Article:
Hopkins, M orcid.org/0000-0002-7655-0215, Gibbons, C, Caudwell, P et al. (5 more authors) (2014) The adaptive metabolic response to exercise-induced weight loss influences both energy expenditure and energy intake. European Journal of Clinical Nutrition, 68 (5). pp. 581-586. ISSN 0954-3007

https://doi.org/10.1038/ejcn.2013.277

THE ADAPTIVE METABOLIC RESPONSE TO EXERCISE-INDUCED WEIGHT LOSS INFLUENCES BOTH ENERGY EXPENDITURE AND ENERGY INTAKE.

Mark Hopkins[1, 2], Catherine Gibbons[2], Phillipa Caudwell[2], Per M. Hellström[3], Erik Näslund[4], Neil A. King[5], Graham Finlayson[2] & John E. Blundell[2].

[1]Academy of Sport and Physical Activity, Faculty of Health and Wellbeing, Sheffield Hallam University, Sheffield, UK. [2]Institute of Psychological Sciences, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom. [3]Department of Medical Sciences, Uppsala University, Uppsala, Sweden. [4]Division of Surgery, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden. [5]School of Exercise and Nutrition Sciences, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia.

Corresponding author:

Mark Hopkins,
Academy of Sport and Physical Activity,
Faculty of Health and Wellbeing,
Sheffield Hallam University,
Sheffield,
United Kindom.

Tel: +44 (0) 1142 255368.
Email: M.Hopkins@shu.ac.uk.

Running Title: Exercise-Induced Adaptive Thermogenesis.

Conflicts of Interest and Disclosure of Funding:

The authors declare no conflicts of interest. This research was supported by BBSRC grant numbers BBS/B/05079 and BB/G005524/1 (DRINC), EU FP7 Full4Health (#266408) and the Stockholm county council (ALF).

ABSTRACT

Background: A decline in resting energy expenditure (REE) beyond that predicted from changes in body composition has been noted following dietary-induced weight loss. However, it is unknown whether a compensatory down-regulation in REE also accompanies exercise-induced weight loss, or whether this adaptive metabolic response influences energy intake (EI). **Methods:** Thirty overweight and obese women (BMI = 30.6 ± 3.6kg·m^{-2}) completed 12 weeks of supervised aerobic exercise (EX). Body composition, metabolism, EI and metabolic-related hormones were measured at baseline, week six and post-intervention. The metabolic adaptation i.e. difference between predicted and measured REE was also calculated post-intervention (MA_{post}), with REE predicted using a regression equation generated in an independent sample of 66 overweight and obese women (BMI = 31.0 ± 3.9kg·m^{-2}). **Results:** While mean predicted and measured REE did not differ post-intervention, 43% of participants experienced a greater than expected decline in REE (-102.9 ± 77.5kcal·day^{-1}). MA_{post} was associated with the change in leptin ($r = 0.47$; $p = 0.04$), and the change in resting fat ($r = 0.52$; $p = 0.01$) and carbohydrate oxidation ($r = -0.44$; $p = 0.02$). Furthermore, MA_{post} was also associated with the change in EI following EX ($r = -0.44$; $p = 0.01$). **Conclusions:** Marked variability existed in the adaptive metabolic response to EX. Importantly, those who experienced a down-regulation in REE also experienced an up-regulation in EI, indicating that the adaptive metabolic response to exercise influences both physiological and behavioural components of energy balance.

KEY WORDS: Exercise-induced weight loss, energy intake, resting energy expenditure, leptin.

INTRODUCTION

While a reduction in resting energy expenditure (REE) following dietary energy restriction is well documented (1), it has been suggested that some individuals experience a greater than expected decline in REE based on changes in fat mass (FM) and fat-free mass (FFM) (2). This compensatory down-regulation in REE is thought to be an auto-regulatory response that acts to attenuate the prescribed energy deficit and protect against sustained weight loss (3). Importantly, this adaptive response in energy expenditure is characterised by marked individual variability (4), and may help explain the disparity between predicted and actual weight loss observed during weight loss interventions (5). However, it should be noted that the existence and clinical importance of such adaptive thermogenesis during weight loss has been contested (6, 7).

