

Does metabolic compensation explain the majority of less-than-expected weight loss in obese adults during a short-term severe diet and exercise intervention?

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1 **Title:** Does metabolic compensation explain the majority of less-than-expected weight loss in obese
2 adults during a short-term severe diet and exercise intervention?

3

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21 **Running Head:** Compensatory responses with energy restriction

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28 **Abstract**

29 **Objective:** We investigated to what extent changes in metabolic rate and composition of weight loss
30 explained the less-than-expected weight loss in obese men and women during a diet-plus-exercise
31 intervention.

32 **Design:** 16 obese men and women (41 ± 9 years; BMI 39 ± 6 kg/m²) were investigated in energy
33 balance before, after and twice during a 12-week VLED (565–650 kcal/day) plus exercise (aerobic
34 plus resistance training) intervention. The relative energy deficit (EDef) from baseline requirements
35 was severe (74-87%). Body composition was measured by deuterium dilution and DXA and resting
36 metabolic rate (RMR) by indirect calorimetry. Fat mass (FM) and fat-free mass (FFM) were
37 converted into energy equivalents using constants: 9.45 kcal/gFM and 1.13 kcal/gFFM. Predicted
38 weight loss was calculated from the energy deficit using the '7700 kcal/kg rule'.

39 **Results:** Changes in weight (-18.6 ± 5.0 kg), FM (-15.5 ± 4.3 kg), and FFM (-3.1 ± 1.9 kg) did not
40 differ between genders. Measured weight loss was on average 67% of the predicted value, but ranged
41 from 39 to 94%. Relative EDef was correlated with the decrease in RMR ($R=0.70$, $P<0.01$) and the
42 decrease in RMR correlated with the difference between actual and expected weight loss ($R=0.51$,
43 $P<0.01$). Changes in metabolic rate explained on average 67% of the less-than-expected weight loss,
44 and variability in the proportion of weight lost as FM accounted for a further 5%. On average, after
45 adjustment for changes in metabolic rate and body composition of weight lost, actual weight loss
46 reached 90% of predicted values.

47 **Conclusion:** Although weight loss was 33% lower than predicted at baseline from standard energy
48 equivalents, the majority of this differential was explained by physiological variables. While lower-
49 than-expected weight loss is often attributed to incomplete adherence to prescribed interventions, the
50 influence of baseline calculation errors and metabolic down-regulation should not be discounted.

51
52 **Key Words:** metabolic compensation, adaptive thermogenesis, predicted weight loss, resting
53 metabolic rate, energy restriction, exercise, metabolic downregulation

54

55

56 **Introduction**

57 A common approach to facilitate weight loss is to reduce energy intake. When determining the
58 expected weight loss from a dietary intervention, the method often undertaken is to calculate the
59 energy deficit from weight maintenance requirements at baseline; then multiply by duration of deficit;
60 and then divide the total accumulated deficit by a value such as the Wishnofsky constant (e.g. 7700
61 kcal/kg) (1). However, baseline energy deficit calculations such as these commonly overestimate the
62 actual weight loss achieved (2, 3). While a lack of adherence is often cited as the primary reason for
63 the shortfall in weight loss (2-4), it is also recognised that biological compensatory responses are
64 elicited when energy restriction is imposed, essentially acting to reduce energy expenditure (5), which
65 in turn reduces the energy deficit and can reduce the weight loss (6-11). Furthermore, the energy
66 density of weight loss is not uniform, and initial body fat, the magnitude of weight loss, and use of
67 resistance exercise or high protein diets may influence the applicability of the Wishnofsky constant
68 (12).

69
70 As it is the largest component of total daily energy expenditure, researchers have long been interested
71 in changes to resting metabolic rate (RMR) that accompany energy restriction, and the extent to which
72 variance in RMR may differentiate levels of success in weight loss interventions. Although there is
73 considerable debate as to whether the change in RMR with weight loss is prognostic of successful
74 long-term weight maintenance (13-16), it is well accepted that RMR decreases substantially during
75 energy restriction even before significant weight loss has occurred (16-18). The seminal research
76 undertaken in the Minnesota semi-starvation trials on lean men demonstrated that the decline in RMR
77 was most rapid in the first 2 weeks, indicating that the reduced metabolic activity of the body tissues
78 occurred quickly in response to energy deficiency (19). These adaptive responses are equally evident
79 in obese individuals when energy restricted despite them having substantial energy stores (16).

80
81 To accurately predict the amount of weight loss that is physiologically possible requires appropriately
82 accounting for biological compensatory responses that alter the energy deficit trajectory during energy
83 restriction. The extent to which metabolic adjustments may explain the less-than-expected weight loss

84 has been examined using RMR data collected in energy balance before and after the weight loss
85 intervention (2, 3, 20). However, predictions of expected weight loss must account for the reductions
86 in energy expenditure that occur *during* energy restriction, and which are greater than is evident in the
87 weight-reduced energy balance state. Another alteration to daily energy expenditure that accompanies
88 energy restriction is the reduction in dietary-induced thermogenesis (DIT). DIT is the increase in
89 energy expenditure above resting values as a consequence of digestion, absorption and processing of
90 nutrients, as well as the associated sympathetic nervous system response (21). Even without any
91 improved metabolic efficiency in DIT (i.e. reduced thermogenesis per calorie ingested) during energy
92 restriction, a modest to severe reduction in energy intake will result in a meaningful absolute decrease
93 in DIT, particularly for individuals with a large habitual energy intake. Without accounting for this
94 reduction in energy expenditure, the expected weight loss during energy restriction can be
95 miscalculated.

96

97 In light of each of these potential sources of error, the current study was undertaken to examine the
98 extent to which changes in metabolic rate and the composition of weight loss explained the less-than-
99 expected weight loss in obese men and women undergoing short-term severe caloric restriction during
100 a diet-plus-exercise intervention.

101

102

103 **Subjects and Methods**

104 *Study Participants*

105 Sixteen participants (41 ± 9 years; BMI 39 ± 6 kg/m²) were recruited for the study. Eligibility was
106 dependent upon being euthyroid, non-diabetic, ambulatory, having a BMI >30 kg/m², having been
107 weight stable (± 2 kg) for at least 6 months, and being sedentary. Sedentary was defined as no regular
108 physical activity (>60 minutes per week) including work-related physical activity. Respondents were
109 ineligible for inclusion if they were taking medication known to affect body composition or electrolyte
110 balance, pregnant or lactating, planning to fall pregnant in the next 12 months, postmenopausal, or non-
111 ambulatory. The University Human Research Ethics Committee approved the study and signed
112 informed consent was obtained from all participants before enrolment. Participants were required to be
113 available for testing on the same day and time of day each month, and to complete exercise training at
114 the University four times per week.

