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# **Metabolic Adaptations during Negative Energy Balance and their Potential Impact on Appetite and Food Intake**

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1 **Abstract**

2 This review examines the metabolic adaptations that occur in response to negative energy balance  
3 and their potential putative or functional impact on appetite and food intake. Sustained negative  
4 energy balance will result in weight loss, with body composition changes similar for different  
5 dietary interventions if total energy and protein intake are equated. During periods of underfeeding,  
6 compensatory metabolic and behavioural responses occur that attenuate the prescribed energy  
7 deficit. While losses of metabolically active tissue during energy deficit results in reduced energy  
8 expenditure, an additional down-regulation in expenditure has been noted that cannot be explained  
9 by changes in body tissue (e.g. adaptive thermogenesis). Sustained negative energy balance is also  
10 associated with an increase in orexigenic drive and changes in appetite-related peptides during  
11 weight loss that may act as cues for increased hunger and food intake. It has also been suggested  
12 that losses of fat-free mass could also act as an orexigenic signal during weight loss, but more data  
13 is needed to support these findings and the signalling pathways linking fat-free mass and energy  
14 intake remains unclear. Taken together, these metabolic and behavioural compensatory responses to  
15 weight loss point to a highly complex and dynamic energy balance system in which perturbations to  
16 individual components can cause co-ordinated and inter-related compensatory responses. The  
17 strength of these compensatory responses is individually subtle, and early identification of this  
18 inter-individual variability may help identify individuals that respond well or poorly to an  
19 intervention.

## 20 1.0 Introduction

21 A negative energy balance will result in weight loss if sustained over time<sup>(1)</sup>. Despite the apparent  
22 simplicity of energy balance i.e. energy intake (EI) vs. energy expenditure (EE), most weight loss  
23 maintenance attempts are unsuccessful and weight loss recidivism is high<sup>(2-5)</sup>. The development of  
24 strategies that promote successful weight loss and prevent weight regain therefore remains a  
25 priority. While a lack of sustained weight loss can in part be explained by a failure to adhere to  
26 dietary and physical activity guidelines<sup>(6, 7)</sup>, compensatory metabolic and behavioural responses to  
27 energy deficit also act to undermine weight loss and promote weight regain<sup>(8, 9)</sup>. A better  
28 understanding of the compensatory responses to energy deficit and surfeit are needed if more  
29 effective long-term weight maintenance strategies are to be developed. However, such strategies are  
30 complicated by the large inter-individual variability typically seen in body weight responses to  
31 weight loss interventions<sup>(10-12)</sup>, and the lack of robust predictors of this response variability<sup>(13)</sup>.

32 The mechanisms that oppose a negative energy balance are inter-related and complex, individually  
33 subtle and often difficult to quantify<sup>(9, 13)</sup>. Metabolic and behavioural determinants of energy  
34 balance interact in a co-ordinated fashion during energy deficit and surfeit, but the mechanisms  
35 through which physiology drives behaviour are rarely acknowledged in the context of weight loss  
36 and weight regain<sup>(13)</sup>. Methodological limitations associated with the measurement of EI and EE  
37 have long frustrated energy balance research, and have limit our understanding of the putative  
38 signals that link physiology to behaviour. These limitations have also contributed to debate over the  
39 primary cause of weight gain and secular trends in obesity prevalence<sup>(14)</sup>. However, given the  
40 fundamental relationships between components of EE, body composition and EI, it might argued  
41 that successful weight loss and weight loss maintenance strategies will only be developed if the  
42 inter-relationships between physiology and behaviour are explicitly acknowledged and incorporated  
43 in their design<sup>(15, 16)</sup>.

44 To this end, there is renewed interest in integrative models of energy balance regulation that  
45 consider the dynamic relationships between body composition, EE and physiological function, and  
46 the way these interactions influence appetite and EI<sup>(17-20)</sup>. Recent research has focused on the  
47 functional associations between components of body composition, EE and EI, and indicate that fat-  
48 free mass (FFM) and resting metabolic rate (RMR) are associated with a drive to eat that reflects  
49 the energetic demand of metabolically active tissue<sup>(21-26)</sup>. However, it is unclear how changes in  
50 body composition and EE during weight loss influence appetite control. Therefore, the main aims  
51 of the present review are to i) examine the metabolic adaptations that occur in response to negative

52 energy balance, and ii) to consider the putative or functional effects that these adaptations may have  
53 on appetite control and EI.