The adaptive suppression of REE during weight loss is thought to result from a down-regulation in sympathetic nervous system (SNS) activity, which is mediated through weight-induced changes in thyroid hormones (8, 9) and in particular, leptin (10, 11). However, although leptin influences the regulation of energy expenditure and energy intake (EI), the impact of adaptive thermogenesis on EI during weight loss has not been examined. Furthermore, while adaptive thermogenesis has been established following dietary-induced weight loss, its existence during exercise-induced weight loss (i.e. exercise alone) has yet to be examined. This is of importance as the biological and behavioural responses to dietary-and-exercise-induced weight loss may differ. Therefore, this study aimed to examine the extent of adaptive thermogenesis during exercise-induced weight loss, and its effect on compensatory eating during 12 weeks of supervised aerobic exercise.

MATERIALS AND METHODS

PARTICIPANTS

Thirty overweight and obese women (BMI = 30.6 ± 3.6kg·m^{-2}) participated in the present study. Participants were recruited from the University of Leeds, UK and surrounding areas using poster advertisements and recruitment emails. Participants were physically inactive (≤ 2hrs·wk^{-1} of exercise over the previous six months), weight stable (± 2kg for the previous three months), non-smokers and not taking medication known to effect metabolism or appetite. All participants provided written informed consent before taking part, and ethical approval was granted by the Institute of Psychological Sciences Ethics Board, University of Leeds, and the Leeds West NHS Research Ethics Committee (09/H1307/7).

STUDY DESIGN

Participants completed a 12 week supervised aerobic exercise program (EX) designed to expend 2500kcal·wk^{-1}. Body composition, REE, EI and fasting glucose, insulin and leptin were measured at baseline, week six and post-intervention. To disclose any change in REE that could not be explained by changes in body composition, the difference between predicted and measured REE was calculated during EX. To predict REE, a regression equation based on FM and FFM was generated in an independent reference population of 66 sedentary women, matched for age and body composition (BMI = 31.0 ± 3.9kg·m^{-2}).

EXERCISE PROTOCOL

Participants in EX completed a 12 week aerobic exercise program, expending 500kcal per session at 70% of age-predicted maximum heart rate (i.e. 220 - age), five days per week. All exercise sessions were supervised in the research laboratory, and participants could choose from a range of exercise modes (running, cycling or rowing stepping). Individual exercise

prescriptions were calculated using standard stoichiometric equations (12), based on the relationship between heart rate and VO_2/VCO_2 during a maximal incremental treadmill test. To account for changes in cardiovascular fitness during the intervention, the incremental test was performed at baseline, week six and post-intervention, with the exercise prescription adjusted accordingly. To verify and record the duration and intensity of exercise, participants wore heart rate monitors during each session (Polar RS400, Polar, Kempele, Finland). Total exercise-induced energy expenditure during the intervention was 27960 ± 3479kcal, which represented >98% of the prescribed exercise-induced energy expenditure.

PHYSIOLOGICAL MEASURES

At baseline, week six and post-intervention, REE, body composition and maximal aerobic capacity (VO_{2peak}) were measured in the morning (7-9am) following an overnight fast (10-12hrs). Baseline measures were taken prior to the start of EX (i.e. in a sedentary state), while post-intervention measures were taken during the week following the completion of EX (with a minimum of 48hrs between the final exercise session). Upon arrival, REE was initially measured using an indirect calorimeter fitted with a ventilated hood (GEM, Nutren Technology Ltd, Cheshire, UK), using the procedures outlined by The American Dietetic Association (13). Participants remained awake but motionless in a supine position for 45 minutes, with REE calculated using the Weir equation (14) from respiratory data averaged over the final 30 minutes of assessment. The non-protein respiratory exchange ratio (RER) was calculated as the ratio of VCO_2 to VO_2, while fat and carbohydrate (CHO) oxidation rates were calculated using standard stoichiometric equations (12). These calculations were based on the assumption that nitrogen excretion was negligible.