115

116 *Study Design*

117 Participants were required to maintain dietary habits and usual level of physical activity for the three
118 weeks between recruitment and baseline testing; the mean weight change during this period was $0.2 \pm$
119 0.5 kg (-0.7 to $+1.0$ kg). Participants undertook two graded exercise treadmill tests during this 3-week
120 period to determine maximal aerobic power and blood lactate thresholds using methods published
121 previously (22). One week preceding the start of the intervention, participants underwent baseline
122 testing of RMR and body composition. Participants were prescribed a 12-week very-low-energy-diet
123 (VLED) plus exercise training program. Body composition and metabolic measures were repeated
124 after the 4th and 8th week of energy restriction, and 7–10 days after completion of the intervention
125 with a weight maintaining (energy balance) diet imposed.

126

127 *Intervention*

128 Very-Low-Energy Diet (VLED)

129 The ketogenic VLED incorporated replacement of two meals a day with a liquid formula. Each 40 g
130 supplement provided 640 kJ (15.2 g of protein, 1.8 g fat, and 19.2 g of carbohydrate), with 40% of the

131 energy from protein, 10% from fat, and 50% from carbohydrate. Each 40 g supplement of the formula
132 provided 50% of the recommended daily allowance for essential vitamins and minerals. Participants
133 were instructed in how to prepare the third major meal of the day from lean meat (cooked weight: 120
134 g for females and 210 g for males) and non-starch vegetables. Additionally, participants were
135 instructed to take two multivitamin supplements per day. The energy intake was 650 kcal/d (2730
136 kJ/d) for males and 565 kcal/d (2373 kJ/d) for females. Protein intake was 0.94 ± 0.14 g/kg for males
137 and 0.90 ± 0.16 g/kg for females. The diet was medically monitored, and all participants attended a
138 weekly consultation with a medical practitioner. Adherence to the diet was evaluated each week
139 through assessment of urine acetoacetic acid concentration (mmol/L) using Ketostix™ reagent strips
140 (Bayer Corp, USA). Participants with urinary ketone concentrations less than 1.5 mmol/L, indicative
141 of negative or trace values, were educated as to appropriate dietary protocol. No participant recorded
142 low ketone concentrations more than once during the study.

143

144 Exercise Training

145 The training program provided consisted of four aerobic, and two resistance weight training, sessions/
146 week which were supervised and offered between 0600-2200 hrs six days/week. The aerobic training
147 involved participants walking around a marked grass track at a heart rate 5-10% below the anaerobic
148 threshold, verified using heart rate monitors (Polar 620i, Polar Electro, Oulu, Finland). The aerobic
149 exercise duration began at 30 min/session for the first four weeks, and progressively increased to 60-
150 min during the third month of the intervention. The resistance training sessions involved eight
151 resistance exercises per session: shoulder press, chest press, lat pull down, leg press, bench press,
152 quarter-to-half squats, upright row, and abdominal exercises. In the first month two sets of each
153 exercise were completed per session (set 1 = 10 reps, set 2 = maximal reps to failure while
154 maintaining proper form). The intensity of the exercise was 60% 1-RM week 1, 70% 1-RM week 2
155 and 3, and 80% 1-RM week 4. The second and third months incorporated three sets/session at 80% 1-
156 RM (set 1/2 = 10 reps, set 3 = maximal reps to failure). All participants completed >95% of the
157 required exercise training sessions.

158

159 ***Anthropometry and Body Composition***

160 Body height (stretch stature) was measured to the nearest tenth of a centimetre using a Harpenden
161 stadiometer, and body weight was measured to the nearest 100 grams recorded on a Wedderburn
162 digital scale (BWB600). Body composition was determined by dual energy x-ray absorptiometry
163 (DXA; Lunar DPX, Lunar, Madison, WI) (23) and from measurements of total body water (TBW)
164 using the stable, non-radioactive, non-toxic isotope deuterium ($^2\text{H}_2\text{O}$) as previously published (24).

165

166 ***Resting Metabolic Rate (RMR)***

167 RMR was measured using a ventilated hood system (Deltatrac II, Datex, Helsinki, Finland) calibrated
168 before each measurement with standardised gases. All testing was conducted between 0700-0900 hrs
169 after a 12-hour overnight fast. Participants arrived at the laboratory by car and were instructed to
170 minimise physical activity prior to arrival. Prior to RMR measurement, all participants rested for 45-
171 min during a whole body DXA measurement. Testing was performed in a thermoneutral environment
172 with participants lying supine in a comfortable position, head on a pillow, and a transparent ventilated
173 hood placed over their head. Plastic sheeting attached to the hood was placed around the participant
174 to form a seal between the air inside and outside the hood. During the measurement period
175 participants remained supine, breathed normally, were instructed not to talk or fidget, and listened to
176 quiet music to reduce boredom and remain awake. After a 10-min adaptation to the hood, VO_2 and
177 VCO_2 were measured continuously for 30-min, and the data with the lowest 10-min coefficient of
178 variation was used for analyses as we have previously published (25). RMR was calculated using the
179 Weir equation (26).

180

181 ***Calculations of energy requirements and energy deficit***

182 Baseline weight maintenance energy requirements ($\text{WM}_{\text{baseline}}$) were calculated as RMR multiplied by
183 a physical activity level (PAL) of 1.5. We have recently presented data from a similar cohort
184 demonstrating that weight stability can be maintained over 4 weeks in obese adults using this
185 approach (27). The baseline energy deficit for each participant was calculated as the baseline WM
186 plus exercise energy expenditure minus intervention energy intake. The energy expenditure of aerobic

187 exercise was determined from an individualised regression equation between HR and the indirect
 188 calorimetry-derived energy expenditure developed using steady state data from the GXT. The energy
 189 expenditure of the resistance training sessions was calculated using values derived from previous
 190 studies using comparable exercises (28-30). The energy equivalence of FM and FFM loss was
 191 determined from standard caloric equivalents: 9.45 kcal/gFM and 1.13 kcal/gFFM (31, 32).