54

## 55 **2.0 Energy Balance: A Dynamic Regulatory System**

56 It has been suggested that an energy deficit of 3500 kcal would lead to 1 pound of lost body weight  
57 (~454 grams)<sup>(27)</sup>, but this simplistic approach is known to overestimate weight loss<sup>(28)</sup>. The '3500  
58 kcal per pound' rule assumes that the composition of weight lost would be 100% body fat (based on  
59 the assumption that the energy value of 1 gram of fat is 9 kcal and adipocytes are composed of 85-  
60 90% of triglyceride) and fails to account for dynamic changes in the biological components of EE  
61 seen with weight loss (e.g. reductions in RMR and the energy cost of muscular activity). **Therefore,**  
62 **even though the energy content of fat remains constant (i.e. 3500kcal per 1lb or ~454g), a**  
63 **concomitant reduction in EE during weight loss will attenuate the prescribed energy deficit and lead**  
64 **to a lower than predicted weight loss (as the actual energy deficit will be lower than that prescribed**  
65 **via dietary restriction for example)<sup>(29)</sup>.** Large inter-individual variability in weight loss and other  
66 physiological behavioural responses are also apparent following lifestyle (diet or exercise)<sup>(8, 12)</sup>,  
67 pharmacological<sup>(12)</sup> and surgical<sup>(30)</sup> weight loss interventions. The clinical significance<sup>(31)</sup> and  
68 statistical methods<sup>(32)</sup> used to quantify such variability have been debated, but this inter-individual  
69 variability in treatment response appears to be a biological norm<sup>(33)</sup>.

70 Although adherence to a prescribed intervention is likely to contribute to such variability<sup>(7)</sup>,  
71 metabolic and behavioural compensatory adaptations will also underlie differences in treatment  
72 response. This is evidenced by the lower than expected weight loss typically observed in studies  
73 that predict changes in bodyweight based on 'static' mathematical models (e.g. the '3500 kcal per  
74 pound' rule), and it should not be assumed that a linear relationship exists between the prescribed  
75 energy deficit and actual weight loss. Rather, energy balance should be viewed as a dynamic  
76 regulatory system in which perturbation to an individual component may produce co-ordinated  
77 responses in other components of the system that act to attenuate the gap between EI and EE. For  
78 instance, compensatory responses to negative energy balance such as a greater than predicted  
79 decreases in RMR<sup>(11, 34, 35)</sup> and increased muscular efficiency<sup>(36, 37)</sup> have been observed (relative to  
80 that predicted based on changes in metabolically active tissue). Additionally, spontaneous increases  
81 in EI have also been reported following caloric restriction<sup>(38, 39)</sup>. Thus, the apparent simplicity of  
82 energy balance belies a dense and complex network of inter-related biological, nutritional,  
83 psychological and behavioural determinants of EI and EE<sup>(16)</sup>, and multiple regulatory systems and

84 feedback loops that operate concurrently to influence energy homeostasis (see Fig. 1). It is also  
85 tempting to try and explain overconsumption and weight gain solely in terms of a failure in innate  
86 biological or homeostatic regulation. However, such biological reductionism fails to adequately  
87 acknowledge the importance of psychological and behavioural aspects of energy balance during  
88 weight gain or loss<sup>(40)</sup>. Psychological factors such as cognitive restraint remain robust predictors of  
89 EI when considered alongside physiological determinants of EI (such as body composition and  
90 RMR), and indeed, have the potential to play a mediating role between physiological and  
91 behavioural outcomes<sup>(41)</sup>.

### 92 **Figure 1 here**

93 Compensation to energy imbalance appears asymmetrical, with the forces that resist weight loss  
94 stronger than the ones that resist weight gain (Fig. 2)<sup>(42)</sup>. This asymmetry may help account for the  
95 apparent ease at which people gain weight but typically fail to sustain weight loss over the long  
96 term<sup>(43)</sup>. However, studies examining compensation to controlled over rather than underfeeding are  
97 less common<sup>(44)</sup>, and considerable inter-individual variability in the magnitude of weight gain and  
98 the extent of compensation also exists with overfeeding<sup>(45)</sup>. While EE and its components may  
99 change in response to energy imbalance in a quantitatively important manner, changes in appetite  
100 and EI may have a greater capacity to perturb energy balance and body composition<sup>(46)</sup>. For  
101 example, Polidori et al.<sup>(47)</sup> recently estimated that the increase in appetite seen following a 52- week  
102 placebo- controlled trial using canagliflozin (a sodium glucose co- transporter inhibitor) was  
103 approximately three times greater than the corresponding change in EE (~100 kcal/day vs. ~30  
104 kcal/day per kilogram of weight lost). Elevations in EE may also provide “limited auto-regulatory  
105 capacity” to dissipate excess EI during periods of energy surfeit, with Siervo et al.<sup>(48)</sup> reporting that  
106 total daily EE increased by just 11.4% after progressive overfeeding (3 wks at 120%, 3 wks at  
107 140% and 3 wks at 160% of baseline intake). Such findings would point to the relative importance  
108 of appetite and EI as the primary means to compensate for energy deficit and surfeit in humans.

