ORIGINAL ARTICLE

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Metabolic adaptation delays time to reach weight loss goals

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Abstract

Objective: The aim of this study was to determine whether metabolic adaptation, at the level of resting metabolic rate, was associated with time to reach weight loss goals, after adjusting for confounders.

Methods: A total of 65 premenopausal women with overweight (BMI: 28.6 ± 1.5 kg/m^2; age: 36.4 ± 5.9 years; 36 were White, and 29 were Black) followed an 800-kcal/d diet until BMI ≤25 kg/m^2. Body weight and composition were measured at baseline and after weight loss. Dietary adherence was calculated from total energy expenditure, determined by double labeled water, and body composition changes. Metabolic adaptation was defined as a significantly lower measured versus predicted resting metabolic rate (from own regression model). A regression model to predict time to reach weight loss goals was developed including target weight loss, energy deficit, dietary adherence, and metabolic adaptation as predictors.

Results: Participants lost on average 12.5 ± 3.1 kg ($16.1\% \pm 3.4\%$) over 155.1 ± 49.2 days. Average dietary adherence was $63.6\% \pm 31.0\%$. There was significant metabolic adaptation after weight loss (-46 ± 113 kcal/d, $p = 0.002$) and this variable was a significant predictor of time to reach weight loss goals ($\beta = -0.1$, $p = 0.041$), even after adjusting for confounders (R^2 adjusted $= 0.63$, $p < 0.001$).

Conclusion: In premenopausal women with overweight, metabolic adaptation after a 16% weight loss increases the length of time necessary to achieve weight loss goals.

INTRODUCTION

The existence or lack of, and clinical relevance, of metabolic adaptation in response to weight loss has been one of the most controversial issues in the obesity field (1-7). A careful examination of the available literature suggests that differences among studies derive from inconsistencies related to the status of energy balance (EB) and/or weight stability of the participants when measurements are taken. As such, longitudinal studies tend to report metabolic adaptation (8-13), whereas cross-sectional studies, which compare weight-reduced individuals with BMI-matched controls, tend not to report metabolic adaptation (14-18). We were recently able to show that EB status did modulate the extent of metabolic adaptation, at the level of resting metabolic rate (RMR) (19), and that if measurements were taken under conditions of weight stability, differences between measured and predicted RMR were minimal (on average 50 kcal/d) (19,20).

Regardless of the extent of metabolic adaptation, its clinical relevance remains to be fully determined. It was initially suggested that metabolic adaptation could be a potential explanatory mechanism

for long-term weight regain (relapse), as well as resistance to weight loss (1-5). However, until recently, very little evidence existed in favor or against it, except for Fothergill and colleagues (11), who showed in 2016 that metabolic adaptation after weight loss was not correlated with weight regain at 6-year follow-up in participants of The Biggest Loser competition. We have confirmed these findings in two recent studies (19,20) by showing that metabolic adaptation at the level of RMR, after weight loss, was not associated with weight regain up to 2 years of follow-up. Moreover, in another recently published manuscript, our research group showed that metabolic adaptation at the level of RMR was associated with less weight and fat mass (FM) loss in response to a low-energy diet, in men and women with obesity (21). However, it remains to be investigated whether metabolic adaptation contributes to resistance to weight loss by increasing the time necessary to achieve weight loss goals.

Therefore, the aim of this secondary analysis was to determine whether metabolic adaptation, at the level of RMR, was associated with time to reach weight loss goals, after adjusting for adherence to the diet, in a population of premenopausal women with overweight.

METHODS

Participants

Participants in this analysis were White and Black premenopausal women with overweight. They were 20 to 41 years of age, sedentary (no more than one time per week regular exercise), and had normal glucose tolerance (2-hour glucose ≤140 mg/dL following 75-g oral dose), family history of overweight/obesity in at least one first-degree relative, and no use of medications that affect body composition or metabolism. All women were nonsmokers and they reported a regular menstrual cycle. The two studies included in this retrospective analysis were both approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham (UAB). All women provided informed consent before participating in the study.