192

193 Five different approaches were employed to determine predicted weight loss:

194 **Approach 1:** Predicted weight loss was initially calculated from the baseline EDef \div 7700

195 $[(WM_{\text{baseline}} + \text{exercise energy expenditure (ExEE)} - \text{intervention energy intake (EI)}) \times 84 \text{ days} \div 7700$
 196 kcal/kg ; where EI is 650 kcal/d for men and 565 kcal/d for women.

197 **Approach 2:** Approach 1 + adjustment for the decrease in dietary-induced thermogenesis (DIT)

198 $[(WM_{\text{baseline}} + \text{ExEE} - \text{EI}) - \text{decrease in dietary-induced thermogenesis (DIT)}] \times 84 \text{ days} \div 7700$
 199 kcal/kg ; where the decrease in DIT = $0.1 \times WM_{\text{baseline}} - 0.1 \times \text{EI}$.

200 **Approach 3:** Approach 2 + adjustment for the monthly changes in RMR

201 $[(RMR_{\text{month2}} \times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days} + (RMR_{\text{month3}} \times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days} + (RMR_{\text{month4}}$
 202 $\times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days}] \div 7700 \text{ kcal/kg}$.

203 **Approach 4:** Approach combining changes in DIT and RMR

204 $\{[(RMR_{\text{month2}} \times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days} + (RMR_{\text{month3}} \times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days} + (RMR_{\text{month4}}$
 205 $\times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days}] - [(0.1 \times WM_{\text{baseline}} - 0.1 \times \text{EI}) \times 84 \text{ days}]\} \div 7700 \text{ kcal/kg}$.

206 **Approach 5:** Approach 4 with individual adjustment for the energy equivalence of the FM and FFM
 207 loss rather than using the Wishnofsky constant.

208 $\{[(RMR_{\text{month2}} \times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days} + (RMR_{\text{month3}} \times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days} + (RMR_{\text{month4}}$
 209 $\times 1.5 + \text{ExEE} - \text{EI}) \times 28 \text{ days}] - [(0.1 \times WM_{\text{baseline}} - 0.1 \times \text{EI}) \times 84 \text{ days}]\} \div \text{energy equivalence of the}$
 210 $\text{FM and FFM loss for each individual in kcal/kg}$; where 9.45 kcal/gFM and 1.13 kcal/gFFM.

211

212 **Statistical Analysis**

213 Differences in metabolic and body composition measures between males and females were examined
 214 using independent t-tests. Repeated measures ANOVA were employed to compare if RMR and body

215 composition changed over time. RMR before, during and after the intervention was compared using
216 repeated measures ANCOVA with sex, FFM and FM as covariates. Repeated measures ANOVA were
217 also employed to compare actual weight loss with expected weight loss values determined from the
218 five prediction approaches, and Bonferroni post-hoc tests were performed to locate differences among
219 means. Pearson product correlations were computed to determine potential interrelations between
220 outcome variables, and linear regression analysis was used to explore factors that might explain the
221 less-than-expected weight loss. All statistical calculations were performed using SAS version 9.02
222 (SAS Institute, Inc, Cary, NC) with $P < 0.05$ considered significant. Data are presented as mean \pm SD
223 as specified.

224

225 **Results**

226 Baseline body weight and body composition data are presented in **Table 1** for the whole cohort and
227 for the sexes separately. There was no sex difference in absolute or relative weight loss, FM or FFM
228 loss, or the proportion of weight loss as FM as a result of the 12-week intervention. In terms of the
229 combined cohort, the intervention resulted in a significant weight loss (18.6 ± 5.0 kg; $16.3 \pm 3.1\%$),
230 with a large proportion of the weight lost being FM ($84 \pm 6\%$). **Figure 1** displays FM, FFM and RMR
231 before, during and after the intervention. While the change in FFM over the intervention was not
232 statistically significant, FM decreased by $\sim 10\%$ each month. Protein intake was negatively related to
233 the loss of FFM, i.e. lower protein intake resulted in greater loss of FFM ($R = -0.55$; $P < 0.05$), but not
234 with loss of FM ($P = 0.13$).

235 Absolute RMR (kcal/day) at week 4 was significantly lower than baseline and, on average, did not
236 change appreciably after this point (**Figure 1**). Repeated measures ANCOVA was undertaken to
237 compare RMR adjusted for sex and body composition in energy balance with measures taken during
238 energy restriction. RMR adjusted for sex, FFM and FM in energy balance (baseline: 1803 ± 122
239 kcal/d, post-intervention: 1864 ± 128 kcal/d) was significantly higher than during energy restriction
240 (week 4: 1714 ± 122 kcal/d, week 8: 1757 ± 117 kcal/d) ($P < 0.01$).

241 Weight lost each month of the intervention compared with predicted values (Approach 1) is presented
242 in **Figure 2**. There was no significant difference ($P = 0.8$) between actual and predicted values in the
243 first month of the intervention (9.3 ± 3.3 kg and 9.5 ± 2.5 kg, respectively). As much as 1-2 kg of the
244 actual weight loss in the first 2 weeks of the intervention may be attributed to glycogen and associated
245 water losses. However, this is speculative as glycogen was not measured. However the weight losses
246 in the second month (5.1 ± 1.3 kg) and third month (4.2 ± 1.4 kg) of the intervention were
247 significantly ($P < 0.0001$) lower than the predicted values. The differential between actual weight loss
248 and baseline calculations (Approach 1) was significantly correlated with the absolute change in RMR
249 from baseline to the third month of energy restriction, and the relationship remained after adjusting
250 for the magnitude of actual weight loss (**Table 2**). Larger decreases in RMR correlated with a greater
251 discrepancy between predicted and actual weight loss. Furthermore, the differential between actual

252 weight loss and that predicted using baseline values (Approach 1), was significantly correlated with
253 the calculated reduction in DIT over the dietary intervention ($R = 0.71$, $P < 0.01$).