### 109 **Figure 2 here**

110 In relation to our understanding of the peripheral physiological mechanism involved in the  
111 regulation of appetite, **there is a growing number** of gut peptides purported to play unique roles in  
112 hunger and satiety signalling<sup>(49)</sup>. However, not all of these peptides have a close association with the  
113 temporal profiles of hunger and fullness<sup>(50)</sup>, and eating behaviour reflects the combined influence of  
114 multiple hormonal and metabolic stimuli (as depicted in the satiety cascade<sup>(51)</sup>). An area that has  
115 been a target of recent interest is the role of FFM and RMR in appetite control, with studies

116 demonstrating that FFM and RMR play important roles in the excitatory drive to eat in weight  
117 stable individuals<sup>(46, 52, 53)</sup>. It remains unclear though how the functional relationships between body  
118 composition, EE and EI operate during periods of negative energy balance and weight loss.  
119 Decreases in body composition and EE will influence energy balance by reducing total daily EE  
120 during weight loss, but such responses may also promote changes in EI that further attenuate the  
121 energy gap. As such, a clear understanding of these adaptations and their impact on bodyweight and  
122 appetite regulation during negative energy balance could be a key factor in improving weight  
123 maintenance.

### 124 **3.0 Metabolic Adaptations in Response to Negative Energy Balance**

#### 125 **3.1 Resting energy expenditure**

126 RMR, used interchangeably with resting EE and basal metabolic rate in this review, represents the  
127 energy requirements to fuel the body's basic functions in a resting state. It is thought to account for  
128 up to 70% of total daily EE, depending on physical activity and exercise levels<sup>(54, 55)</sup>. It has been  
129 postulated that changes in RMR could influence weight loss and maintenance success since  
130 associations between a lower RMR and future weight gain have been observed<sup>(56, 57)</sup>, although this  
131 hypothesis has been questioned<sup>(58)</sup>. RMR is primarily determined by the quantity of FFM, which  
132 accounts for 63%<sup>(59)</sup> and up to 75% of variability between individuals<sup>(46)</sup>. Factors such as fat-mass  
133 (FM), age and sex also contribute to the between-subject variability in RMR<sup>(59)</sup>, but an unknown  
134 component typically remains in models examining between-subject differences in RMR.

135 There is a decrease in RMR during periods of negative energy balance that occurs primarily as a  
136 result of losses of metabolically active tissue<sup>(46, 59, 60)</sup>. However, during the first stages of fasting /  
137 starvation (i.e. ~2 days), a transient increase in RMR (5-10%) can be observed<sup>(61)</sup>, possibly due to  
138 an increase gluconeogenesis as this is a more energy-demanding pathway<sup>(62)</sup>. There also appears to  
139 be an additional downregulation in EE not explained by changes in FFM or FM<sup>(63-65)</sup>, even after  
140 adjusting for losses in organ mass<sup>(66)</sup>. This phenomenon has been termed adaptive thermogenesis,  
141 and is usually defined as a greater than predicted decrease in EE after adjusting for changes in body  
142 composition<sup>(36)</sup>. A 5-10% lower than predicted decrease in RMR has been observed following  
143 weight loss which could subvert continued weight loss or weight maintenance<sup>(34, 35, 65, 67)</sup>, although  
144 the existence and functional significance of adaptive thermogenesis has been questioned<sup>(64, 68)</sup>. It is  
145 worth noting that studies examining the presence of adaptive thermogenesis typically only adjust  
146 for changes in FFM as a single homogenous tissue compartment, and assume that losses in FFM are  
147 uniform across its constituent components (e.g. skeletal muscle and organs) and that tissue

