# The role of appetite-related hormones, adaptive thermogenesis, perceived hunger and stress in long term weight loss maintenance: a mixed methods study

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**Running title:** Role of appetite hormones, hunger and stress in weight regain

**Keywords:** weight loss maintenance, appetite hormones, GLP-1, adaptive thermogenesis, hunger, stress, obesity

**Abstract**

**Background/objectives**: Weight loss maintenance is challenging, and few succeed in the long term. This study aimed to explain how appetite-related hormones, adaptive thermogenesis, perceived hunger and stress influence weight loss maintenance.

**Subjects/methods**: Fifteen adult women (age, 46.3±9.5 years; BMI, 39.4±4.3 kg/m$^2$) participated in a 24-month intervention, which included 3-5 months total diet replacement (825–853 kcal/d). Body weight and composition (Magnetic Resonance Imaging), resting metabolic rate (indirect calorimetry), and fasting plasma concentration of leptin, ghrelin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and growth differentiation factor 15 (GDF-15) were measured at baseline and after weight loss, around 6 months. Perceptions relating to weight loss maintenance were explored using qualitative interviews.

**Results**: Mean (SD) changes in body weight (-13.8±6.3kg) and total adipose tissue (-11.5±4.9 kg) were significant (P<0.001). Weight loss was associated with a significant reduction in resting metabolic rate (-291±226kcal/day, P<0.001) and adaptive thermogenesis (-150±162kcal/day, P=0.003), reduction in leptin (P<0.001) and GLP-1 (P=0.015), an increase in ghrelin (P<0.001), and no changes in PYY and GDF-15. Weight regain between 6 and 24 months (6.1±6.3 kg, P<0.05) was correlated positively with change in GLP-1 (r= 0.5, P=0.037) and negatively with GLP-1 at baseline (r= -0.7, P=0.003) and after weight loss (r= -0.7, P=0.005). Participants did not report increased hunger after weight loss, and stress-related/emotional eating was perceived as the main reason for regain.

**Conclusions**: Weight regain is more likely with lower fasting GLP-1 and greater reduction in GLP-1 after weight loss, but psychological aspects of eating behaviour appear as important in attenuating weight loss maintenance.

66 **Key words**: weight loss maintenance, appetite hormones, adaptive thermogenesis, hunger,
67 stress, obesity

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69 The study was registered at clinicaltrials.gov as NCT02340793.

70

71 **Introduction**

72 Overweight and obesity affects more than two-thirds of adults in the UK, >2 billion people
73 worldwide (1) and is an important risk factor for several causes of premature morbidity and
74 mortality (2). The probability of achieving a healthy body weight once obesity becomes
75 established is low (3) but modest weight loss (5-10%) can significantly improve health (4)
76 and more substantial losses (>10-15%) can make dramatic improvements, such as remission
77 of type 2 diabetes (5). However, few people are able to maintain diet-induced weight losses
78 (4, 6) in the face of physiological, environmental and behavioural factors (7) that combine to
79 draw them back to their initial weight. It is widely believed that efforts to reduce energy
80 intake and lose weight are resisted through interacting pathways, resulting in an increased
81 drive to eat and a reduction in energy expenditure (8), mechanisms which probably evolved
82 to protect against starvation (9).

83 The homeostatic control of appetite is largely controlled by the hypothalamic arcuate
84 nucleus which integrates peripheral signals coming from adipose tissue (e.g. leptin) and
85 gastrointestinal peptides (e.g. GLP-1, PYY, ghrelin) (10). Compensatory changes to pathways
86 regulating appetite following diet-induced weight loss are thought to favour increased
87 energy intake (11), though whether hormonal adaptations persist in the long-term is
88 unclear, and contradictory findings have been reported (11, 12). Adaptive thermogenesis,
89 generally assessed as the reduction in energy expenditure beyond what can be explained by
90 changes in body size and composition, may further undermine weight loss maintenance (13,
91 14). Three models have been proposed to explain this phenomenon (15), but whilst energy
92 expenditure adaptations may influence maintenance success, it is changes in appetite
93 regulation that are considered the main driver of weight regain (16). The extent to which

94 these mechanisms are causal remains largely speculative since evidence linking both
95 hormonal (11, 17-19) and energy expenditure (20) adaptations with weight regain is lacking.