254 **Table 3** summarises the energy deficit and predicted weight loss from the five different calculation
255 approaches investigated. Actual weight loss was significantly ($P < 0.001$) lower than the values
256 predicted from baseline measures and using the Wishnofsky constant (e.g. 7700 kcal/kg; Approach 1),
257 with an average discrepancy of 9.9 ± 5.8 kg (1.2–22.2 kg). While there was no sex difference in the
258 magnitude of the discrepancy, the variance in shortfall was in part because the proportional energy
259 restriction provided by the VLED was not the same for all participants. The relative energy restriction
260 ranged between 74 and 87% of baseline weight maintenance requirements, with the magnitude of the
261 restriction being greater for larger participants. Consequently, there was a significant relationship
262 between the energy deficits (using Approach 1) calculated either in absolute or relative terms and the
263 magnitude of decrease in RMR during energy restriction; with larger deficits resulting in greater
264 reductions in RMR (**Table 2**).

265 After the calculated energy deficit was corrected for the change in DIT (Approach 2), the discrepancy
266 was 7.4 ± 5.4 kg being statistically significant ($P < 0.01$). Similarly, when the calculated energy deficit
267 was corrected for the monthly change in RMR (Approach 3), the discrepancy of 5.8 ± 5.1 kg was
268 statistically significant ($P < 0.05$). However, when energy deficit was calculated with adjustments made
269 for both the change in DIT and monthly change in RMR (Approach 4), the actual weight loss reached,
270 on average, 87% of the predicted value, and the discrepancy of 3.3 ± 4.8 kg was not statistically
271 different from the predicted values ($P = 0.13$). Finally, the energy deficit calculated with adjustments
272 made for both the change in DIT and monthly change in RMR was divided by the energy equivalence
273 of the FM and FFM loss for each individual (Approach 5). Using this approach, the actual weight loss
274 was, on average, 90% of the predicted values, with the shortfall of 2.8 ± 5.0 kg not statistically
275 significant from the predicted values ($P = 0.20$). The comparisons between actual and predicted values
276 are shown graphically in **Figure 3**.

277

278 **Discussion**

279 Dietary weight loss interventions in obese individuals are often described as being unsuccessful when
280 the weight loss achieved is less than the amount anticipated from baseline energy deficit calculations.
281 The less-than-expected weight loss experienced with energy restriction could be likened to missing
282 the target when hitting a golf ball. The factors contributing to missing the weight loss target may be
283 considered in two categories: [1] *errors off the tee*: errors from baseline such as miscalculating
284 WM_{baseline} , use of the Wishnofsky constant, or not accounting for the immediate reduction in DIT
285 consequent to the reduced energy intake; and [2] *errors in flight*: deviations from the target that occur
286 as a result of intervening factors once the energy restriction has been imposed such as metabolic
287 depression or behavioural non-compliance. The aims of the current study were to quantify [1] the
288 extent to which actual weight loss matched the baseline predictions, and [2] if variables which can be
289 objectively measured with high precision in the laboratory; i.e. energy expenditure and body
290 composition, explain the less-than-expected weight loss in obese men and women during a diet-plus-
291 exercise intervention.

292

293 The primary finding of the current study was that actual weight loss was significantly less than the
294 weight loss expected from baseline calculations, averaging only 67% of the predicted values. This is
295 comparable with the 65% of predicted weight loss seen after 10 weeks of 50% caloric restriction in
296 lean males in the seminal, tightly-controlled, Minnesota weight loss study (33). Physiological
297 compensatory responses acting to increase metabolic efficiencies are likely to have contributed to this
298 less-than-expected weight loss. Such metabolic compensation, particularly during severe energy
299 restriction, was recognised in 1950 by Ancel Keys who noted: *It might seem entirely reasonable that*
300 *the energetic processes of the body diminish in intensity as the exogenous food supply is reduced. It is*
301 *reasonable in the sense that a wise man will reduce his expenditure when his income is cut* (19).
302 Research on both lean and obese cohorts has demonstrated that RMR reduces rapidly when
303 individuals are placed in energy restriction, with the magnitude of the decrease being greater than can
304 be accounted for by tissue loss (16, 34). RMR of overweight women has been reported to fall 6%

305 within 10 days of commencing energy restriction (800 kcal/d; ~40% $WM_{baseline}$) (16), and a
306 comparable (~6%) decrease in resting oxygen consumption was reported after only 4 days of severe
307 energy restriction (450 kcal/day; <25% $WM_{baseline}$) in very obese women (35). In obese women, Bray
308 et al. (35) noted that a weight loss of 1 kg every 4 days would be expected based on the baseline
309 calculated energy deficit. However, the actual weight loss in days 16-20 of restriction was 0.7 kg, and
310 in days 20-24 of restriction the weight loss was only 0.3 kg. The authors proposed that the less-than-
311 expected weight loss could in part be attributed to a 15% reduction in energy expenditure during this
312 period. There was also strong evidence of enhanced efficiency of cellular energy production with
313 energy restriction (35). More recent studies demonstrate rapid alterations in gene expression of
314 processes regulating cellular metabolism, and that these are in response to changes in energy intake
315 *per se* rather than as a consequence of weight loss (7, 36).

316

317 In the current study, the average decrease in absolute RMR was 228 kcal/d (11%) within the first
318 month of the intervention. Consequently, from at least this point in time, the EDef estimates derived at
319 baseline were incorrect, leading to an overestimation of the expected weight loss. Previous studies
320 that have considered the influence of changes in RMR on less-than-expected weight loss have relied
321 on measurements taken in energy balance before and after energy restriction (2-4). Consequently the
322 extent to which the reduced RMR during ER may have accounted for the less-than-expected weight
323 loss was likely underestimated. In the study from Del Corral et al. (2), a daily kilocalorie discrepancy
324 was determined from averaging the TEE measured (via doubly-labelled water) in energy balance at
325 baseline and after ~12 kg (15.5%) weight loss, then subtracting the energy intake during energy
326 restriction (800 kcal/d) to get the 'actual' energy deficit, and from this the 'expected' weight loss was
327 determined. This calculated energy deficit value was compared with the energy equivalent of the FM
328 and FFM loss, or the 'actual' kilocalorie loss, and was assumed to be a measure of dietary adherence.
329 While this study has many methodological strengths, given there was no correction made for
330 metabolic compensations that accompany energy restriction, the calculations of dietary adherence
331 may be strongly questioned. The authors propose that any changes in RMR would have been
332 relatively small. However using the same study design, this group has previously reported that the

333 RMR of comparably sized overweight women fell 6% (~95 kcal/d) within 10 days of commencing
334 energy restriction (800 kcal/d) (16). Furthermore, we can estimate that the DIT may have decreased
335 on average by ~120 kcal/d from consuming the WM_{baseline} diet (~2000 kcal/d) to consuming the
336 energy restricted diet. Collectively, this ~215 kcal/d metabolic conservation during energy restriction
337 would reduce the proposed daily kcal discrepancy by about 60%, and hence suggests a much better
338 dietary adherence than was proposed.