148 hydration loss remains constant during underfeeding. However, reductions in organ mass during  
149 weight loss have been reported<sup>(34, 69, 70)</sup>, and it may be that after accounting for changes in more  
150 energy-demanding structures such as the heart and kidneys, which expend approximately 440 kcal  
151 per kg in contrast to 13 kcal per kg for skeletal muscle<sup>(71)</sup>, adaptive thermogenesis becomes  
152 negligible. For instance, after 10% weight loss, it was observed that from a total decrease in RMR (-  
153 136.4 kcal = 7.7%), 40% was attributed to adaptive thermogenesis (~55 kcal) after accounting for  
154 changes in organ mass<sup>(66)</sup>. Reduced sympathetic nervous system output, impaired thyroid activity  
155 (lower free triiodothyronine) and a fall in insulin secretion have been suggested as possible  
156 mechanisms for adaptive thermogenesis<sup>(60, 64, 72)</sup>, but the underlying causes remain to be **fully**  
157 **understood**. From a biological standpoint, it makes sense that the body reacts in order to reduce the  
158 energy gap induced by “voluntary starvation”, becoming more efficient in response to food  
159 restriction. However, it is not fully understood whether adaptive thermogenesis is a permanent  
160 consequence of weight loss or is reversed after a period of weight stability at a newly reduced body  
161 weight<sup>(35, 73)</sup>.

162

## 163 **3.2 Non-resting energy expenditure**

### 164 **3.2.1 Thermic effect of feeding**

165 The thermic effect of feeding, representing the energy expended above RMR<sup>(74)</sup>, represents 10-15%  
166 of an individual's total EE<sup>(54)</sup>. During periods of negative energy balance there is some evidence  
167 that the thermic effect of feeding decreases for the same given meal<sup>(75, 76)</sup>. For instance, after an 11-  
168 week hypocaloric diet (protein supplement modified fast) that lead to a ~12kg weight loss, 5 obese  
169 women showed a decrease of ~19.1% in the thermic effect of feeding in response to a fixed meal  
170 (60% of RMR) over a 300 minute period<sup>(77)</sup>. However, after removing one outlier (57.5%  
171 reduction), only a 9.8% decrease was observed (i.e. 5-10 kcal). Furthermore, after 20 days of energy  
172 deficit (760 kcal per day) in 10 young and 9 older men, a decrease of 13% and 23.6%, respectively,  
173 was observed after measuring the thermic effect of feeding for 4 hours in response to a meal  
174 comprised of 25% of total daily EI<sup>(75)</sup>. Even though there may be a decrease in the thermic effect of  
175 feeding during periods of negative energy balance, the extent to which changes in the thermic effect  
176 of feeding contribute to resistance to weight loss and promote weight gain is unclear. Furthermore,  
177 it should be noted that depending on meal composition, measuring the thermic effect of feeding for  
178 less than 6 hours may give an incomplete estimate<sup>(78)</sup>.

### 179 3.2.2 Non-exercise activity thermogenesis and non-exercise physical activity

180 As with the thermic effect of feeding, changes in physical activity (or the EE associated with such  
181 activity) during periods of negative energy balance are yet to be fully understood. When  
182 considering the changes in physical activity during periods of negative energy balance, it is  
183 important to distinguish between metabolic and behaviour adaptations. For instance, non-exercise  
184 activity thermogenesis (NEAT) refers to the EE of a determined activity<sup>(79)</sup>. However, quantifying  
185 the number of steps or the amount of time spend in sedentary or vigorous activities refers to non-  
186 exercise physical activity. This is an important distinction because NEAT is not a volitional  
187 component, while non-exercise physical activity levels could be influenced by behaviour change  
188 interventions.

189 An increase in NEAT has been observed during periods of overfeeding with weight gain ranging  
190 from 1.4 kg to 7.2 kg after 8 weeks in an energy surplus of 1000 kcal/d<sup>(79)</sup>. A decrease in non-  
191 exercise physical activity and NEAT during periods of energy deficit has also been observed<sup>(80, 81)</sup>,  
192 but a recent systematic review indicated that the majority of evidence does not support a reduction  
193 in non-exercise physical activity with weight loss<sup>(82)</sup>. It could be that as observed by Levine<sup>(79)</sup>  
194 during phases of overfeeding where some individuals were more resistant to body fat storage, a  
195 large variability between individuals is present during periods of underfeeding making one more  
196 resistant or responsive to weight loss, permitting the identification of specific phenotypes (e.g.  
197 susceptible vs resistant). In line with this, Reinhardt<sup>(83)</sup> reported that the change in EE following a  
198 24-hour period of either fasting or overfeeding (200%) was associated with weight loss during a  
199 subsequent 6 week period of dietary energy restriction. A smaller reduction in 24-h EE during  
200 fasting, and a larger response to overfeeding, was found to be associated with greater weight loss  
201 over the 6 weeks. These findings led the authors to suggest that individuals could be categorised as  
202 displaying either “thrift” or “spendthrift” EE phenotypes, with spendthrift individuals losing more  
203 weight during the intervention as they displayed an attenuated reduction in EE during weight loss.  
204 An increase in muscular efficiency (i.e. lower EE for the same activity) has also been observed  
205 following weight loss<sup>(34-37)</sup>. For instance, a 26.5% increase in muscular efficiency during a graded  
206 cycle ergometer protocol was observed after 10% weight loss<sup>(37)</sup>. However, whether between-  
207 subject differences in muscular efficiency following weight loss contribute to resistant or  
208 susceptible weight loss phenotypes is unclear.