96 Eating behaviour is strongly influenced by environmental determinants (21), and disconnect
97 between expected actions of GLP-1 and PYY and subjective measures of appetite and energy
98 intake (22, 23) suggest that humans may be more responsive to external stimuli than
99 internal biological cues (24). A recent systematic review of theoretical explanations
100 identified five main themes as important for behaviour change maintenance: motivation
101 (including enjoyment and identity); self-regulation (including skills and coping); habit (to
102 create and break); cognitive resources (including limits due to stress, tiredness); and
103 environmental and social influences (including support) (25). Most studies have been
104 directed at either physiological, endocrine, or psychological determinants of weight control
105 (26). The present study was designed to integrate the contribution of these components
106 and investigate their role in regain after weight loss using a low-calorie diet intervention in
107 women with obesity.

108 **Subjects and methods**

109 **Participants**

110 Weight-stable (≤5kg weight loss in previous 6 months) females aged 18-65 years with body
111 mass index (BMI) 30-45 kg/m$^2$ were recruited by posters advertising the study in a local
112 hospital. Main exclusion criteria were clinically significant illness (e.g. heart disease/cancer),
113 severe depression, taking medications known to affect body weight, diagnosed eating
114 disorder or history of substance abuse. The study was approved by the West of Scotland
115 Research Ethics Committee (reference number: 14/WS/1164) and NHS Greater Glasgow &
116 Clyde Research and Development department and conducted in accordance with the

Declaration of Helsinki. All participants provided written informed consent. The study was registered prospectively with the Clinical Trials registry, identifier number: NCT02340793.

**Study design**

This was a single arm weight-loss and maintenance intervention study, which measured body weight before the weight management programme, at the point of approximate maximal body weight loss (around 6 months), and at 24 months to coincide with the end of the weight loss maintenance phase. Body composition and resting metabolic rate were measured and fasting blood samples collected at baseline and 6 months. In addition, a sample of participants (n=11) completed semi-structured qualitative interviews, at baseline and programme end, and at intervals throughout the programme.

**Weight management programme**

Participants were asked to follow the Counterweight Plus weight management programme (27), which starts with an intensive period of low calorie diet. The intervention was delivered by a registered dietitian over a 24-month period and included three phases. Phase 1: 'Total Diet Replacement' to initiate weight loss (3-5 months shakes/soups; 825-853kcals/day; 59% carbohydrate, 13% fat, 26% protein, 2% fibre), Phase 2: 'Food Reintroduction' (1-2 months stepped increase in calorie intake to reach stable body weight) and Phase 3: 'Weight Loss Maintenance' which offered longer term support, optional meal replacements and relapse management strategies (approximately 18 months). Study visits of 20-40 minutes were fortnightly during Phase 1 and Phase 2, and monthly during Phase 3.

**Anthropometry and body composition**

Body weight was measured to the nearest 0.1 kg by calibrated scales. Whole-body Magnetic Resonance Imaging (MRI) was used to assess volumes of total adipose tissue (TAT) and skeletal muscle (Philips Ingenia 1.5T scanner; Best, Netherlands). Each participant was scanned twice, before and after weight loss. Images were obtained from elbow to ankle using a transversal T1-weighted protocol (TR/TE = 416/6ms, matrix size = 480x480, FoV = 558x558mm$^2$ voxel size = 1.15x1.15x5mm$^3$), using the scanner body coil. Due to higher BMI of participants, whole body coverage was achieved by scanning the maximum FoV available and participants were first scanned with one arm up, then the second arm was scanned by itself. Total scanning time was 45-60 minutes. Volumes of TAT were segmented by using a combination of manual and threshold MR signal segmentation with the aid of the extended MR workspace Philips software. All images were segmented by an MRI physicist (RLG) with 14 years MRI experience. Total muscle and adipose volumes were converted from cm$^3$ to litres, and then to mass using the assumed densities of 1.04kg/l and 0.92kg/l, respectively. Small sites of adipose tissue below the voxel size in organs and other tissues were below detection limits, due to partial volume effects, and classified as non-adipose tissue.