Following the measurement of REE, body composition was measured using air-displacement plethysmography (BOD POD Body Composition System, Life Measurement, Inc., Concord,

USA). After voiding, participants were weighed (to the nearest 0.01kg) and instructed to sit in the BOD POD. Measurements were then taken according to manufacturers' instructions, with thoracic gas volumes estimated using the manufacturer's software. Finally, VO_{2peak} was determined using a validated maximal incremental treadmill test (15), with expired air (Sensormedics Vmax29, Yorba Linda, USA) and heart rate (Polar RS400, Polar, Kempele, Finland) continoulsy measured. Respiratory and heart rate data from the incremental treadmill test were also used to determine the relationship between VO_2/VCO_2 and heart rate during exercise, and used alongside standard stoichiometric equations (12) to calculate individual exercise prescriptions.

METABOLIC AND APPETITE RELATED HORMONES

Fasting glucose, insulin and leptin were measured at baseline, week six and post-intervention in a sub-sample of 20 participants who completed EX. Fasting venous blood samples were collected into EDTA-containing monovette tubes. After collection, blood samples were centrifuged for 10min at 4˚C at 3500 rpm and were immediately pipetted into eppendorf tubes and stored at -80˚C until analysis. Insulin and leptin were analysed using a magnetic bead based multiples kit (Millipore, Billerica, MA, USA). Insulin sensitivity was calculated using the homeostatic model of assessment (HOMA) (16).

ASSESSMENT OF FOOD INTAKE

Food intake was measured at baseline, week six and post-intervention using a laboratory-based test meal protocol. At each time point, participants completed two meal days (separated by at least one day) in which they consumed test meals at 4-hourly intervals during the day that were either high (>50% of energy from fat) or low in fat (<20% of the energy from fat). The order of these days was randomized and counter-balanced, and no exercise was performed on these days. The mean proportion of energy contributed by fat, protein, and

carbohydrate to total daily EI during the high fat meal days was 54.4%, 7.9%, and 37.7%, respectively. During the low fat meal days, the mean proportion of energy contributed by fat, protein, and carbohydrate to total daily EI was 19.3%, 8.3%, and 72.4%, respectively. During these meal days, participants consumed only the foods/drinks provided to them, but *ad libitum* water consumption was permitted. Meals consisted of an individualised energy breakfast (*ad libitum* at baseline and then fixed at baseline levels for the remainder of EX), a fixed energy lunch (800kcals) and *ad libitum* dinner meal. After the dinner meal, participants were free to leave the research unit but were given an *ad libitum* snack box of foods to consume if desired during the evening. A detailed description of the foods provided can be found elsewhere (17).

All meals consumed in the research unit were eaten in isolation, with participants instructed to eat as much or as little as they wanted until comfortably full (during *ad libitum* meal consumption). Food was provided in excess of expected consumption, with participants able to request further food and water if required. Energy intake was calculated by weighing the food before and after consumption to the nearest 0.1g, and with reference to the manufacturers' energy values. To calculate test meal EI, the energy equivalences used for protein, fat and carbohydrate were 4, 9 and 3.75kcal$\cdot$g^{-1}, respectively. Before commencing the study, participants completed a food preference questionnaire, and if they strongly disliked any of the test foods, they were excluded if a suitable alternative (matched for macronutrient composition) could not be found.

CALCULATION OF THE METABOLIC ADAPTATION

In order to predict REE during the intervention, a regression equation was generated from an independent sample of overweight and obese women (REF). This reference population did not include individuals who participated in EX, and REE and body composition were

measured in REF using the same procedures described in the present study. As can be seen in Tables 1 and 2, no differences existed between REF and EX at baseline in terms of age, body composition, REE or RER. Initially, age, FM and FFM were entered as independent variables into a stepwise multiple regression model, based on previous findings indicating these variables to be independent determinants of REE (18). In the present study, FM and FFM were retained in the model (probability of F to enter, $p < 0.05$), and the following predictive equation was constructed:

$$REE = 407.034 + (18.796*FFM) + (7.889*FM).$$

This equation was then used to predict REE at week six and post-intervention, using the measured values of FM and FFM at these time points. To disclose any adaptations in REE not accounted for by changes in FM and FFM, the residual between predicted and measured REE (i.e. the metabolic adaptation; MA) was then calculated at week six (MA_{six}) and post-intervention (MA_{post}).

