

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

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34 **ABSTRACT**

35

36 **Background:** A decline in resting energy expenditure (REE) beyond that predicted from
37 changes in body composition has been noted following dietary-induced weight loss.
38 However, it is unknown whether a compensatory down-regulation in REE also accompanies
39 exercise-induced weight loss, or whether this adaptive metabolic response influences energy
40 intake (EI). **Methods:** Thirty overweight and obese women ($BMI = 30.6 \pm 3.6 \text{ kg m}^{-2}$)
41 completed 12 weeks of supervised aerobic exercise (EX). Body composition, metabolism, EI
42 and metabolic-related hormones were measured at baseline, week six and post-intervention.
43 The metabolic adaptation i.e. difference between predicted and measured REE was also
44 calculated post-intervention (MA_{post}), with REE predicted using a regression equation
45 generated in an independent sample of 66 overweight and obese women ($BMI = 31.0 \pm$
46 3.9 kg m^{-2}). **Results:** While mean predicted and measured REE did not differ post-
47 intervention, 43% of participants experienced a greater than expected decline in REE (-102.9
48 $\pm 77.5 \text{ kcal day}^{-1}$). MA_{post} was associated with the change in leptin ($r = 0.47$; $p = 0.04$), and the
49 change in resting fat ($r = 0.52$; $p = 0.01$) and carbohydrate oxidation ($r = -0.44$; $p = 0.02$).
50 Furthermore, MA_{post} was also associated with the change in EI following EX ($r = -0.44$; $p =$
51 0.01). **Conclusions:** Marked variability existed in the adaptive metabolic response to EX.
52 Importantly, those who experienced a down-regulation in REE also experienced an up-
53 regulation in EI, indicating that the adaptive metabolic response to exercise influences both
54 physiological and behavioural components of energy balance.

55

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

58 **INTRODUCTION**

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

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

80

81

82 MATERIALS AND METHODS

83 PARTICIPANTS

84 Thirty overweight and obese women ($BMI = 30.6 \pm 3.6 \text{kg}\cdot\text{m}^{-2}$) participated in the present
85 study. Participants were recruited from the University of Leeds, UK and surrounding areas
86 using poster advertisements and recruitment emails. Participants were physically inactive (\leq
87 $2 \text{hrs}\cdot\text{wk}^{-1}$ of exercise over the previous six months), weight stable ($\pm 2 \text{kg}$ for the previous
88 three months), non-smokers and not taking medication known to effect metabolism or
89 appetite. All participants provided written informed consent before taking part, and ethical
90 approval was granted by the Institute of Psychological Sciences Ethics Board, University of
91 Leeds, and the Leeds West NHS Research Ethics Committee (09/H1307/7).

92

93 STUDY DESIGN

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

101 EXERCISE PROTOCOL

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

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

114

115 **PHYSIOLOGICAL MEASURES**

116 At baseline, week six and post-intervention, REE, body composition and maximal aerobic
117 capacity ($\text{VO}_{2\text{peak}}$) were measured in the morning (7-9am) following an overnight fast (10-
118 12hrs). Baseline measures were taken prior to the start of EX (i.e. in a sedentary state), while
119 post-intervention measures were taken during the week following the completion of EX (with
120 a minimum of 48hrs between the final exercise session). Upon arrival, REE was initially
121 measured using an indirect calorimeter fitted with a ventilated hood (GEM, Nutren
122 Technology Ltd, Cheshire, UK), using the procedures outlined by The American Dietetic
123 Association (13). Participants remained awake but motionless in a supine position for 45
124 minutes, with REE calculated using the Weir equation (14) from respiratory data averaged
125 over the final 30 minutes of assessment. The non-protein respiratory exchange ratio (RER)
126 was calculated as the ratio of VCO_2 to VO_2 , while fat and carbohydrate (CHO) oxidation rates
127 were calculated using standard stoichiometric equations (12). These calculations were based
128 on the assumption that nitrogen excretion was negligible.