Study design

Participants included in this retrospective analysis come from two different studies (ROMEO and JULIET), performed at the Department of Nutritional Sciences at UAB, with exactly the same sequence of events (see flowchart in online Supporting Information) and same methodology and both aiming to identify metabolic predictors of weight regain. In the ROMEO study, all participants achieved weight loss with diet alone (single-arm longitudinal study with repeated measurements). In the JULIET study, participants were randomly assigned to one of three groups: (1) weight loss with aerobic exercise training three times per week; (2) weight loss with resistance exercise training three times per week; and (3) weight loss with diet alone (same diet as in ROMEO). For this secondary analysis, we included all participants from the ROMEO study and the participants randomized

Study Importance

What is already known
► The existence of metabolic adaptation is dependent on the energy balance status of the participants.
► A potential association between metabolic adaptation and weight regain in the long term remains unclear.
► Metabolic adaptation has been shown to reduce the magnitude of weight and fat mass loss in response to low-energy diets.

What does this study add?
► Metabolic adaptation increases the length of time necessary to achieve weight loss goals in premenopausal women with overweight, even after adjusting for dietary adherence.
► For each 10-kcal/d increase in metabolic adaptation, time to reach weight loss goals increased by 1 day.

How might these results change the focus of clinical practice?
► Clinicians need to consider metabolic adaptation when assessing resistance to weight loss.

to diet only from the JULIET study. During weight loss, all participants were provided an 800-kcal diet until reaching BMI ≤25 kg/m^2. Food was provided (20% to 22% fat, 20% to 22% protein, and 56% to 58% carbohydrate) by the General Clinical Research Center (GCRC) Kitchen. For detailed information about the ROMEO and JULIET studies, see Weinsier et al. (22) and Hunter et al. (23), respectively.

Testing was done, after a 4-week weight stabilization period, at baseline and after weight loss. Therefore, testing was done on average 28 days after the end of the weight loss phase. During the 4-week weight stabilization period, participants were weighed three times per week the first 2 weeks while eating their own food and weighed five times per week with food provided by GCRC the last 2 weeks. Variation in body weight during the last 2 weeks of the stabilization period, after weight loss, was −1.0 ± 1.4 kg. All testing was conducted in the follicular phase of the menstrual cycle during a 4-day GCRC inpatient stay (to ensure that physical activity and diet were standardized). Testing was done in a fasted state in the morning after spending the night in the GCRC.

Data collection

The following measurements were conducted at baseline and after weight loss, after a 4-week weight stabilization period (at both time points)

Body weight and composition

Body composition was determined by using the four-compartment model (4CM) (24), which includes in the analysis bone mineral content, total body water, and total body density to take into consideration interindividual variations in body density and the fact that Black women generally have a greater bone mineral content than do White women (25). The 4CM includes the following density assumptions: 0.9 kg/L for fat, 0.99 kg/L for water, 3.042 kg/L for total mineral (osseous and cellular), and 1.34 kg/L for the unmeasured fraction of the body composed of protein and glycogen. The model is used to calculate the percentage of FM from independent measures of total body density, total body water, and bone mineral content. Total body density was determined by whole body air displacement plethysmography using the BodPod version 1.69 (Body Composition System; Life Measurement, Concord, California) as described previously (26). Each participant was tested in a one-piece swimsuit and swim cap. Same-day repeat measures of body density by the BodPod in our laboratory had an intraclass correlation of $r = 0.98$ and standard error of the mean of 0.00365 (g/cm^3). The room that housed the BodPod was well ventilated between tests. Body weight was measured with an electronic scale while the participants were in a fasting state and immediately after they had voided in the morning. Total body water was determined by doubly labeled water (DLW). FM, fat-free mass (FFM), and bone mineral content were determined by dual-energy x-ray absorptiometry (DXA) (DPX-L; Lunar Corp, Madison, Wisconsin) with the use of software version 1.5g (Lunar).