339

340 When predicting expected weight loss, few studies have accounted for the reduced DIT that
341 accompanies energy restriction. Any given change in meal size is matched by a corresponding change
342 in postprandial peak metabolism and duration of the thermic response, and thus DIT (21). Due to the
343 severe degree of energy restriction employed in the current study, the calculated decrease in DIT from
344 baseline was on average 236 kcal/d (~80%). Thus, although DIT is a markedly smaller component of
345 total daily energy expenditure than RMR, the absolute energy conservation associated with RMR and
346 DIT during severe energy restriction in this cohort was comparable. Unfortunately, a limitation of the
347 current study is that DIT was not measured, but predicted. However, the energy associated with
348 processing the WM_{baseline} (2958 ± 662 kcal/d) would be expected to have decreased markedly with the
349 change to the energy restricted diet (597 ± 45 kcal/d), and whatever error is incurred by this prediction
350 is likely to be small in absolute terms. It is also important to note that a marked decrease would be
351 experienced whether or not there was improved efficiency in postprandial processing of meals in
352 these underfed participants (37).

353

354 Considering both the change in RMR and DIT within the first month of the intervention, the collective
355 metabolic compensation was on average (228 kcal/d + 236 kcal/d) 464 kcal/d, or 16% of WM_{baseline} .
356 We investigated the extent to which these efficiencies impacted on the weight loss achieved. After
357 accounting for the change in calculated DIT and measured RMR during the intervention, the actual
358 weight loss was 87% of the predicted value and, on average, was not statistically different to predicted
359 values. Thus 60% of the apparent discrepancy between predicted and actual weight loss could be
360 attributed to overestimation of actual energy needs during energy restriction. Interestingly, this is of

361 the same magnitude as we have estimated in the study by Del Corral et al (2). Accounting for these
362 compensatory metabolic responses, the actual less-than-predicted weight loss in the current study was,
363 on average, only 3.3 kg rather than the 9.9 kg discrepancy indicated from using baseline calculations.
364 Importantly, RMR was measured only twice during energy restriction – additional assessments may
365 enable better quantification of the metabolic compensation.

366

367 We also examined if the tissue composition of the weight loss may further explain the weight loss
368 discrepancy. The average loss of FFM over the intervention was modest (3.1 ± 1.9 kg). It is also
369 worth noting that despite the severe EDef, the majority of FFM was lost in the first month, and that
370 even by the end of the intervention the participants were still experiencing consistent FM losses. With
371 the reasonably stable values for RMR in the second and third month of the intervention, this indicates
372 that the energy equivalent of the weight loss was consistent for the majority of the intervention. The
373 Wishnofsky constant (7700 kcal/kg) is based on the assumption that the composition of weight loss is
374 79% FM and 21% FFM (1). In the current study, FM ranged from 71 – 96% of the weight loss, and so
375 the actual energy deficit per kilogram weight lost ranged 7006 – 9116 kcal/kg. In their study of
376 overweight/obese women undergoing a less energy restrictive diet but without supervised exercise
377 training, Goele et al. (3) reported a much wider range in the energy deficit per kilogram weight lost:
378 3097 – 16401 kcal/kg. Taking into account the variance in energy equivalence of the weight loss in
379 the current study, a further 0.6 kg of the less-than-expected weight loss was accounted for, leaving the
380 shortfall of 2.8 kg on average, with the actual weight loss not statistically different from this
381 recalculated expected value. The proportion of the less-than-expected weight loss that was accounted
382 for by the body composition of the weight loss in the current study (~5%) was much less than that
383 reported by Goele et al.(3) (14%). However this could be attributed to Goele et al. not having the
384 opportunity to account for changes in RMR during the energy restriction *per se*, and thus
385 overestimating the expected weight loss, particularly in larger individuals who may also have had a
386 larger energy equivalence of the weight lost. After adjusting for the changes in RMR and DIT, and the
387 variance in the composition of the weight loss, actual weight loss averaged approximately 90% of
388 predicted values.

389 It is worth considering what other biological factors may explain the remaining shortfall of the actual
390 from predicted weight loss, and the variance in this shortfall. Another factor is the possible within-
391 individual changes, and between-individual differences, in activity energy expenditure (AEE). AEE is
392 a function both of the total amount of physical movement and the efficiency, or energy cost, per unit
393 of the movement. We have recently shown in obese pregnant women that, over gestation, the energy
394 cost of movement can decrease, and that this is both due to behavioural (walking more slowly) and
395 biological (improved walking economy) compensations (38). Further, we, and others, have shown
396 reductions in non-exercise activity thermogenesis (NEAT) in overweight and obese individuals in
397 response to exercise training and/or caloric restriction interventions (39-41). Given accurate
398 measurement of daily physical activity and AEE can be challenging in studies of free-living humans,
399 it is useful to consider evidence from highly-controlled animal studies. High inter-animal variability
400 in weight loss was reported in a recent study of MF1 mice which were restricted to 70% of their
401 individual baseline food intake for 28 days. Interestingly, the mice losing more weight had increased,
402 whereas mice losing less weight had decreased, physical activity levels (42). In the current study, we
403 had no measure of NEAT from accelerometry or questionnaires. However, it is possible that reduction
404 in physical movement outside of the exercise training sessions, and reduction in the energy cost of
405 movement *per se* when in severe EDef, may account for some of the less-than-expected weight loss. It
406 is unfortunate that this information is not available to qualify the extent to which variations in
407 physical activity explain the variance in weight loss.

408

409 Finally, we must consider that a less-than-expected weight loss may be attributed to non-compliance
410 with the prescribed intervention. Considerable effort was made in the current study to enable and
411 monitor compliance. The low-energy ketogenic diet replaced 2 meals per day with supplements, and
412 participants were provided sample recipes to assist with the preparation of the daily self-prepared
413 meal. Adherence was evaluated through weekly consultations and assessment of urine acetoacetic
414 acid concentration. All participants completed >95% of the required exercise training sessions, and
415 sessions were supervised and workload monitored by the same investigator (NMB). Consequently, we
416 are confident that adherence to the intervention was high.

