusted 24hEE at baseline before CR. Classification of participants was based on higher- or lower-than-median adjusted 24hEE prior to CR (2446 kcal/day). Error bars denote the 95% confidence interval. Paired t-test was used to compare within-group differences, unpaired t-test was used to compare between-group differences (denoted as "group difference").

24hEE, 24-hour energy expenditure, CR, caloric restriction; FU, follow-up.

Table 1.

Baseline characteristics and changes in body weight and composition after 6-week CR and after 1-year follow-up.

	Total (n=11)	Individuals with *high* adjusted 24hEE (n=5)	Individuals with *low* adjusted 24hEE (n=6)
Demographic characteristics			
Male (%)	8 (72.7)	4 (80.0)	4 (80.0)
Ethnicity	5 CAU, 1 HIS, 5 NA	4 CAU, 1 NA	1 CAU, 1 HIS, 4 NA
Age (years)	32 ± 9.3 (22.1, 47.3)	32.4 ± 11.6 (22.1, 47.3)	31.6 ± 8 (23.2, 40.5)
Height (cm)	155.5 ± 52.3 (1.7, 190)	141.7 ± 78.8 (1.7, 190)	167 ± 12.2 (151, 184)
Anthropometrics			
Body weight (kg)	112.9 ± 23.5 (81.6, 162.9)	117.7 ± 29.3 (81.6, 162.9)	108.9 ± 19.3 (85.1, 131.7)
BMI (kg/m^2)	39 ± 8.7 (28.9, 57.4)	38.8 ± 11.5 (28.9, 57.4)	39.1 ± 6.7 (32.4, 49.6)
Body fat (%)	36.1 ± 6.4 (26.6, 46.8)	34.2 ± 7.8 (26.6, 46.8)	37.6 ± 5.4 (32.1, 45.2)
FM (kg)	40.8 ± 13.1 (29, 76.2)	41.5 ± 19.8 (29, 76.2)	40.2 ± 5.1 (36.2, 49.5)
FFM (kg)	72.1 ± 14.9 (46.6, 86.7)	76.2 ± 13.5 (52.5, 86.7)	68.7 ± 16.3 (46.6, 82.2)
Energy expenditure measures during energy balance at baseline			
24hEE (kcal/day)	2482 ± 468 (1657, 3211)	2722 ± 449 (1987, 3211)	2282 ± 415 (1657, 2673)
Adjusted 24hEE (kcal/day)[1]	2446 ± 150 (2232, 2653)	2585 ± 58 (2495, 2653)*	2331 ± 83 (2232, 2422)*
Food intake (kcal/day)	2468 ± 540 (1516, 3154)	2700 ± 420 (2009, 3154)	2275 ± 586 (1516, 2755)
Energy balance (%)	2.9 ± 19.7 (−27.4, 55.3)	0.7 ± 2.3 (−1.4, 4.2)	4.8 ± 27.6 (−27.4, 55.3)
Respiratory quotient (ratio)	0.84 ± 0.04 (0.79, 0.92)	0.81 ± 0.03 (0.79, 0.85)*	0.87 ± 0.03 (0.83, 0.92)*
SPA (% of time)	6.3 ± 4 (1.3, 12.2)	5.8 ± 3.1 (3.3, 10.9)	6.7 ± 4.9 (1.3, 12.2)
Change in weight and body composition after 6-week CR			
Weight loss (kg)	−9.7 ± 3.8 (−12.4, −7.0)	−11.2 ± 2.6 (−14.4, −8.0)	−8.2 ± 4.5 (−13.8, −2.5)
Rate of weight loss (kg/day)	−0.19 ± 0.05 (−0.27, −0.11)	−0.21 ± 0.05 (−0.28, −0.15)	−0.18 ± 0.06 (−0.24, −0.12)
FM loss (kg)[2]	−3.4 ± 1.2 (−5.6, −2.1)	−4.1 ± 1.2 (−5.6, −2.7)*	−2.7 ± 0.6 (−3.4, −2)*
FFM loss (kg)[2]	−6.3 ± 3.6 (−11, −0.4)	−7.1 ± 3 (−10.8, −3.4)	−5.5 ± 4.2 (−10.8, −0.2)
Weight regain measures at 1 year follow-up after completing CR (n=10)			
Weight regain (kg)	+5.7 ± 9.0 (−12.4, −7.0)	13.8 ± 9.4 (−1.1, 28.8)*	0.3 ± 2.6 (−2.4, 3.0)*
Rate of weight regain (kg/month)	0.33 ± 0.73 (−0.52, 1.86)	0.75 ± 0.88 (−0.35, 1.84)	−0.02 ± 0.33 (−0.37, 0.32)
FM regain (kg)[3]	0.7 ± 5 (−5.5, 10.9)	4.8 ± 4.4 (−2.2, 11.7)*	−2.6 ± 2.4 (−5.5, 0.3)*
FFM regain (kg)[3]	5.6 ± 5.5 (0, 17.8)	9.1 ± 6.5 (−1.3, 19.5)	2.9 ± 2.8 (−0.5, 6.3)

Baseline values are presented as mean ± SD for continuous variables or number (frequency) for categorical variables with minimum and maximum in parentheses. Changes in weight, FM, and FFM are presented as mean ± SD with 95% CI in parentheses.

[1:]Multivariate regression analysis was used to assess the predictors of 24hEE using FFM and FM as independent variables. Adjusted 24hEE was calculated in all 11 subjects by adding their average unadjusted 24hEE to the residual values obtained by regression analysis.

Individuals with *high*/*low* 24hEE were arbitrarily defined as those with higher/lower-than-median (2446 kcal/day) adjusted 24hEE prior to CR, respectively. Unpaired t-test was used to compare between-group differences. Significant differences between both groups are denoted with (*).

[2:] Data available from n=10 subjects.

[3:] Data available from n=8 subjects.

24hEE, 24-h energy expenditure; BMI, body mass index; CI, confidence interval; CR, caloric restriction; FM, fat mass; FFM, fat-free mass; SPA, spontaneous physical activity.