Total energy expenditure

The DLW technique was used to measure total energy expenditure (TEE), both immediately before and after the weight loss intervention (i.e., during the last 2 weeks of the 4-week supervised weight stabilization phase, see "Study design" section). In brief, a baseline urine sample (10 mL) was collected, followed by a mixed oral dose (~0.10 g/kg ^{18}O and 0.08 g ^{2}H/kg body mass) administration of DLW. The average initial isotope enrichments of two urine samples were obtained the morning after dosing, and on the 14th day, two additional final samples were obtained and the results averaged. All urine samples were analyzed in triplicate for ^{2}H and ^{18}O by isotope ratio mass spectrometry at the Metabolism Core Laboratory of the Clinical Nutrition Research Center and the GCRC at UAB. A description of the technical aspects has been previously described (27).

Resting metabolic rate

Prior to each test, the calorimetry system (Delta Trac II; Sensor Medics, Yorba Linda, California) was calibrated with standard calibration gases. An in-house, quality control alcohol burn was performed quarterly and whenever problems or questions arose. At all times during the project, the instrument generated respiratory quotient values between 0.64 and 0.69, which are reflective of accurate function, as indicated in the manufacturer's guidelines. In addition, the instrument was serviced annually by the manufacturer to assure accurate function and calibration.

Three consecutive mornings after an overnight stay in the GCRC and a 12-hour fast, RMR was measured immediately after awakening between 6 and 7 am. Participants were not allowed to sleep, and measurements were made in a quiet, softly lit, well-ventilated room. Temperature was maintained between 22°C and 24°C. Participants were allowed to use a cover if desired. Measurements were made supine on a comfortable bed, with the head enclosed in a plexiglass canopy. After resting for 15 minutes, RMR was measured for 30 minutes with a computerized, open-circuit, indirect calorimetry system with a ventilated canopy. The last 20 minutes of measurement was used for analysis. Oxygen uptake (VO$_2$) and carbon dioxide production (CO$_2$) were measured continuously, and values were averaged at 1-minute intervals. Coefficient of variation for the repeat RMR was <4%.

Adherence to the diet

Dietary adherence was determined as proposed by del Corral and colleagues (28). First, the average TEE was assessed by DLW during EB immediately before and after the intervention. The provided energy intake (800 kcal/d) was subtracted from the average of the two TEE values to calculate the expected daily kilocalorie loss (expected daily kilocalorie loss = average TEE – 800 kcal (diet)). Second, to convert losses of FM and FFM (from DXA) to energy lost (i.e., kilocalories lost), we used energy coefficients of 9.3 kcal/g for FM and 1.1 kcal/g for FFM lost (kilocalories lost = [9.3 kcal × ΔFM(g)] + [1.1 kcal × ΔFFM(g)]). For participants accruing FFM, an energy coefficient of 1.8 kcal/g was used (29,30): total kilocalories lost when FFM was gained = [9.3 kcal × ΔFM (g)] + [1.8 kcal × ΔFFM(g)]. Third, kilocalories lost per day during the intervention were calculated by dividing total kilocalories lost during the intervention by days needed to reach the goal (number of days on diet): kilocalories lost per day = total kilocalories lost/days to goal. Fourth, knowing the actual daily kilocalories lost and the expected daily kilocalories lost, we then calculated the daily kilocalorie discrepancy, an index of dietary adherence: daily kilocalorie discrepancy = actual daily kilocalories lost – expected daily kilocalories lost. A daily kilocalorie discrepancy of zero represents 100% adherence. A positive number indicates a greater than expected daily kilocalorie loss, whereas a negative number suggests less than expected daily kilocalorie loss. Fifth, we expressed dietary adherence in relative terms: percent daily kilocalorie adherence = (actual daily kilocalorie loss/expected daily kilocalorie loss) × 100.

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 22 (IBM Corp., Armonk, New York), with data presented as mean ± SD

and statistical significance set at $p < 0.05$. Changes in body weight/composition (from DXA) and RMR over time were assessed with paired sample t tests. The presence of metabolic adaptation was tested by paired t tests, comparing measured RMR (RMRm) and predicted RMR (RMRp) at the same time points. An equation to predict RMR was derived from baseline data of the participants included in this analysis (with body composition data from 4CM):

$$\text{Model: RMRp (kilocalories/day)} = 540.680$$
$$- (4.911 \times \text{Age (years)})$$
$$- (140.760 \times \text{Race (0 for White and 1 for Black)})$$
$$+ (4.851 \times \text{FM (kg)})$$
$$+ (21.362 \times \text{FFM (kg)}). \ R^2 = 0.32; \ p < 0.001.$$

This small R^2 is due to the study design of the parent studies in which a very narrow range of BMI and age and only women were included.