Insert figure 1 here.

CLASSIFICATION OF POSITIVE AND NEGATIVE METABOLIC ADAPTATION

In order to highlight the impact of the adaptive response in REE on the physiological and behavioural responses to weight loss, the direction of the post-intervention difference between predicted and measured REE was used to classify participants as either experiencing a negative metabolic adaptation i.e. a greater than predicted decline in REE, or a positive metabolic adaptation i.e. a change in REE equal to or greater than predicted.

STATISTICAL ANALYSIS

Data are reported as mean ± SD throughout. Statistical analyses were performed using IBM SPSS for windows (Chicago, Illinois, Version 20). The contribution of age, FM and FFM to the observed between-subject variation in REE within REF was examined by stepwise multiple linear regression (probability of F to enter, $p < 0.05$). Changes in body composition and metabolism were examined using one-way repeated measures ANOVA, with group (i.e. positive or negative metabolic adaptation) entered as a between-subject factor. To examine changes in EI on the high and low fat probe days, a two-way ANOVA (Time*Condition) with repeated measures was used. Where appropriate, Greenhouse-Geisser probability levels were used to adjust for sphericity and Bonferoni adjustments were applied to control for multiple *post-hoc* comparisons. The average EI (EI_{ave}) during the high and low fat meal days was also calculated at baseline, week six and post-intervention. After controlling for baseline differences between predicted and measured REE, partial correlations were used to test the associations between MA_{six} and MA_{post} and substrate oxidation, EI, fasting glucose and insulin. Similarly, hierarchical multiple regression was used to test the associations between MA_{six} and MA_{post} and fasting leptin (after controlling for change in FM).

RESULTS

CHANGES IN BODY COMPOSITION AND FOOD INTAKE.

Compared to baseline values, body mass ($p = 0.034$) and FM ($p = 0.004$) were significant lower post-intervention, while the increase in FFM following EX failed to reach significance ($p = 0.057$). However, examination of the individual responses in body composition revealed marked individual variability (Figure 2), with the change in BM and FM ranging from -7.7kg to +3.8kg and -8.4kg to +2.0kg, respectively. Similarly, the change in FFM ranged from-1.8kg to +3.1kg. This variability could not be explained by differences total exercise-induced

energy expenditure, with simple linear regression indicated that differences in total exercise-induced energy expenditure only account for 4% ($F_{(1, 29)} = 1.165$, $p = 0.290$; $R^2 = 0.04$) and less than 1% ($F_{(1, 29)} = 0.082$, $p = 0.776$; $R^2 = 0.00$) of the variance in the change in BM and FM, respectively.

Insert figure 2 here.

Post-intervention values of EI_{HF} and EI_{LF} (or EI_{ave}) did not differ from baseline (individual p values > 0.05), but EI was significantly higher during the high fat meal days than during the low fat days ($p < 0.001$; Table 1).

Insert table 1 here.

THE METABOLIC ADAPTATION

As can be seen in Table 2, measured REE did not differ significantly from baseline at week six ($p = 0.070$) or post-intervention ($p = 0.247$). Similarly, post-intervention values of resting RQ ($p = 0.081$), resting fat oxidation ($p = 0.252$) or CHO oxidation ($p = 0.174$), fasting glucose ($p = 0.451$), fasting insulin ($p = 0.657$) or the HOMA index ($p = 0.108$) did not change significantly from baseline. However, there was a significant decline in fasting leptin following EX ($p = 0.041$).

Insert table 2 here.