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

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

140 **METABOLIC AND APPETITE RELATED HORMONES**

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

148 **ASSESSMENT OF FOOD INTAKE**

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

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

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

175 **CALCULATION OF THE METABOLIC ADAPTATION**

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

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

186

$$187 \text{ REE} = 407.034 + (18.796 * \text{FFM}) + (7.889 * \text{FM}).$$

188

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

194

195 Insert figure 1 here.

196

197 **CLASSIFICATION OF POSITIVE AND NEGATIVE METABOLIC ADAPTATION**

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

203

204 **STATISTICAL ANALYSIS**

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

220 **RESULTS**

221 **CHANGES IN BODY COMPOSITION AND FOOD INTAKE.**

222 Compared to baseline values, body mass ($p = 0.034$) and FM ($p = 0.004$) were significant
223 lower post-intervention, while the increase in FFM following EX failed to reach significance
224 ($p = 0.057$). However, examination of the individual responses in body composition revealed
225 marked individual variability (Figure 2), with the change in BM and FM ranging from -7.7kg
226 to +3.8kg and -8.4kg to +2.0kg, respectively. Similarly, the change in FFM ranged from-
227 1.8kg to +3.1kg. This variability could not be explained by differences total exercise-induced

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

232

233 Insert figure 2 here.

234

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

238 Insert table 1 here.

239

240 **THE METABOLIC ADAPTATION**

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

247

248 Insert table 2 here.

249

250 While predicted and measured REE did not differ at week six ($p = 0.465$) or post-intervention
251 ($p = 0.710$; 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 = $-102.9 \pm$
256 $77.5\text{kcal}\cdot\text{day}^{-1}$). 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: $-1.1 \pm 2.5\text{kg}$ vs. $-1.9 \pm 2.9\text{kg}$) and FM (27% difference: $-1.9 \pm 2.1\text{kg}$ vs. $-2.6 \pm$
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 = $129.5 \pm$
261 $113.5\text{kcal}\cdot\text{day}^{-1}$).

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

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

278 **THE METABOLIC ADAPTATION AND FOOD INTAKE.**

279 MA_{post} was negatively associated with the change in EI_{HF} ($r = -0.54$; $R^2 = 0.24$; $p = 0.003$)
280 and EI_{ave} following EX ($r = -0.45$; $R^2 = 0.20$; $p = 0.015$; Figure 3), such that a compensatory
281 down-regulation in REE was associated with increased food intake following EX. Again,
282 these associations between MA_{post} and food intake remained after controlling for baseline
283 differences in predicted REE. Furthermore, changes in EI_{HF} ($+79.7 \pm 338.3\text{kcal}\cdot\text{day}^{-1}$ vs. -
284 $342.7 \pm 256.3\text{kcal}\cdot\text{day}^{-1}$; $p = 0.001$) and EI_{ave} ($-34.0 \pm 296.2\text{kcal}\cdot\text{day}^{-1}$ vs. $-257.9 \pm$
285 $255.7\text{kcal}\cdot\text{day}^{-1}$; $p = 0.038$) following EX differed significantly between those who
286 experienced a negative and positive metabolic adaptation, respectively.

287

288 Insert Figure 3 here.

289

290 **DISCUSSION**

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

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

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

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

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

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

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

364 **CONCLUSION**

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

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

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379 **DISCLOSURES**

380 The authors declare no conflicts of interest.

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472 **FIGURE CAPTIONS**

473

474 **Figure 1:** Scatter plots illustrating the relationship between predicted and measured resting
475 energy expenditure at baseline, week six and post-intervention (n = 30). The proportion of
476 variance in measured resting energy expenditure explained at baseline was 70% ($r = 0.84$; R^2
477 $= 0.70$; $p < 0.001$), 59% at week six ($r = 0.77$; $R^2 = 0.59$; $p < 0.001$) and 30% post-
478 intervention ($r = 0.55$; $R^2 = 0.30$; $p = 0.002$).

479

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

482

483 **Figure 3:** Scatter plot illustrating the relationship between the post-intervention metabolic
484 adaptation and the change in energy intake following the 12 week exercise intervention (n =
485 **30**).

486

487 **TABLES**

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

490

491 *Table Footnote:*

492

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

499

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

502

503 *Table Footnote:*

504

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