Correlation analysis was performed between metabolic adaptation after weight loss and time to reach weight loss goal using Spearmen correlation coefficients. The time to reach a given threshold of body weight (BMI <25kg/m^2 in this case) for each participant depends on the amount of weight needed to be lost (target weight loss), the energy deficit induced by the diet (baseline TEE – 800), as well as the adherence to the diet and potential degree of metabolic adaptation. Therefore, a regression model to predict time to reach weight loss goal (days) was constructed using target weight loss (kilograms), energy deficit (kilocalories/day), dietary adherence, and metabolic adaptation after weight loss as predictors. Target weight loss was calculated as the difference between baseline weight and weight at BMI of 25. There was no multicollinearity among the independent variables included in the model (variance inflation factor <1.3). The study from which participants were recruited (ROMEO or JULIET) was not a predictor of time to reach weight loss goal ($\beta = -5.344$, $p = 0.545$) and as such was not included in the model.

Observed rate of weight loss was calculated as weight loss (kilograms)/duration (weeks). Predicted rate of weight loss was estimated using the factor of 9.3 kcal/g of FM lost and 1.1 kcal/g of FFM lost and assuming that 87% of the weight lost was FM (as observed in the present analysis). First, we calculated energy deficit/day as TEE baseline – 800 (energy content of the diet). Then we converted the energy deficit into weight loss as (energy deficit × 0.87)/9.3)) + (energy deficit × 13)/1.1)). Finally, we converted weight loss in grams per day into kilograms per week by multiplying by 0.007. We used two approaches to estimate energy needs: (A) using TEE at baseline and (B) using the average between TEE at baseline and TEE after weight loss.

RESULTS

Sixty-five women (37 White) with an average BMI of 28.6 ± 1.5 kg/m^2 and an average age of 36.4 ± 5.9 years were included in the present analysis. Changes in body weight and composition and RMR can be seen in Table 1. Average weight loss was 12.5 ± 3.1 kg (16.1% ± 3.4%)

TABLE 1 Anthropometrics and resting metabolic rate at baseline and after weight loss

	Baseline	After weight loss	p value
Weight (kg)	77.8 ± 6.9	65.3 ± 5.9	<0.001
FM (kg)	32.5 ± 4.7	21.6 ± 4.2	<0.001
FFM (kg)	41.5 ± 3.6	40.5 ± 3.6	<0.001
RMRm (kcal/d)	1,440 ± 203	1,305 ± 129	<0.001
RMRp (kcal/d)	1,440 ± 115	1,351 ± 106	<0.001
RMRm-p (kcal/d)	0 ± 167	−46 ± 113[a]	

Note: Data given as mean ± SD.

Abbreviations: FM, fat mass; FFM, fat-free mass; RMR, resting metabolic rate; RMRm, RMR measured; RMRp, RMR predicted.

[a] $P = 0.002$ for the comparison between RMRm-p.

achieved over an average of 22 ± 7 weeks (155 ± 49 days). Adherence to the diet was on average 64% ± 31%. RMRm was significantly lower than RMRp after weight loss (1,305 ± 129 vs. 1,351 ± 106 kcal/d, $p = 0.002$), resulting in a metabolic adaptation of −46 ± 113 kcal/d. The average expected weight to achieve BMI of 25 kg/m^2 was 68.0 ± 5.1 kg and the observed weight after the intervention was 65.2 ± 6.0 kg. The difference was 2.8 ± 2.7 kg and was statistically significant ($p < 0.001$).