417 ***Future Directions***

418 There are two avenues through which RMR can be reduced during energy restriction: a reduction
419 attributed to the loss of tissues, and a reduction beyond that explained by the loss of tissue – or
420 adaptive thermogenesis. Future studies could consider undertaking frequent serial measures of RMR
421 soon after the imposition of an energy deficit, and continued throughout the phases of weight loss.
422 This will provide the basis to better understand the extent to which energy conservation resulting from
423 the adaptive reduction in thermogenesis contributes to the overall reduction in RMR and to the
424 discrepancy between actual and predicted weight loss.

425

426 ***Conclusions***

427 While less-than-expected weight loss is often attributed to incomplete adherence to prescribed
428 interventions, the influence of baseline calculation errors and compensatory metabolic responses
429 should not be discounted. Strategies to monitor factors that impact energy expenditure are needed
430 during interventions, to enable those trying to lose weight, to stay on course.

431

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434 ***Conflict of Interest***

435 None of the authors have any competing financial interests in relation to the work described in this
436 manuscript.

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545 **Figure 1** Fat mass (FM; black bars), fat-free mass (FFM; white bars) and resting metabolic rate
546 (RMR; \blacktriangle) in energy balance before and after the 12-week intervention, and during the intervention
547 at the 4th and 8th week of energy restriction. † RMR significantly different from baseline (P <0.05);
548 FM significantly different from baseline; * P<0.05, ** P<0.01. FFM did not differ significantly from
549 baseline values.

550 **Figure 2** Actual versus Predicted weight loss after 4 weeks (Month1; \blacklozenge), 8 weeks (Month2; \square) and
551 12 weeks (Month3; \circ) of diet-plus-exercise intervention. Dashed line (---) represents the line-of-
552 identity.

553 **Figure 3** Actual versus Predicted weight loss. (A) Predicted weight loss calculated from the baseline
554 energy deficit \div 7700; (B) After adjustment for the decrease in dietary-induced thermogenesis (DIT);
555 (C) After adjustment for the monthly changes in resting metabolic rate (RMR); (D) After adjustment
556 for changes in both DIT and RMR; (E) After adjustment for changes in both DIT and RMR, and the
557 energy equivalence of the FM and FFM loss rather than using the Wishnofsky constant.
558

559 **Table 1** Baseline descriptive data, and changes in body weight and body composition
 560 measures with the intervention for the total cohort and by sex.

	Total Cohort	Males	Females
	(N = 16)	(N = 8)	(N = 8)
Age (years)	40.5 ± 9.0	42.2 ± 4.5	39.5 ± 11.0
Height (cm)	168.7 ± 6.7	173.3 ± 2.7	165.9 ± 6.9 ^b
Weight (kg)	114.4 ± 23.7	128.1 ± 21.0	106.2 ± 22.1 ^a
Body mass index (kg.m⁻²)	39.3 ± 6.3	41.2 ± 7.7	38.2 ± 5.5
Fat mass (kg)	58.4 ± 14.2	56.6 ± 14.7	53.7 ± 14.6
Fat-free mass (kg)	59.6 ± 12.0	71.5 ± 6.5	52.5 ± 6.5 ^c
Percent body fat (%)	47.7 ± 4.7	44.9 ± 4.3	50.5 ± 3.3 ^b
Weight loss (kg)	18.6 ± 5.0	20.4 ± 3.5	17.6 ± 5.6
Weight loss (%)	16.3 ± 3.1	16.1 ± 3.2	16.4 ± 3.2
Fat mass loss (kg)	15.5 ± 4.3	17.4 ± 3.1	14.5 ± 4.6
Fat-free mass loss (kg)	3.1 ± 1.9	3.0 ± 2.0	3.1 ± 1.9
Fat mass loss as a proportion of weight loss (%)	83.6 ± 7.8	85.6 ± 8.8	82.4 ± 7.3

561 Statistically significant differences between males and females: ^a P < 0.05; ^b P < 0.01; ^c P < 0.001

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564

565 **Table 2** Associations between resting metabolic rate and body composition changes and the
 566 difference between actual weight loss and the weight loss predicted from baseline calculations.

	Energy Deficit (kcal/d)	Energy Deficit (%)	Predicted – Actual Weight loss (kg) ^b
Change RMR (kcal/d) ^a	0.64^{**}	0.70^{**}	0.51[*]
Change RMR (kcal/d) ^a adjusted for weight loss	0.57[*]	0.65^{**}	0.57[*]
Fat-free mass loss (kg)	0.47	0.55[*]	0.12
Fat-free mass loss as a proportion of weight loss (%)	0.20	0.31	0.20
Energy Deficit (kcal/d)	---	---	0.74^{**}
Energy Deficit (%)	---	---	0.68^{**}

567 Abbreviations: RMR, resting metabolic rate. ^a Change from baseline to 3rd month of intervention (i.e.
 568 during energy restriction). ^b Weight loss predicted from baseline calculations (Approach 1).