**Resting metabolic rate**

RMR was measured following a 12-hour overnight fast by means of a computerised open-circuit ventilated hood system (Oxycon Pro, Jaeger GmbH, Hoechberg, Germany) in line with standard procedures (28). Participants were free-living but asked to avoid exercise for the 24 hours prior to testing and travelled to the human nutrition metabolic laboratory by car or taxi. Participants rested in a supine position for a period of 20 minutes prior to RMR measurement, which took place in a thermoneutral environment. Each measurement

followed a 20-minute protocol, with rate of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) being recorded every 30 seconds. To ensure steady state conditions were achieved, data obtained during the first 5 minutes were discarded and $\dot{V}O_2$ and $\dot{V}CO_2$ measured during the following 15 minute period were required to have a coefficient of variation ≤10% to be considered for the calculation of resting metabolic rate using standard indirect calorimetry equations (29). The accuracy of the Oxycon Pro system was validated by alcohol-burning tests (30) which were included in the Standard Operating Procedure of the system and conducted weekly with an averaged coefficient of variation of 1.6%. Volume and gas calibrations were performed prior to each measurement and were accepted if differences were ≤±1%.). The validity of the Oxycon Pro system for RMR measurement was previously determined by our group by comparing resting oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) measured by the Oxycon Pro system and the Douglas bag method. Bland and Altman analyses demonstrated minimal low bias and narrow limits of agreement. In addition, test-retest reliability of Oxycon Pro measurements during rest in normal body weight healthy individuals was reported to be high (22).

**Adaptive Thermogenesis**

Baseline data from all 15 participants were used to generate a sample-specific linear regression equation to predict RMR as a function of TAT (kg), skeletal muscle mass (SMM) residuals (kg) and age ($R^2$= 0.78):

RMR (kcal/day) = 1449.1 + 12.2*TAT (kg) + 51.8*SMM residuals (kg) -8.7*Age (years).

The individual predicted RMR of each participant was calculated using this equation along with the corresponding TAT (kg), SMM residuals (kg) and age measured after weight loss,

and adaptive thermogenesis was calculated as measured-minus-predicted RMR and considered present if values were different from zero.

**Blood collection and analysis**

Venous blood samples were collected into EDTA vacuette tubes (Greiner Bio-One, Kremsmünster, Austria). After centrifugation (4°C, 3000 rpm for 15 min) the plasma was collected and frozen at -80°C until analysis. ELISA kits were used to measure fasting concentrations of plasma leptin, PYY, total ghrelin, total GLP-1 (all Merck Millipore, UK Ltd) and GDF-15 (R&D Systems, UK). All assays were performed according to the manufacturers' instructions and quality controls were within pre-specified limits. Coefficients of variation (CV) were ≤8% for all measures: leptin (4.2%), GDF-15 (2.9%), PYY (6.5%), total ghrelin (2.3%), and total GLP-1 (8.0%).

**Statistical analysis**

Data are presented as mean ± standard deviation (SD). Data normality was assessed using the Shapiro-Wilk test, and visual inspection of the accompanying histograms, normal Q-Q plots and box plots. Changes in metabolic and body composition measures were analysed by paired t-test or non-parametric Wilcoxen signed rank test. Spearman's correlation coefficient was used to test associations between adaptive thermogenesis, leptin, PYY, ghrelin, GLP-1, GDF-15 and weight change between 6 and 24-months. All statistical analyses were conducted using SPSS version 24.0 (Armonk, NY: IBM Corp). Statistical significance was set at $P<0.05$. There were no prior data from which to do a power calculation, but the results will permit a retrospective power estimate.

206 **Qualitative interviews**

207 Semi-structured qualitative interviews were conducted longitudinally and informed by a
208 topic guide (additional information in supplementary appendix) which was developed in line
209 with a theoretical model outlining psychological determinants of maintenance (25).
210 Discussion was prompted around five key themes: maintenance motives, psychological
211 resources, self-regulation, habits and social/environmental influences. The current study
212 investigated difficulties with adherence during weight loss maintenance, specifically relating
213 to how perceived hunger/appetite and stress influence eating behaviour. All interviews
214 were conducted by one researcher (GT) by telephone, audio-recorded and transcribed.
215 Interviews were scheduled at baseline and programme end, up to monthly during Phase 1
216 and 2, and 3-monthly during Phase 3. Interview frequency was reduced if discussions
217 became repetitive, and discontinued when data saturation was reached on the main
218 analytical themes.