While predicted and measured REE did not differ at week six ($p = 0.465$) or post-intervention ($p = 0.710$; Table 2), the proportion of variance accounted for by the predictive equation

252 decreased from 70% at baseline (r = 0.84; R^2 = 0.70; p < 0.001) to 30% post-intervention (r =
253 0.55; R^2 = 0.30; p = 0.002; Figure 1). Indeed, examination of the individual responses in
254 MA_{post} revealed marked between-subject variability, with 43% (n = 13) of participants
255 experiencing a greater than expected decline in REE following EX (mean decline = -102.9 ±
256 77.5kcal·day^{-1}). Furthermore, those who experienced a negative metabolic adaptation i.e. a
257 greater than predicted decline in REE (n = 13) exhibited attenuated losses in body mass (42%
258 difference: -1.1 ± 2.5kg vs. -1.9 ± 2.9kg) and FM (27% difference: -1.9 ± 2.1kg vs. -2.6 ±
259 2.7kg) following EX as compared to those experiencing a positive metabolic adaptation i.e. a
260 change in REE equal to or greater than predicted (n = 17; mean increase in REE = 129.5 ±
261 113.5kcal·day^{-1}).

262 **THE METABOLIC ADAPTATION, RESTING SUBSTRATE OXIDATION AND**
263 **LEPTIN.**

264 After controlling for the change in FM, hierarchical multiple regression indicated that the
265 change in fasting leptin following EX was positively correlated with MA_{six} (r = 0.81; R^2 =
266 0.44; p < 0.001) and MA_{post} (r = 0.46; R^2 = 0.21; p = 0.048), such that a greater decline in
267 leptin was associated with a greater compensatory down-regulation in REE (n = 20).
268 Furthermore, those who experienced a negative metabolic adaptation exhibited larger
269 reductions in leptin following EX (mean reduction = -20.3%) than those who experienced a
270 positive metabolic adaptation (mean reduction = -3.5%). MA_{post} was positively associated
271 with the change in resting fat oxidation following EX (r = 0.53; p = 0.005), with a
272 compensatory down-regulation in REE was associated with an attenuated increase in resting
273 fat oxidation. Changes in resting fat (r = 0.59; p = 0.012) and CHO oxidation (r = -0.61; p =
274 0.009) following EX were also associated with the change in fasting leptin (independent of
275 changes in FM and FFM). Furthermore, the associations between the metabolic adaptation

(i.e. MA_{six} and MA_{post}), fasting leptin and resting fat oxidation remained after controlling for baseline differences in predicted REE (using hierarchical multiple regression).

THE METABOLIC ADAPTATION AND FOOD INTAKE.

MA_{post} was negatively associated with the change in EI_{HF} ($r = -0.54$; $R^2 = 0.24$; $p = 0.003$) and EI_{ave} following EX ($r = -0.45$; $R^2 = 0.20$; $p = 0.015$; Figure 3), such that a compensatory down-regulation in REE was associated with increased food intake following EX. Again, these associations between MA_{post} and food intake remained after controlling for baseline differences in predicted REE. Furthermore, changes in EI_{HF} (+79.7 ± 338.3kcal·day^{-1} vs. -342.7 ± 256.3kcal·day^{-1}; $p = 0.001$) and EI_{ave} (-34.0 ± 296.2kcal·day^{-1} vs. -257.9 ± 255.7kcal·day^{-1}; $p = 0.038$) following EX differed significantly between those who experienced a negative and positive metabolic adaptation, respectively.

Insert Figure 3 here.

DISCUSSION

This study aimed to examine the extent of adaptive thermogenesis during exercise-induced weight loss, and whether this adaptive metabolic response influenced both EI and EE. Here, we have demonstrated that despite the overall preservation of FFM and REE, marked individual variability existed in the metabolic adaptation to exercise-induced weight loss. Indeed, 43% of individuals experienced a greater than predicted decline in REE following the exercise intervention which could not be explained by changes in FM and FFM. Importantly, those individuals who experienced a compensatory down-regulation of REE also experienced a concomitant up-regulation in food intake following the exercise intervention.

While adaptive thermogenesis has been disclosed following dietary-induced weight loss, whether a similar compensatory response in REE exists following exercise-induced weight loss has not previously been examined. Importantly, we show here that marked individual variability existed in the adaptive metabolic response in REE following EX. Although the mean values of predicted and measured REE did not differ post-intervention, 43% of individuals experienced a decline in REE that was greater than would be expected based on the changes in body composition (mean decline: -102.9 ± 77.5kcal·day^{-1}). This adaptive metabolic response occurred despite a mean weight loss of only -1.3 ± 2.7kg following the intervention. However, consistent with previous findings (19-21), the group changes in body composition masked marked individual variability (Figure 2). Therefore, these data indicate that in some individuals, exercise-induced weight loss is characterised by a compensatory down-regulation in REE that moderates the capacity of chronic exercise to reduce body weight. Indeed, large differences existed in the loss of body mass (42%) and FM (27%) between those who experienced a negative and positive metabolic adaptation.