### 209 4.0 Impact of Metabolic Adaptations on Energy Intake

210 While a compensatory change in one component of total daily EE during negative energy balance  
211 may have limited impact on subsequent weight loss, compensation in multiple components of total  
212 daily EE may exert stronger influence. It is also plausible that changes in EE **may be** accompanied,  
213 or indeed, trigger responses in eating behaviour. Marked weight loss is associated with both a  
214 decrease in EE and an increase in orexigenic drive<sup>(84, 85)</sup>. In the past it was thought that the long-  
215 term metabolic influences on EI and EE were mainly due to changes in FM and peripheral leptin  
216 concentrations<sup>(86)</sup>. A reduction in leptin is thought to promote increased hunger and EI via a down-  
217 regulation in pro-opiomelanocortin and  $\alpha$ -melanocyte-stimulating hormone expression, and an up-  
218 regulation in neuropeptide Y and agouti-related protein expression<sup>(87)</sup>. There is also limited  
219 evidence in humans that changes in fasting leptin concentrations are associated with changes in  
220 subjective appetite<sup>(88-90)</sup> and food reward<sup>(91)</sup> during dietary and exercise-induced weight loss,  
221 respectively. Exogenous leptin administration in a weight reduced state also reverses the adaptive  
222 suppression of multiple metabolic, autonomic and neuroendocrine functions<sup>(92, 93)</sup>, and potentially  
223 improves satiety<sup>(94)</sup>.

224 Changes in appetite-related peptides during weight loss may also act as physiological cues for  
225 increased EI during energy deficit. Decreased concentrations of anorexigenic hormones and  
226 increased concentrations of orexigenic hormones following short-term energy deficit (2-7 days),  
227 **that would favour an increase in EI, have been observed with and without** concomitant reductions in  
228 body weight<sup>(38, 95-98)</sup>. Furthermore, an increase in the orexigenic hormone ghrelin<sup>(99)</sup>, and a reduction  
229 in the fasting<sup>(100-104)</sup> and postprandial<sup>(100, 103-105)</sup> concentrations of the anorexigenic hormones  
230 cholecystokinin, peptide YY, and glucagon-like peptide-1 have been reported following longer-term  
231 dietary weight loss. Limited evidence also suggests that these changes in appetite-related peptides  
232 may persist in the weight reduced state<sup>(106-108)</sup>, with Sumatran et al.<sup>(106)</sup> reporting that 8% weight  
233 loss, induced by a very low calorie diet, lead to persistent changes circulating appetite-related  
234 hormones and increased hunger 12 months after weight loss. However, persistent changes in  
235 appetite-related peptides during weight loss maintenance are not always reported<sup>(109)</sup>. Taken  
236 together, these metabolic responses to weight loss appear to create a 'biological pressure'<sup>(110)</sup> that  
237 promotes increased EI and weight regain. However, it is now increasingly **recognised** that the  
238 energetic demand of metabolically active tissue<sup>(111)</sup> and metabolic processes also creates a  
239 functional drive to eat<sup>(112)</sup>. This drive from metabolic energy need acts alongside the tonic inhibition  
240 arising from leptin and insulin and the acute modulating influence of episodic gut peptides in the  
241 overall expression of appetite and food intake.

#### 242 **4.1 Functional associations between body composition, energy expenditure and food intake**

243 A conceptual model highlighting a drive to eat based on energy needs has previously been  
244 proposed<sup>(113)</sup>, but only now are studies beginning to fully recognise EE and its main determinants  
245 (e.g. body composition and activity-related EE) as important excitatory features of homeostatic  
246 appetite control. Interestingly, previous research had already reported that lean tissues were  
247 associated with EI and hunger<sup>(22, 114)</sup>. Almost 30 years ago, Lissner<sup>(22)</sup> observed that EI was  
248 associated with lean mass, but not FM, while Cugini<sup>(114)</sup> reported 10 years later the potential role of  
249 FFM as a driver of appetite by observing that hunger sensations were positively associated to FFM,  
250 but negatively to FM (a finding consistent with other research demonstrating an inhibitory effect of  
251 FM on appetite through the action of leptin that promotes a reduction in hunger and EI<sup>(115-117)</sup>).