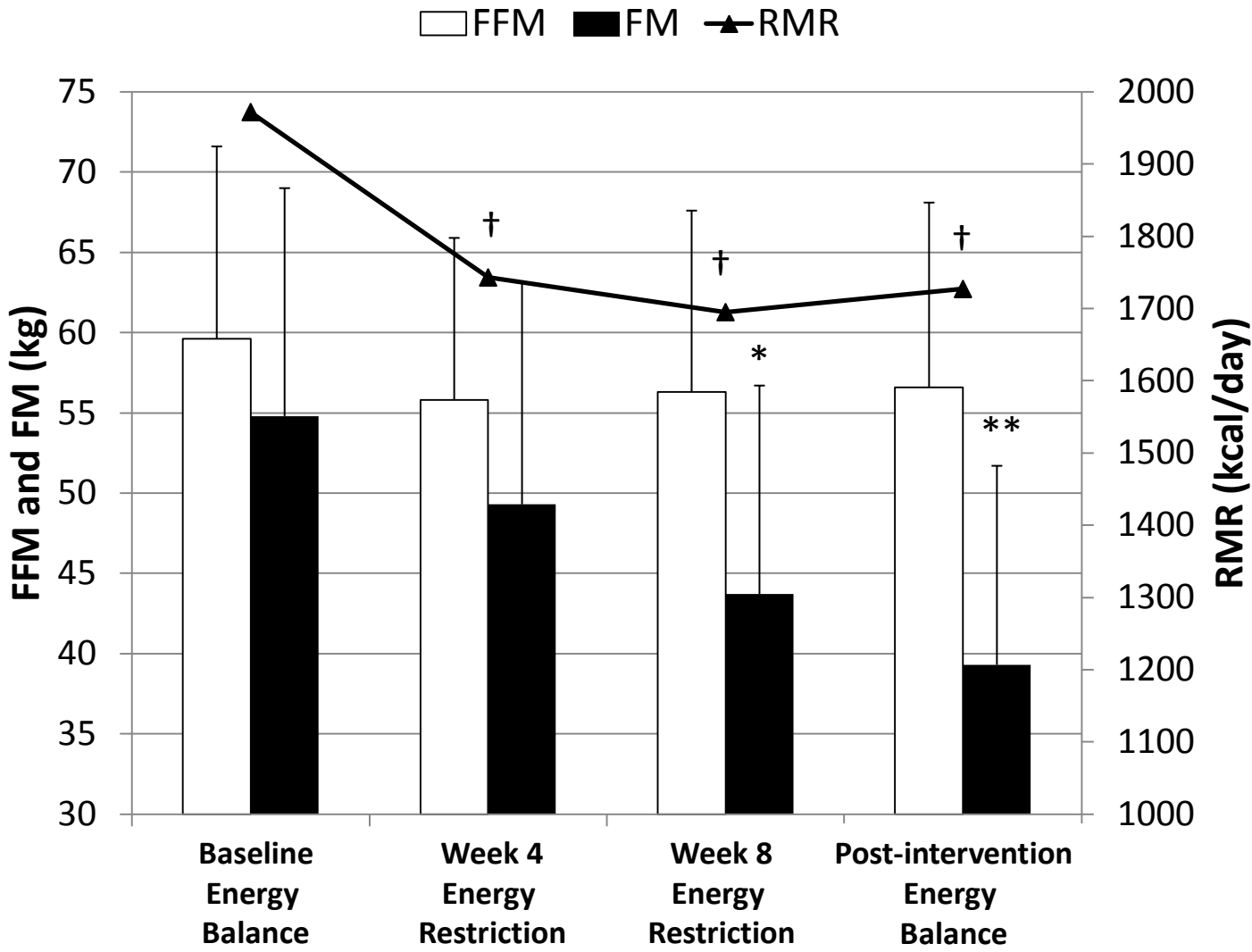
569 * $P < 0.05$, ** $P < 0.01$. Pearson correlation coefficients and partial correlation analysis (R values after
 570 adjustment).

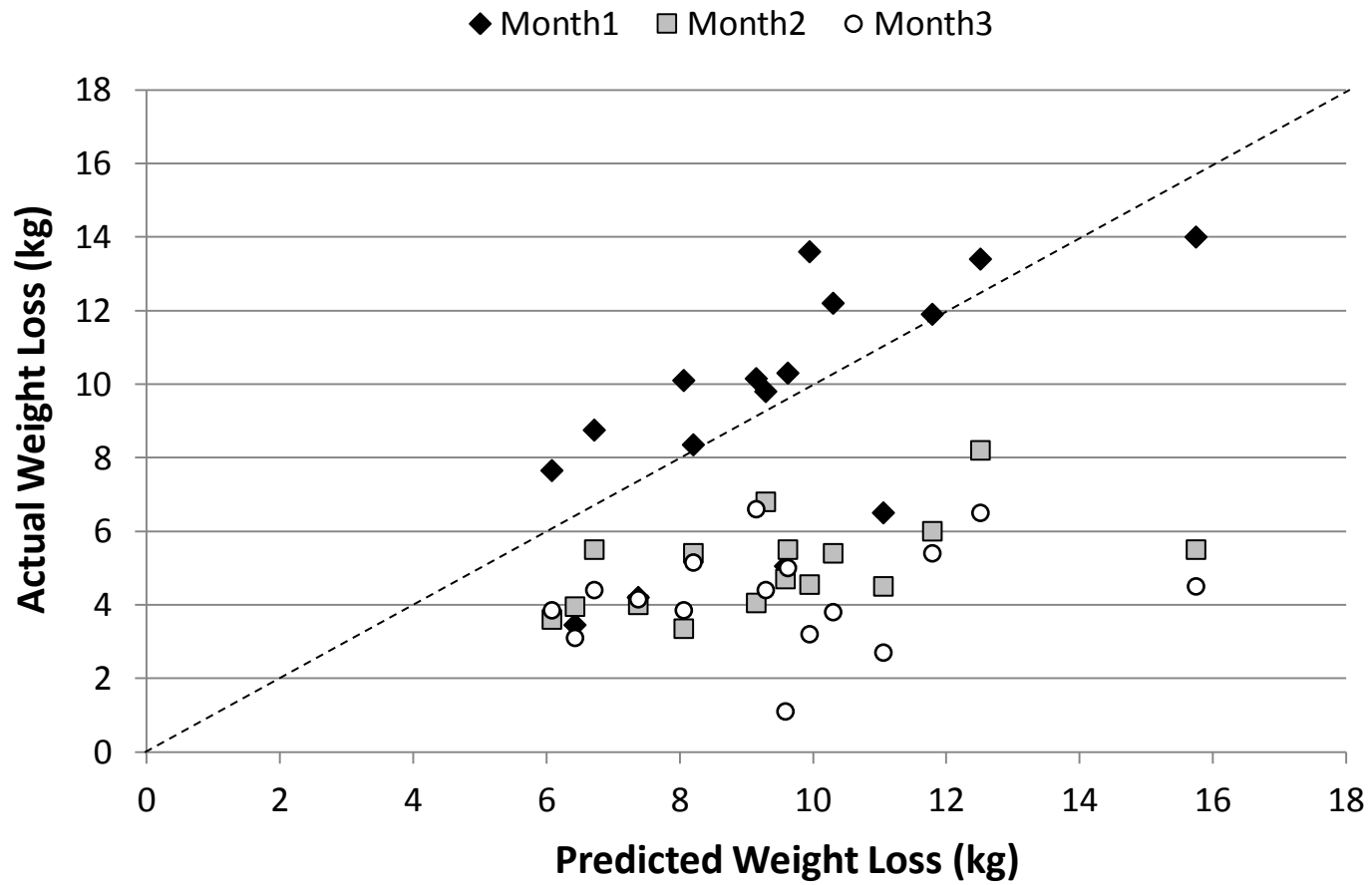
571 **Table 3** Energy deficit and weight loss predicted from baseline calculations, and after adjusting for changes to dietary induced thermogenesis, resting
 572 metabolic rate and/or body composition.