In agreement with studies examining dietary-induced weight loss (11, 22, 23), the compensatory down-regulation in REE observed in the present study was associated with the change in fasting leptin following EX (independent of changes in FM). Baseline fasting leptin concentrations decreased by 13% during EX, and this decline was related to the change in FM. However, the change in leptin was also related to MA_{six} and MA_{post}, such that a greater decline in leptin following EX was associated with a greater compensatory down-regulation in REE (independent of FM). Leptin has been causally implicated in dietary-induced adaptive thermogenesis, as decreased levels of circulating leptin have been shown to decrease SNS activity and EE (24). Indeed, it has been suggested that in those who experience an adaptive suppression of REE, weight loss and the weight-reduced state is interpreted by the brain as one of relative leptin deficiency, despite an actual surplus of stored energy i.e. FM (25).

Another important feature of the adaptive metabolic response to EX was that individuals who experienced a greater than expected decline in REE also demonstrate a reduced ability to up-regulate resting fat oxidation in response to the exercise intervention. Taken together, the changes in energy expenditure and substrate oxidation would favour the defence of body weight rather than promote weight loss. Indeed, the change in resting RER has been shown to be an independent predictor of the change in FM following chronic aerobic exercise (20), while a greater reliance on CHO oxidation at rest has been shown to predict future weight gain (26-28). As the changes in resting substrate oxidation were strongly associated with the change in leptin in the present study, the relationship between MA_{post} and the changes in resting substrate oxidation may again relate to a leptin-induced blunting of SNS activity, as the SNS is known to regulate both substrate oxidation and energy expenditure (29).

A strength of the present study was the objective measurement of food intake alongside body composition and metabolism. Importantly, this approach disclosed novel relationships between the adaptive metabolic response to EX and food intake. Indeed, a major finding was that a compensatory down-regulation in REE was also associated with up-regulation in food intake during EX. Indeed, significant differences existed in the change in EI between those who experienced negative or positive metabolic adaptations. While MA_{post} was not associated with the change in EI_{LF}, this likely reflects the varying energy density of the two conditions i.e. a smaller change in the amount consumed would have had a larger effect on daily EI under the high fat rather than the low fat condition. It should also be noted that food intake was measured during this study using a laboratory-based test meal protocol. While this approach allowed for the sensitive measurement of volitional intake (free from contamination from external factors), it is acknowledged that laboratory based feeding protocols do not necessarily reflect food intake in the (more turbulent) free-living environment.

Importantly, a down-regulation in REE and up-regulation in EI in susceptible individuals would act synergistically to attenuate any exercise-induced energy deficit. However, while these data are suggestive of a coordinated adaptive metabolic and behavioural response in some individuals, further studies are required to determine the mechanisms underlying this relationship. However, leptin may again be central to this, as exogenous leptin administration has not only been shown to reverse the adaptive suppression of REE in weight-reduced individuals (30), but also the decline in satiation associated with weight maintenance (31).

In the present study, MA_{post} was characterised by a marked individual variability. While this variability will in part reflect errors in the measurement and prediction of REE, the fact that MA_{post} was associated with a range of independent metabolic and behavioural variables suggests that this variance was primarily biologically driven (rather than due to methodological caprice). Indeed, a noticeable characteristic of dietary-induced adaptive thermogenesis is the large individual variability observed (4).It should also be noted that body composition was measured using a 2-compartmental model in the present study, and as such, it was not possible to examine how changes in the composition of FFM, or in the distribution of different fat depots, influenced the metabolic adaptation.