252  
253 More recently, several studies have observed associations between FFM and EI, with higher levels  
254 of FFM associated with greater EI in individuals at or close to energy balance<sup>(21, 23, 53, 112, 118-120)</sup>. For  
255 instance, after 12 weeks of imposed aerobic exercise (5 sessions per week), a positive association  
256 was observed between self-selected meal size and daily EI with FFM both at baseline and post-  
257 intervention in 58 individuals ( $\beta=0.33$ ,  $P<0.01$  and  $\beta=0.28$ ,  $P<0.02$  respectively). Interestingly,  
258 there were no correlations between meal size or EI and FM or BMI. This result is confirmed by the  
259 findings of Cameron<sup>(120)</sup>, in which after adjusting for age, sex, height and physical activity, FFM  
260 ( $\beta=21.9$ ,  $p=0.007$ ) and skeletal muscle ( $\beta=25.8$ ,  $p=0.02$ ), but not FM, were predictors of EI in 304  
261 post-pubertal adolescents. Additionally, Weise<sup>(21)</sup> observed an association between FFM index and  
262 daily EI in 184 individuals. The relationship between FFM and EI seems to be mediated by RMR<sup>(52)</sup>  
263 (Fig. 3), suggesting that the influence of FFM on EI is primarily due to the energetic demand (EE)  
264 that it creates in terms of energy turnover. Additionally, Piaggi<sup>(118)</sup> observed that the association  
265 between FFM and EI was mediated by total daily EE ( $P=0.01$ , partial  $R^2=7\%$ ), indicating EE per se  
266 may exert influence over food intake. However, given skeletal muscle's role as an endocrine organ,  
267 specific signalling pathways linking FFM to appetite and EI cannot be ruled out.

268

269

**Figure 3 here**

270

271 **4.2 Do changes in fat-free mass or energy expenditure act as an orexigenic signal during**  
272 **weight loss?**

273 While the aforementioned studies indicate robust associations between FFM, RMR and EI under  
274 conditions of energy balance, these data are typically cross-sectional in nature and do not provide  
275 evidence of the mechanisms that drive EI during weight loss or gain. While evidence is limited at  
276 present, associations between changes in FFM and EI have been reported during periods of weight  
277 change. For example, during Ancel Keys' Minnesota semi-starvation experiment<sup>(121)</sup>, a group of 32  
278 healthy individuals went through a period of 24 weeks of semi-starvation (~25% weight loss),  
279 followed by 12 weeks of controlled refeeding and 8 weeks of *ad libitum* refeeding. Twelve of these  
280 participants completed all phases of this intervention. During the 8 weeks of *ad libitum* re-feeding a  
281 significant hyperphagic response was observed (n = 12), which only abated after FFM was  
282 completely restored. Interestingly, there was evidence of 'fat overshoot' in which FM increased  
283 significantly above baseline values. This observation is not exclusive to this intervention. For  
284 instance, after losing approximately 12% of initial bodyweight, Nindl<sup>(122)</sup> also observed a  
285 hyperphagic response in 10 healthy young men until FFM levels were restored. However, even  
286 though this restoration of FFM was noted at week 5, it was accompanied by an above baseline  
287 increase in FM. This happens because after a period of underfeeding, restoration seems to be faster  
288 for FM than for FFM. Additionally, in a more recent intervention<sup>(123)</sup>, after 5 weeks of a very-low  
289 calorie diet or 12 weeks of a low-calorie diet, there was a significant association between  
290 percentage of FFM loss during the weight loss phase and weight regain (r=0.325, P=0.018).

291  
292 Although there is renewed interest in the role of FFM and its associated energetic demand on food  
293 intake, the idea that lean tissue acts as a driver of appetite and food intake has been previously  
294 suggested e.g. the protein-stat<sup>(124)</sup> and aminostatic<sup>(125)</sup> theories of appetite regulation, respectively.  
295 Millward's protein-stat theory suggests lean mass, and in particular skeletal muscle, is tightly  
296 regulated and that food intake (dietary protein) is directed to meet the needs of lean tissue growth  
297 and maintenance<sup>(124)</sup>. This theory is based on the existence of an 'aminostatic' feedback mechanism  
298 in which food intake is adjusted in response to amino acid availability to meet the protein demands  
299 of lean tissue growth and maintenance. When coupled with the metabolic demand for fuel,  
300 Millward suggests that appetite control allows 'substrate intake to match overall nutrient  
301 demand'<sup>(124)</sup>. However, evidence to date to support such a feedback mechanism remains limited. As  
302 noted by Stubbs et al.<sup>(46)</sup>, there are also some interesting parallels between the differential recovery  
303 trajectories of FM and FFM and the hyperphagia seen during the Minnesota study, and the changes  
304 in whole body 'catch-up growth' in undernourished children (i.e. repletion of body weight for a  
305 given growth trajectory). When a child's individualised pattern of growth is impeded by

306 malnutrition (or infection), a period of catch-up growth is typically observed in body weight for  
307 height, and, height for age<sup>(126)</sup>. Of note though, catch-up growth in body weight for height occurs  
308 before any catch-up growth in height for age is seen, and the catch-up growth in body weight for  
309 height is accompanied by a marked increase in appetite and EI that subsequently declines once a  
310 normal body weight for height is achieved<sup>(126)</sup>.