There was a trend for metabolic adaptation to be inversely associated with time to reach weight loss goal ($r = -0.240$, $p = 0.055$, $n = 65$) (Figure 1). After adjusting for target weight loss, energy deficit, and adherence to the diet, metabolic adaptation was a significant predictor of time to reach weight loss goal, and the overall model explained 63% of the variation ($p < 0.001$) (Table 2). Time to reach weight loss goal (days) = 283 + 2.7 target weight loss (kilograms) – 0.1 energy deficit (kilocalories/day) – 1.3 adherence to the diet (percentage) – 0.1 metabolic adaptation (kilocalories/day). Target weight loss, energy deficit, and dietary adherence were all significant predictors of time to reach weight loss goal in the regression model ($p = 0.006$, $p < 0.001$, and $p < 0.001$, respectively). However, when performing simple correlation, only dietary adherence was significantly correlated with time to reach weight loss goal ($r = -0.705$, $p < 0.001$, $n = 65$). If adherence to the diet is not included, then the model is not significant (R^2 adj = 1.7%, $p = 0.258$), and none of the variables in the model are significant predictors.

No significant associations were seen between metabolic adaptation and target weight loss ($r = -0.109$, $p = 0.386$, $n = 65$), energy deficit ($r = -0.004$, $p = 0.978$, $n = 65$), or dietary adherence ($r = 0.181$, $p = 0.149$, $n = 65$).

There was a tendency for those participants with negative metabolic adaptation (RMRm < RMRp, $n = 46$) to take a longer time to reach their weight loss goals compared with those with positive metabolic adaptation (RMRm > RMRp, $n = 19$) (165 ± 55 vs. 139 ± 42 days, respectively, $p = 0.071$).

No significant association was found between metabolic adaptation and rate of weight loss (kilograms/week) ($r = -0.092$, $p = 0.463$, $n = 65$) or difference between observed and predicted rate of weight loss ($r = -0.036$, $p = 0.703$ and $r = -0.02$, $p = 0.873$ for approach A and B, respectively).
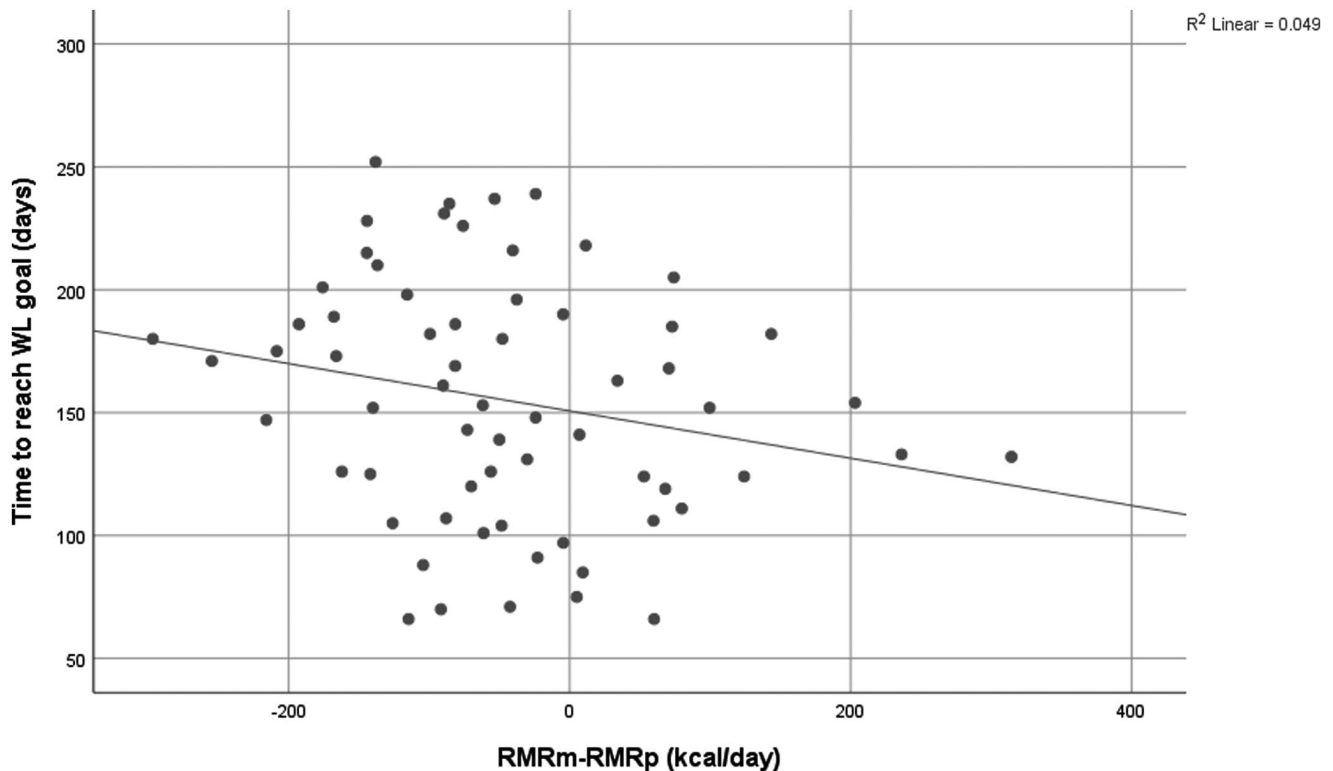
FIGURE 1 Simple correlation between metabolic adaptation at the level of RMR (RMRm-RMRp) and time to reach WL goal (days). The larger the metabolic adaptation, the longer was the time needed to reach WL goal. RMR, resting metabolic rate; RMRm, RMR measured; RMRp, RMR predicted; WL, weight loss