219 **Qualitative data analysis**

220 Coding's were made in NVivo12 using the framework method (31), guided by the underlying
221 maintenance model (25). Analysis used a four-step process to understand the link between
222 appetite-related hormones, perceived hunger/appetite and weight loss maintenance. Step 1
223 involved data familiarisation, where each transcript was read, and high-level descriptors for
224 each participant were constructed. Step 2 was coding each transcript. Step 3 involved
225 specifically examining hunger/appetite as a motivator for eating, and Step 4 was identifying
226 other factors perceived by participants to influence eating behaviour during weight loss
227 maintenance, specifically relating to stress and difficulties with adherence to understand
228 their role in weight regain.

## Results

### Participants

Figure 1 shows study format, enrolment and drop-out. Overall, 22 women met the inclusion criteria and started the programme. Seven withdrew during Phase 1 (Total Diet Replacement) and did not attend follow up measurements. Therefore, data from 15 participants (age, 46.3 ± 9.5 years, BMI, 39.4 ± 4.3 kg/m$^2$) are presented in this manuscript. Venous access could not be obtained for one individual, thus hormone data are based on 14 participants. Characteristics of all participants are presented in Table 1.

Eleven of the study participants (aged 44.9 ± 9.8 years; BMI 40.3 ± 4.0 kg/m$^2$) took part in qualitative interviews, and 9/11 completed the 24-month weight management programme. One dropped out due to work commitments and the other could not tolerate the dietary intervention in Phase 1, but both completed exit interviews during the follow-up period. On average, interviews lasted 40 minutes (range: 10-100 minutes), and participants completed a median of 6 (range: 4-8) interviews. Mean weight losses at 6 months (14.7 ± 7.1 kg) and at 24-months (8.5 ± 8.5 kg) for those who completed the qualitative studies (Table 2) were similar to the overall cohort.

### Body weight and body composition

Individual changes in body weight are displayed in Figure 2, and as a group in Table 1. At 6 months, participants lost 13.8 ± 6.3 kg, equivalent to 13.5 ± 5.5% of total body weight ($P<0.001$). Reductions in TAT (-11.5 ± 4.9 kg) were significant ($P<0.001$) and change in skeletal muscle mass was small and not significant (-0.40 ± 0.88 kg; $P=0.012$) (Table 1). Between 6 and 24-months body weight increased by 6.1 ± 6.3 kg ($P=0.002$) but remained 7.7 ± 9.7 kg below baseline ($P=0.009$). A retrospective power calculation using the present data

252 confirms that this study, which found an effect size of -11.5 kg in TAT, was sufficiently
253 powered to detect or exclude an effect size above 3.5 kg for change in TAT, with SD=4.9 kg
254 and n=15, at 80% power.

255 **Appetite-related hormones**

256 Weight loss at 6 months was associated with significant reductions in fasting plasma leptin
257 and GLP-1 concentrations, an increase in ghrelin, but no changes in GDF-15 or PYY (Table 1),
258 and large individual variability was observed (Figure 3). Body weight regain from 6 to 24
259 months was positively correlated with changes in fasting GLP-1 concentration (r= 0.5,
260 P=0.037) and negatively with GLP-1 concentration, measured before dietary intervention (r=
261 -0.7, P=0.003) and at the point of maximal body weight loss (r= -0.7, P=0.005) (Figure 4).
262 There were no significant correlations between body weight changes between 6 and 24-
263 months and fasting concentrations of leptin, PYY, ghrelin, GDF-15, or changes in their fasting
264 concentrations. The decision to use fasting measurements was influenced by evidence from
265 our other ongoing study which found significant correlations (r=0.8, P=0.001) between
266 fasting and time averaged postprandial concentrations of GLP-1 and PYY measured over 7-
267 hours of the postprandial state in overweight women.