311

312 These data suggest that while FFM may have an impact in the control of EI due to its energy  
313 requirements, it is also possible that there could be feedback signalling between deficits in FFM and  
314 appetite control (as a means of increasing EI in attempt to restore FFM levels). However, a  
315 challenge in this area is to reconcile the differing relationships between FFM and EI under  
316 conditions of energy balance and energy deficit (see Stubbs et al.<sup>(46)</sup> or Dulloo, Miles-Chan &  
317 Schutz<sup>(127)</sup> for a detailed discussion), and to identify the signalling pathways that link EE and EI.  
318 **Notwithstanding, this** data linking FFM and EE to hunger and EI may have relevance in the design  
319 of weight loss and weight loss maintenance strategies, with emphasis placed on the importance of  
320 preserving FFM during periods of energy restriction. Preservation of FFM during periods of energy  
321 restriction (via greater protein intakes<sup>(128, 129)</sup>, slower weight loss rates<sup>(123)</sup> and performing  
322 exercise<sup>(130)</sup> for example) might help offset the increase in orexigenic drive seen with weight loss,  
323 but to date, this remains speculative and more data is needed in order to fully comprehend the  
324 impact of metabolic adaptations on appetite and EI during periods of negative energy balance.

325

#### 326 **4.3 Cross-talk between energy expenditure and energy intake- implications for weight loss?**

327 Given the apparent cross-talk between components of EE and EI, it is plausible to suggest that some  
328 individuals may demonstrate coordinated adaptive metabolic (EE) and behavioural (EI) responses  
329 during energy deficit that act synergistically to attenuate perturbations to energy balance. In other  
330 words, people that show greater than predicted decreases in RMR may also present with a greater  
331 hyperphagic response following negative energy balance. Case in point, even though average  
332 weight loss was small [-1.3 kg (-7.7 to 3.8 kg)], Hopkins et al.<sup>(11)</sup> observed a negative association  
333 between the extent of adaptive thermogenesis and ad libitum EI ( $r=-0.45$ ;  $R^2=0.20$ ,  $p=0.01$ ). These  
334 findings support those of Tremblay et al.<sup>(72)</sup> who showed a strong positive association between  
335 adaptive thermogenesis and hunger ( $r=0.73$ ,  $p<0.05$ ) after reanalysing the data from a previous  
336 study where 54 overweight women followed a calorie restricted diet (~700 kcal/d) for 4-months<sup>(131)</sup>  
337 leading to a mean weight loss of ~5% (-4 kg). These responses would favour the defence of body  
338 weight rather than promoting weight loss, and contribute to the inter-individual variability seen in

339 weight loss. While the underlying mechanisms still need to be determined, common biological  
340 signals such as leptin have been causally implicated in adaptive thermogenesis and compensatory  
341 appetite responses following energy deficit, and support the previously mentioned distinction  
342 between resistant and susceptible individuals suggested by Reinhardt<sup>(83)</sup>. Regarding the thermic  
343 effect of feeding, some authors have observed associations between this EE component and appetite  
344 or EI<sup>(132)</sup>. Since protein has a greater thermic effect of feeding (20-30% in comparison to 0-3% for  
345 fat and 5-10% for carbohydrates)<sup>(133)</sup> and impact on satiety<sup>(134)</sup> in comparison to the remaining  
346 macronutrients, it could be that this component of total EE might be associated with appetite  
347 control. However, a meta-analysis failed to support any link between the thermic effect of feeding  
348 and satiety<sup>(132)</sup>.