TABLE 2 Regression model for predicting time to reach weight loss goal (days) in women with overweight

Model	β	R^2 adjusted	p
		0.63	<0.001
Intercept	283		<0.001
Target weight loss (kg)	2.7		0.006
Energy deficit TEE (kcal/d)	−0.1		<0.001
Adherence to the diet (%)	−1.3		<0.001
Metabolic adaptation (kcal/d)	−0.1		0.041

Abbreviation: TEE, total energy expenditure.

DISCUSSION

The present findings represent the first study examining whether metabolic adaptation, at the level of RMR, was associated with time to reach weight loss goals. We found that the larger the metabolic adaptation (RMRm-RMRp) after weight loss, the longer was the time needed to reach weight loss goals (BMI = 25 kg/m²), even after adjusting for target weight loss, energy deficit, and adherence to the diet, suggesting strategies to decrease metabolic adaptation and increase adherence to diet may expedite weight loss.

In the present analysis, women with overweight who experienced an average weight loss of 13 kg (16.1%) over 155 ± 49 days

had a metabolic adaptation of approximately −50 kcal/d. It needs to be emphasized that this metabolic adaptation was seen after 4 weeks of weight stabilization following the active weight loss phase and, as such, is probably much lower that what would be expected during the active weight loss phase. In line with this, we have recently shown a significant reduction, in fact more than halving, in metabolic adaptation when measurements were done after 4 weeks of weight stabilization, in comparison to when measurements were performed immediately after weight loss (19). More specifically, a significant metabolic adaptation at the level of RMR of −92 ± 110 kcal/d was seen immediately after a 14-kg (13%) weight loss in individuals with obesity, which was significantly reduced, yet still significant (−38 ± 124 kcal/d), after 4 weeks of weight stabilization (19). So measuring RMR immediately after weight loss resulted in a metabolic adaptation that was 2.42 (92/38) times larger compared with when RMR was measured after a period of weight stabilization. Moreover, a significant positive moderate correlation was found between metabolic adaptation immediately after weight loss and metabolic adaptation after 4 weeks of weight stabilization ($r = 0.663$, $p < 0.001$, $n = 71$). Therefore, it is reasonable to expect that metabolic adaptation during active weight loss in the present study may have been closer to −110 kcal/d (−46 × 2.42) than −46 kcal/d.