CONCLUSION

In summary, these data indicate that marked variability exists in the metabolic adaptation to chronic aerobic exercise (i.e. MA_{post}), with some individuals experiencing a greater than expected decline in REE following exercise-induced weight loss. Importantly, those individuals who experienced a compensatory down-regulation in REE also experienced a concomitant up-regulation in food intake. This co-ordinated adaptive response in susceptible individuals would act synergistically to attenuate perturbations to energy balance, favouring the defence of body weight rather than promoting weight loss. As such, these findings may

help explain why some individuals lose less weight than expected following chronic aerobic exercise. Furthermore, while the underlying mechanisms still need to be determined, the change in leptin may play a role in the compensatory down-regulation of REE and promotion of food intake.

GRANTS

This research was supported by BBSRC grant numbers BBS/B/05079 and BB/G005524/1 (DRINC), EU FP7 Full4Health (#266408) and the Stockholm County Council.

DISCLOSURES

The authors declare no conflicts of interest.

REFERENCES

1. Schwartz A, Doucet É. Relative changes in resting energy expenditure during weight loss: a systematic review. Obes Rev. 2010;11(7):531-47.

2. Tremblay A, Royer M, Chaput J, Doucet E. Adaptive thermogenesis can make a difference in the ability of obese individuals to lose body weight. Int. J. Obes. 2013;37(6):759-64.

3. Major G, Doucet E, Trayhurn P, Astrup A, Tremblay A. Clinical significance of adaptive thermogenesis. Int. J. Obes. 2007;31(2):204-12.

4. Dulloo A, Jacquet J, Montani JP, Schutz Y. Adaptive thermogenesis in human body weight regulation: more of a concept than a measurable entity? Obes Rev. 2012;13(S2):105-21.

5. Byrne NM, Wood R, Schutz Y, Hills AP. Does metabolic compensation explain the majority of less-than-expected weight loss in obese adults during a short-term severe diet and exercise intervention. Int J Obes. 2012;36:1472-8.

6. Flatt J. Exaggerated claim about adaptive thermogenesis. Int. J. Obes. 2007;31(10):1626-.

7. Schwartz A, Kuk JL, Lamothe G, Doucet E. Greater than predicted decrease in resting energy expenditure and weight loss: results from a systematic review. Obesity. 2012;20(11):2307-10.

8. Heilbronn L, de Jonge L, Frisard M, DeLany J, Larson-Meyer D, Rood J, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA. 2006;295(13):1539-48.

9. Johannsen DL, Knuth ND, Huizenga R, Rood JC, Ravussin E, Hall KD. Metabolic slowing with massive weight loss despite preservation of fat-free mass. J Clin Endocrinol Metab. 2012;97(7):2489-96.

10. Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. J Clin Endocrinol Metab. 2002;87(5):2391-97.

11. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. J Clin Invest. 2005;115(12):3579.

12. Peronnet F, Massicotte D. Table of nonprotein respiratory quotient: an update. Can J Sport Sci. 1991;16(1):23-9.

13. Compher C, Frankenfield D, Keim N, Roth-Yousey L. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc. 2006;106(6):881-903.

14. Weir JBV. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1-9.

15. Achten J, Jeukendrup AE. Maximal fat oxidation during exercise in trained men. Int J Sports Med. 2003;24(8):603-8.

16. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.

17. Caudwell P, Finlayson G, Gibbons C, Hopkins M, King N, Naslund E, et al. Resting metabolic rate is associated with hunger, self-determined meal size, and daily energy intake and may represent a marker for appetite. Am J Clin Nutr. 2013;97(1):7-14.

18. Johnstone AM, Murison SD, Duncan JS, Rance KA, Speakman JR. Factors influencing variation in basal metabolic rate include fat-free mass, fat mass, age, and circulating thyroxine but not sex, circulating leptin, or triiodothyronine. Am J Clin Nutr. 2005;82(5):941-8.

19. King NA, Hopkins M, Caudwell P, Stubbs R, Blundell JE. Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss. Int J Obes. 2008;32(1):177-84.

20. Barwell N, Malkova D, Leggate M, Gill J. Individual responsiveness to exercise-induced fat loss is associated with change in resting substrate utilization. Metabolism. 2009;58(9):1320-8.

21. Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN. Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women. PLoS One. 2009;4(2):e4515.