349 It could be postulated that some individuals could be more resistant to weight loss (and prone to  
350 weight gain), presenting greater co-ordinated behavioural and metabolic responses that oppose  
351 weight loss and weight loss maintenance. If a “weight loss resistance” phenotype exists, it could be  
352 characterized by a greater than predicted decrease in RMR, as well a smaller thermic effect of  
353 feeding for the same meal and EE for the same activity (i.e. greater muscular efficiency).  
354 Additionally, these responses could act in a synergistic way with greater increases in hunger and  
355 appetite, as well lower satiety and satiation, prompting an individual to regain lost weight.  
356 However, more data incorporating a multi-component analysis assessing changes in body  
357 composition, EE, appetite and EI are needed to fully comprehend the cross-talk in the energy  
358 balance system and determine whether distinct phenotypes are present. Identification of inter-  
359 individual variability in compensation during the initial stages of an intervention may act as a  
360 marker of longer-term success, but whether the identification of such phenotypes leads to more  
361 personalised and efficacious weight loss interventions remains unclear.

362

## 363 **5.0 Conclusions**

364 Even though the regulation of energy balance appears simple when considered in relation to  
365 thermodynamic theory i.e. energy in vs energy out, energy balance is a highly complex dynamic  
366 system involving multiple feedback signals from individual components of EE and EI. Under  
367 conditions of energy deficit, and to a lesser extent energy surfeit, individual components of energy  
368 balance can act in a co-ordinated fashion to resist perturbations elsewhere in the energy balance  
369 system. The strength of these metabolic and behavioural compensatory responses appears to be  
370 individually subtle, and in part, underlie the heterogeneity seen in body weight responses to weight

371 loss interventions. The potency of such compensatory mechanisms means that effective strategies  
372 that promote sustained weight loss and weight loss maintenance have proved remarkably elusive to  
373 date. While it is clear that individuals differ in the susceptibility to weight loss (and their subsequent  
374 ability to sustain this lower body weight), robust predictors of treatment response remain elusive.

375

376 While biological reductionism and a failure in innate biological regulatory mechanisms often  
377 dominates discussions around the putative causes of weight gain, psychological and behavioural  
378 aspects of energy balance are of equal importance when trying to account for overconsumption.  
379 Indeed, there is renewed interest in integrative models of energy balance regulation that consider  
380 the dynamic relationships between body structure, physiological function, and the way these  
381 interactions influence key psychological and behavioural determinants of energy balance such as  
382 appetite. Recent research has focused on the functional associations between components of body  
383 composition, EE and EI, and indicate that FFM and RMR are associated with a drive to eat that  
384 reflects the energetic demands of metabolically active tissue. Future research should examine how  
385 the functional relationships between body composition, appetite and EI operate during periods of  
386 negative energy balance, and the implications that changes in body composition and EE have on  
387 appetite control and EI.

388

#### 389 **AUTHORSHIP**

390 All authors contributed to the writing and editing of the manuscript.

391

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399

#### 400 **CONFLICTS OF INTEREST**

401 None.

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765 **LEGENDS FOR FIGURES**

766

767 **Figure 1:** Schematic overview of energy balance and the nutritional, psychological, behavioural  
768 and physiological influences on total daily energy intake and energy expenditure. Reference values  
769 for organ and tissue contribution to metabolic rate taken from Elia<sup>(135)</sup>, while determinants of resting  
770 metabolic rate taken from Johnstone et al.<sup>(59)</sup>. TDEI, total daily energy intake. TDEE, total daily  
771 energy expenditure. CHO, carbohydrate. NEPA, Non-exercise physical activity. NEAT, non-  
772 exercise adaptive thermogenesis. CCK, cholecystokinin. PP, pancreatic polypeptide. PYY, peptide  
773 YY. GLP-1, glucagon-like peptide-1. FFA, free-fatty acid. AA, amino acid. FFM, fat-free mass.  
774 RMR, resting metabolic rate. AEE, activity energy expenditure. TEF, thermic effect of food.  
775

776 **Figure 2:** Overview of physiological and behavioural responses during: a) energy deficit and b)  
777 energy surfeit. In panel a and b it is possible to observe an asymmetrical response between periods  
778 of energy deficit and surfeit in which there is a greater force resisting weight loss than weight gain.  
779 Figure adapted from Melby et al.<sup>(9)</sup>. EI, energy intake. EE, energy expenditure. TDEE, total daily  
780 energy expenditure. RMR, resting metabolic rate. PAEE, physical activity energy expenditure. TEF,  
781 thermic effect of food. FFM, fat-free mass. FM, fat mass.  
782

783 **Figure 3:** Path diagram for the mediation model with the standardized parameter coefficients for  
784 the direct effects of fat mass and fat-free mass on resting metabolic rate and resting metabolic rate  
785 on energy intake, the indirect effect of fat mass and fat-free mass on energy intake mediated by  
786 resting metabolic rate and the squared multiple correlations ( $R^2$ ) for resting metabolic rate and  
787 energy intake (adapted from Hopkins et al.<sup>(18)</sup>). RMR, resting metabolic rate. NS, non-significant.  
788