268 **Resting metabolic rate and adaptive thermogenesis**

269 RMR measured at 6 months 1497 ± 225 kcals/d was significantly (P<0.001) lower than at
270 baseline (1788 ± 349 kcal/d) and the difference between measured and predicted RMR was
271 also significant (-150 ± 162 kcals/d, P=0.003), with large inter-individual variability in
272 adaptive thermogenesis evident. No significant correlation was found between weight
273 change at 24-months and change in RMR (r = -0.39, P=0.89) or adaptive thermogenesis (r=
274 0.19, P=0.51). Duplicate RMR measurements were taken in 7 weight-stable (±1.0 kg)

individuals to quantify biological variation and random error, and coefficient of variation was 2.3%.

**Appetite and hunger**

Relevant quotes relating to psychological aspects (perceived hunger/appetite and emotions/stress) during weight loss maintenance are displayed in Table 2 along with weight loss outcomes. During Total Diet Replacement (Phase 1), hunger was reported by a few participants, though it was generally tolerable and ways of coping were found. The majority reported not experiencing increased hunger, which was a surprise to some participants given the nature of the dietary regime ("*I was surprised at how easy I found it […] I expected to be hungry and I wasn't…*", P-10, 1-month). As hunger and satiety promoting hormones are assumed to be causal factors in undermining weight loss maintenance (32) participants may be expected to report increased appetite and hunger as drivers of eating behaviour, after weight loss. Despite the physiological findings outlined above (e.g. significant changes in GLP-1, ghrelin and leptin), increased hunger was not reported by most participants during weight loss maintenance (Table 2). One participant who regained 10kg described difficulties with hunger during weight loss maintenance. They had the lowest secretion of ghrelin (hunger biomarker) within the cohort, both before (230 pg/ml) and after (338 pg/ml) weight loss, but also experienced significantly stressful life events, and discussed hunger alongside these difficulties *("…it had been a bit of a fraught week anyway and […] if there's something going on and you're hungry […] you think well you can't always get full control of everything else but you can stop yourself being hungry…*", P-7, 24-months).

296 **Self-regulation of emotions and eating behaviours**

297 Most participants reported eating as a way of dealing with general life stressors and periods
298 of low mood. Episodes of family and work-related stress were common, and prompted
299 participants to seek pleasure in energy dense 'comfort foods'. Those maintaining the most
300 weight loss at 24-months tended to report a greater ability to tolerate stress after weight
301 loss, and used physical activity to manage negative emotions. Those regaining more weight
302 tended to be less consistent in dealing with emotional difficulties, and were more likely to
303 be worn down by ongoing life stressors and food was used as a strategy to deal with and
304 distract from unpleasant feelings.

305 **Discussion**

306 This study found that weight regain at 24-months following an average 13.5% body weight
307 loss was positively associated with change in fasting GLP-1 concentration and negatively
308 with fasting GLP-1 measured before and at maximal weight loss. Qualitative interviews
309 suggested that weight loss maintenance was compromised by lower self-regulation of
310 eating behaviour, which was most commonly a consequence of perceived stress and
311 emotional difficulties. This study suggests that individuals with higher fasting plasma GLP-1
312 concentrations and lower reduction in GLP-1 during diet-induced weight loss, and an ability
313 to manage emotional difficulties without compensatory eating can be expected to be more
314 successful at weight loss maintenance.

315 GLP-1 concentrations were reduced following weight loss, which is in line with other studies
316 (11, 23, 33-35). The role of GLP-1 in body weight-regulation is well documented but finding
317 that inter-individual differences in weight loss maintenance were related to fasting GLP-1 is
318 novel and requires further investigation. These data suggest that individuals with lower

fasting GLP-1 might be more vulnerable to weight regain and require additional help to maintain weight losses. Our findings are consistent with evidence from bariatric surgery studies, reporting that poorer long-term weight loss maintenance outcomes are associated with attenuated GLP-1 response (36). GLP-1 infusion enhances satiety and reduces energy intake (37) and brain imaging studies have demonstrated that higher GLP-1 concentration diminishes the reward value of food (38, 39). GLP-1 analogue therapy is associated with improved weight loss maintenance (40) and identifying individuals with low concentrations of GLP-1 may help to establish who is likely to respond well or poorly to a weight loss intervention (41) and facilitate targeted treatments, with non-pharmalogical approaches to increase endogenous GLP-1 now under study (42). Our findings need to be confirmed using a randomised controlled trial design. A retrospective power analysis using the present data can now provide the basis for likely effect sizes and a sample size estimation. For example, with GLP-1 as the primary outcome in a future study, our data indicate a mean effect size of 13.0 pmol/l with SD 17.3, from a mean weight loss 13.8kg. If the minimum clinically relevant effect size is 10.0 pmol/l, then these data would demand a sample size of 94, to provide 80% power in a two-arm randomised trial (47 in each arm) to detect or exclude this effect size with $p<0.05$.