Our regression model showed that even after adjusting for target weight loss, energy deficit, and adherence to the diet, metabolic adaptation was still a significant predictor of time to reach weight loss goals. For each 10-kcal/d increase in metabolic adaptation,

the time to reach weight loss goal increased by 1 day. This might not seem like much because the average metabolic adaptation was only approximately −50 kcal/d. However, as discussed in detail in the previous paragraph, this value is likely to be underestimated, and a more reasonable estimation would be −120 kcal/d during active weight loss, with a large interindividual variation, ranging from −700 to +750 kcal/d. That means that those with the largest magnitude of metabolic adaptation would need to stay on the diet for 70 additional days (compared with a person with no metabolic adaptation) in order to reach their weight loss goal, even after adjusting for adherence to the diet. This probably helps to explain some of the variation in time needed to reach weight loss goals (range 66 to 252 days). Importantly, this is assuming that metabolic adaptation during active weight loss would occur only at the level of resting energy expenditure, which has been shown not to be the case, and metabolic adaptation might, in fact, be of a larger magnitude at the level of nonresting energy expenditure (8,9).

We and others have shown that metabolic adaptation, either measured during active weight loss (11,19) or after a short period of weight stabilization (4 weeks) (19,20), is not a risk factor for weight regain. However, metabolic adaptation might lead to resistance to weight loss, as shown in the present study. Even though adherence to the diet is clearly the most important determinant of time to reach weight loss goals, the present findings are of great clinical relevance as they mean that individuals who are struggling to achieve weight loss goals, despite assuring compliance with the diet, may indeed be "suffering" from metabolic adaptation during active weight loss.

The present findings are in line with recent data from our group showing that metabolic adaptation at the level of RMR was associated with less weight and FM loss following low-energy diets in individuals with obesity (21). Moreover, Goele and colleagues (31) reported that in women who experienced metabolic adaptation after a low-energy diet, 38% of the difference between measured and predicted weight loss was due to metabolic adaptation at the level of RMR. These two studies and the present analysis suggest that a lower-than-expected weight loss, or a delay in reaching weight loss goals, may not necessarily result from lack of compliance to the intervention. Metabolic adaptation can modify the outcome of a weight loss intervention, albeit to varying degrees (because of the very large interindividual differences in metabolic adaptation). The success in the clinical management of individuals with obesity therefore needs to be tailored according to individual variations for any relevant phenotype, including the presence or absence of metabolic adaptation in response to weight loss.

Our study has both strengths and limitations. Gold-standard procedures were used for the measurements of RMR (after a 4-day GCRC inpatient stay and an overnight sleep, under controlled condition of feeding and physical activity), body composition (4CM), and estimation of diet adherence (TEE by DLW). However, this study also suffers from some limitations. First, it includes a very homogenous sample of premenopausal (20 to 41 years) women with overweight. This prevents the generalization of our results to men, other BMI groups, and older participants. Moreover, this also explains why our

regression model had an R^2 of only 32%, i.e., a truncated range for both BMI and age and only women. Second, metabolic adaptation was measured after 4 weeks of weight stabilization and as such is likely underestimated, which might have weakened the association between metabolic adaptation and time to reach weight loss goals. Third, estimating dietary adherence in free-living conditions is challenging, and there is no perfect method. Our approach has limitations as it includes TEE after weight loss, which will, in itself, contain some degree of metabolic adaptation. However, there was no multicollinearity among the predictors included in the regression model. Moreover, similar approaches have been used by other researchers when estimating dietary adherence and expected weight loss for a given intervention (32,33). Future studies are needed with better measures of adherence to pursue the hypotheses generated here. Finally, we did not assess changes in the anatomical and molecular composition of FFM. Muller and coworkers (34) have recently shown that in order to accurately assess metabolic adaptation, FFM, as well as its composition at the organ/tissue and molecular levels, needs to be taken into account and that the magnitude of metabolic adaptation may be lower than usually estimated based on FFM alone.

CONCLUSION

In conclusion, in premenopausal women with overweight, metabolic adaptation after a 16% weight loss increases the length of time necessary to achieve weight loss goals. Further research should confirm these findings in a population of men and women with obesity.○

AUTHOR CONTRIBUTIONS
GRH designed and conducted the study; CM performed the statistical analysis and had primary responsibility for final content; CM, GRH, and BAG wrote the manuscript; and all authors assisted with data interpretation and read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.