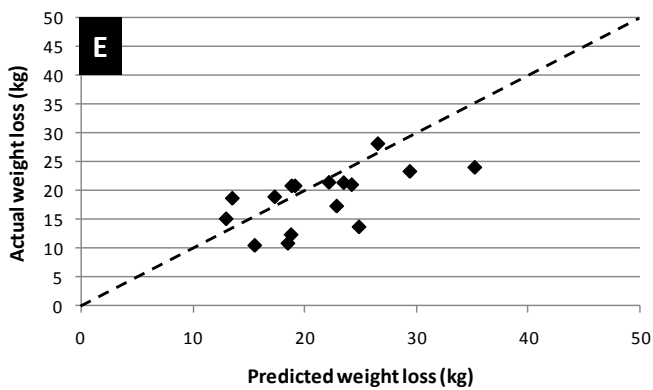
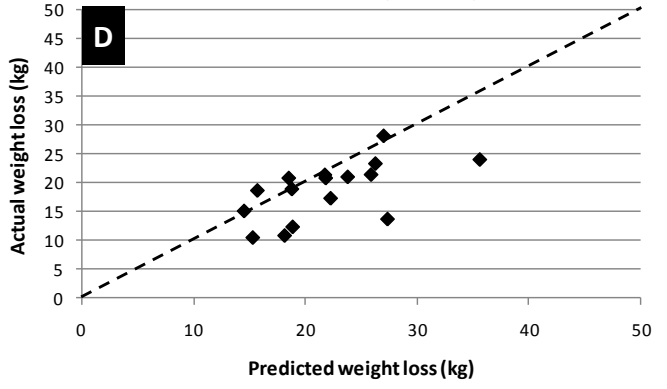
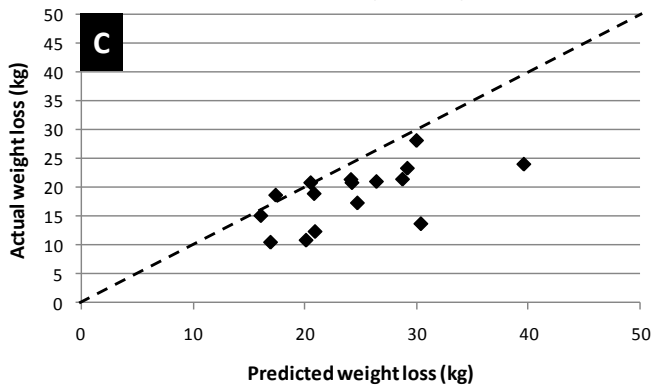
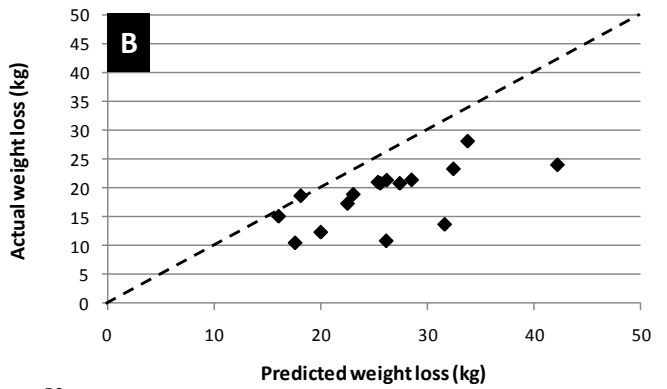
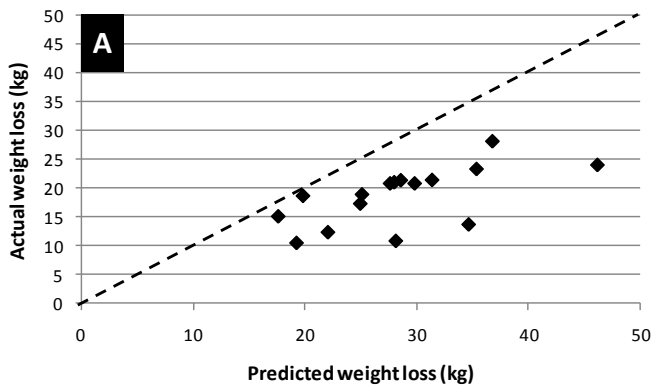
	Energy Deficit	Energy Deficit	Predicted Weight	Actual Vs Predicted
	(kcal/d)	(%)	Loss (kg)	Weight Loss (%)
Approach 1 – Baseline Prediction	2611 ± 677	80.7 ± 3.5	28.5 ± 7.4 †	66.8 ± 15.3
Approach 2 – Adjusting for change to DIT	2387 ± 623	73.7 ± 3.4	26.0 ± 6.8 †	73.1 ± 16.8
Approach 3 – Adjusting for monthly changes to RMR	2236 ± 566	68.3 ± 5.3	24.4 ± 6.2 †	77.8 ± 18.0
Approach 4 – Adjusting for DIT and RMR	2012 ± 509	62.5 ± 4.8	22.0 ± 5.6	86.5 ± 20.0
Approach 5 – Adjusting for DIT, RMR and proportion of weight lost as FM and FFM	2012 ± 509	62.5 ± 4.8	21.4 ± 5.9	89.6 ± 23.8

573 DIT = dietary induced thermogenesis; RMR = resting metabolic rate; FM = fat mass; FFM = fat-free mass.

574 † Statistically significant difference compared with actual weight loss (18.6 ± 5.0 kg).







A – Baseline Prediction

B – Adjusting for change to DIT

C – Adjusting for monthly changes to RMR

D – Adjusting for changes to DIT and RMR

E – Adjusting for DIT, RMR and weight lost as FM and FFM