We observed large inter-individual variability across all variables, which again underlines the challenge of identifying factors which consistently associate with weight loss maintenance/regain (43). Weight loss reduced plasma leptin and increased total ghrelin concentrations, which seems to a large extent to reflect changes in adiposity (44-46). Although reductions in PYY are usually expected following major (11, 18) and modest weight loss (47, 48), we found no change, which has also been reported elsewhere (12, 49). Weight

342 regain was not related to baseline concentrations of leptin, ghrelin, PYY or GDF-15, or
343 intervention-induced changes in these hormones, which supports previous studies (11, 17,
344 18, 50).

345 As expected, weight loss led to a significant fall in RMR. The mean reduction in RMR below
346 values predicted from body weight and composition was also significant and averaged -150
347 kcals/day but did not associate with weight regain at 24-months. Thus, these data do not
348 produce strong evidence to support the concept of adaptive thermogenesis, to explain
349 difficulty in maintaining weight loss, and similar findings have been published elsewhere
350 (20). The presence and possible magnitude of adaptive thermogenesis has been
351 inconsistently documented in human studies and accurately determining its existence in
352 free-living individuals remains difficult (51, 52). The mean reduction in SMM of only 0.4kg
353 muscle loss was unexpected, and lower than has been reported in more detailed studies
354 (53) and may have been influenced by lifestyle habits of participants during the
355 intervention.

356 Whilst physiological adaptations have dominated discussions regarding body weight regain,
357 the mechanisms through which these changes influence behaviour and energy balance are
358 not well understood, and this explanation overlooks the importance of psychological factors
359 in determining treatment outcomes (41). Within this study, hunger was not perceived to be
360 relevant to participants' weight loss maintenance, despite the significant increase in ghrelin.
361 Other researchers have reported increases in perceived hunger after weight loss (11, 18,
362 50). The difference in the findings may relate to methodological differences, to the specific
363 dietary advice, and to timing of appetite data collection. We evaluated hunger by qualitative
364 interview, with questions phrased to elicit reflections over a period of time. Other studies

have used appetite rating scales at set timepoints to coincide with blood collection for appetite hormone measurements (11, 18, 50). Disconnect between subjective appetite ratings and concentrations of appetite-related hormones is not unusual (22, 23), so the degree to which 'appetite hormones' reflect perceived hunger, or memory of hunger, is uncertain. Self-reporting is the only possible way to estimate appetite, so its reliability can never be verified (54). Whether changes in appetite-related hormones are part of a compensatory response contributing to weight regain, or simply a consequence of weight loss still needs to be fully understood (10). Our findings would suggest that any effects on hunger/appetite occur outside of individuals' conscious awareness.

Greater integration of knowledge across disciplines is required to foster deeper understanding of issues relating to weight loss maintenance (26). In this study we combined quantitative and qualitative approaches as an innovative way of addressing some of the most relevant factors considered to contribute to weight regain. It was notable that participants perceived self-regulation difficulties in response to stress and negative mood states as the key factor promoting eating and weight regain, rather than any changes in appetite. Clinicians working in weight management will be familiar with this narrative and the method used to collect qualitative accounts within this study provides robust documentation of this perspective. Stress interferes with emotion regulation, and eating may occur partly because self-control is weakened, and because it helps to reduce stress (55). Participants reported that dietary lapses were most likely under family and work stress, and this is consistent with systematic review findings which reported that adopting healthier eating habits can generate psychological 'tension', where new behaviour patterns fail to meet the need for emotion regulation previously served by obesogenic behaviours

388 (56). Stress can undermine motivation and deplete self-regulatory capacity, which may be a
389 limited resource (57), and it is well established that women are likelier to exhibit stress-
390 eating behaviour than men (58). In an online survey of 2000 men and women following their
391 most recent weight loss attempt, comfort eating for emotional reasons, including stress,
392 was the most common explanation cited for regain (59). Our findings would suggest that
393 emotional and behavioural factors are at least as important in influencing eating behaviour
394 as hormonal factors. Thus, developing effective coping skills to address stress-related
395 'comfort' eating should be a central component of weight loss maintenance interventions.