22. Lecoultre V, Ravussin E, Redman LM. The fall in leptin concentration is a major determinant of the metabolic adaptation induced by caloric restriction independently of the changes in leptin circadian rhythms. J Clin Endocrinol Metab. 2011;96(9):E1512-E6.

23. Doucet E, Pierre SS, Alméras N, Mauriège P, Richard D, Tremblay A. Changes in energy expenditure and substrate oxidation resulting from weight loss in obese men and women: is there an important contribution of leptin? J Clin Endocrinol Metab. 2000;85(4):1550-6.

24. Snitker Sr, Pratley RE, Nicolson M, Tataranni PA, Ravussin E. Relationship between muscle sympathetic nerve activity and plasma leptin concentration. Obes Res. 1997;5(4):338-40.

25. Rosenbaum M, Kissileff HR, Mayer LES, Hirsch J, Leibel RL. Energy intake in weight-reduced humans. Brain Res. 2010;1350:95-102.

454 26. Zurlo F, Lillioja S, Esposito-Del Puente A, Nyomba B, Raz I, Saad M, et al. Low
455 ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ. Am J
456 Physio- Endoc M. 1990;259(5):E650-7.
457 27. Seidell J, Muller D, Sorkin J, Andres R. Fasting respiratory exchange ratio and resting
458 metabolic rate as predictors of weight gain: the Baltimore Longitudinal Study on Aging. Int J
459 Obes Relat Metab Disord. 1992;16(9):667-74.
460 28. Marra M, Scalfi L, Covino A, Esposito-Del Puente A, Contaldo F. Fasting respiratory
461 quotient as a predictor of weight changes in non-obese women. Int J Obes Relat Metab
462 Disord. 1998;22(6):601-3.
463 29. Baak Mv. The peripheral sympathetic nervous system in human obesity. Obes Rev.
464 2001;2(1):3-14.
465 30. Rosenbaum M, Hirsch J, Gallagher D, Leibel R. Long-term persistence of adaptive
466 thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr.
467 2008;88(4):906-12.
468 31. Kissileff HR, Thornton JC, Torres MI, Pavlovich K, Mayer LS, Kalari V, et al. Leptin
469 reverses declines in satiation in weight-reduced obese humans. Am J Clin Nutr.
470 2012;95(2):309-17.
471

FIGURE CAPTIONS

Figure 1: Scatter plots illustrating the relationship between predicted and measured resting energy expenditure at baseline, week six and post-intervention (n = 30). The proportion of variance in measured resting energy expenditure explained at baseline was 70% (r = 0.84; R^2 = 0.70; $p < 0.001$), 59% at week six (r = 0.77; R^2 = 0.59; $p < 0.001$) and 30% post-intervention (r = 0.55; R^2 = 0.30; p = 0.002).

Figure 2: Individual changes in body mass (kg) and fat mass (kg) following **the 12 week exercise intervention. Each pair of histograms represents one participant (n = 30).**

Figure 3: Scatter plot illustrating the relationship between the post-intervention metabolic adaptation and the change in energy intake following the 12 week exercise intervention **(n = 30).**

TABLES

Table 1: Mean (SD) baseline characteristics and changes in body composition and food intake during the exercise intervention (n = 30).

Table Footnote:

Delta Δ, baseline to post-intervention change; EI_{ave}, average energy intake during the high and low fat conditions; EI_{HF}, energy intake during the high fat condition; EI_{LF}, energy intake during the low fat condition. *Significant difference between baseline and post-intervention values in EX ($p < 0.05$). *Significant difference between baseline and post-intervention values in EX ($p < 0.01$). ^{a,b,c}Significant difference in EI between the high and low fat probe days.

Table 2: Mean (SD) baseline characteristics and metabolic changes during the exercise intervention.

Table Footnote:

505 Delta Δ, baseline to post-intervention change; REE, resting energy expenditure; RQ,
506 respiratory quotient; CHO, carbohydrate; FFM, fat-free mass. *Significant difference
507 between baseline and post-intervention values in EX ($p < 0.05$). Of note, fasting glucose,
508 insulin and leptin were measured in 20 individuals only.
509
510