396 This study has several limitations. We obtained only fasting appetite hormone
397 concentrations though more pertinent information for some biomarkers occurs
398 postprandially. However, this places greater burden on participants and it is now recognised
399 that predicting treatment response from fasting measurements strikes an appropriate
400 balance between informational value and feasibility (60). We investigated GLP-1, PYY,
401 ghrelin, GDF-15 and leptin but energy balance in the weight reduced state may also be
402 influenced by other gut appetite hormones (10) and endocrine signals from
403 triiodothyronine, and sympathetic nervous system activity (61). Investigation of adaptive
404 thermogenesis relied on RMR: we did not investigate non-resting energy expenditure, which
405 is also affected by body weight (62). There is always concern about biological variation
406 through subtle behavioural and dietary changes, and random error on RMR measurement,
407 to establish whether apparent changes in RMR are real. To provide a stable RMR, it is
408 necessary, but difficult, to establish precise energy-balance before and after weight loss. We
409 made efforts to standardise diets and behaviours during the 24-hours prior to RMR
410 measurements, and the duplicate measurements in weight stable individuals were

411 reassuring, with low coefficient of variation. We are therefore confident that major random
412 error has been avoided. The study benefitted from rigorous body composition assessment
413 by whole-body MRI, which was the basis for calculating adaptive thermogenesis, whereas
414 other studies have used weaker indirect estimates of body composition. However, methods
415 normalising RMR for TAT and SMM (or fat mass/fat free mass) using regression analysis
416 involve uncertainty, and this is a statistical rather than physiological approach and
417 potentially prone to errors (63). This study may have been strengthened by undertaking a
418 very detailed assessment of FFM composition, by quantifying volumes from MRI and
419 estimating masses of liver, heart, kidneys and brain, and then calculating RMR (and adaptive
420 thermogenesis) using tissue-specific metabolic rates (53, 61). This interesting approach
421 relies on estimates of tissue-specific metabolic rate, usually based on blood flow
422 measurements under fixed experimental conditions which would not be exactly replicated
423 by our participants, and organ-specific metabolic rates are likely to differ before and after
424 major weight loss in the present study. Data are not available for all metabolically active
425 tissues within the lean body mass (e.g. skin, bowel, pancreas and endocrine organs) and
426 some relatively small tissues can exhibit wide fluctuations in metabolic rate (e.g. brown
427 adipose tissue). This type of analysis may thus not be able to provide more reliable
428 estimates of whole-body metabolic rate for a study of major weight loss in free-living
429 human subjects, and it was beyond the scope of the current study. Finally, our results were
430 derived only in Caucasian women.

431 In conclusion, our findings imply that habitually higher fasting GLP-1 concentrations and
432 lower reduction in GLP-1 during diet-induced weight loss form part of a favourable
433 biological profile for long-term weight loss maintenance. However, difficulties in self-

434 regulating eating behaviour whilst experiencing stress and negative emotions may
435 contribute to weight regain.

436 **Acknowledgements**
437 We thank all participants for their time and commitment and Cambridge Weight Plan for providing
438 meal replacement products.
439
440 **Conflicts of interest**
441 GT and NB have received funding from Cambridge Weight Plan for conference attendance and for
442 other departmental research. NB has shares in Counterweight Ltd, and is a previous employee of
443 Counterweight Ltd. MEJL reports personal fees from Counterweight Ltd, grants and personal fees
444 from Novo Nordisk, personal fees from Novartis, personal fees from Eli Lilly, and non-financial
445 support from Cambridge Weight Plan, outside the submitted work. The other study authors declare
446 no conflict of interest.

447
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**Figure/table legends:**

Figure 1: Study flow chart: screening, enrolment and retention

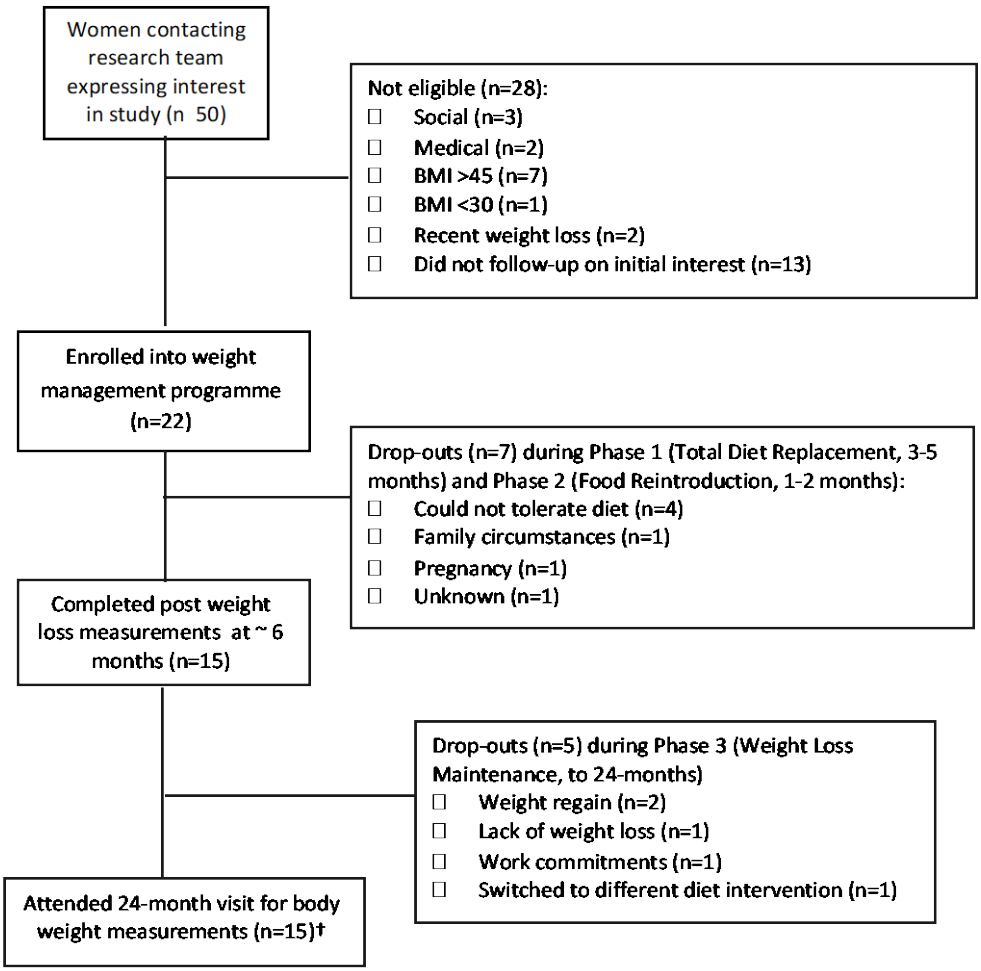
Figure 2: Body weight (kg) at baseline, 6 months and 24 months for each participant

Figure 3: Individual plasma concentrations of a) Leptin, b) GLP-1, c) Ghrelin, d) PYY and e) GDF-15 measured before and after weight loss. Black circles indicate baseline values **(•)** and grey circles indicate post weight loss values **(•)** for each participant. Black dashed lines indicate mean value at baseline **(- - -)** and grey dashed lines indicates mean value after weight loss **(- - -)**

Figure 4: Associations between weight regain (kg) from 6 to 24 months and a) GLP-1 measured at baseline; b) GLP-1 measured after weight loss, and c) change in GLP-1 from baseline to maximal weight loss

Table 1: Weight and body composition, energy expenditure, and fasting plasma hormone and metabolite concentrations before and after weight loss. Values are means ± SD (n=15$^{\dagger}$)

Table 2: Examples of verbatim quotes relevant to hunger, stress and coping during weight loss maintenance




† Five participants dropped out from the intervention during weight loss maintenance but a final body weight measurement was obtained at 24-months

**Figure 1:** Study flow chart: screening, enrolment and retention

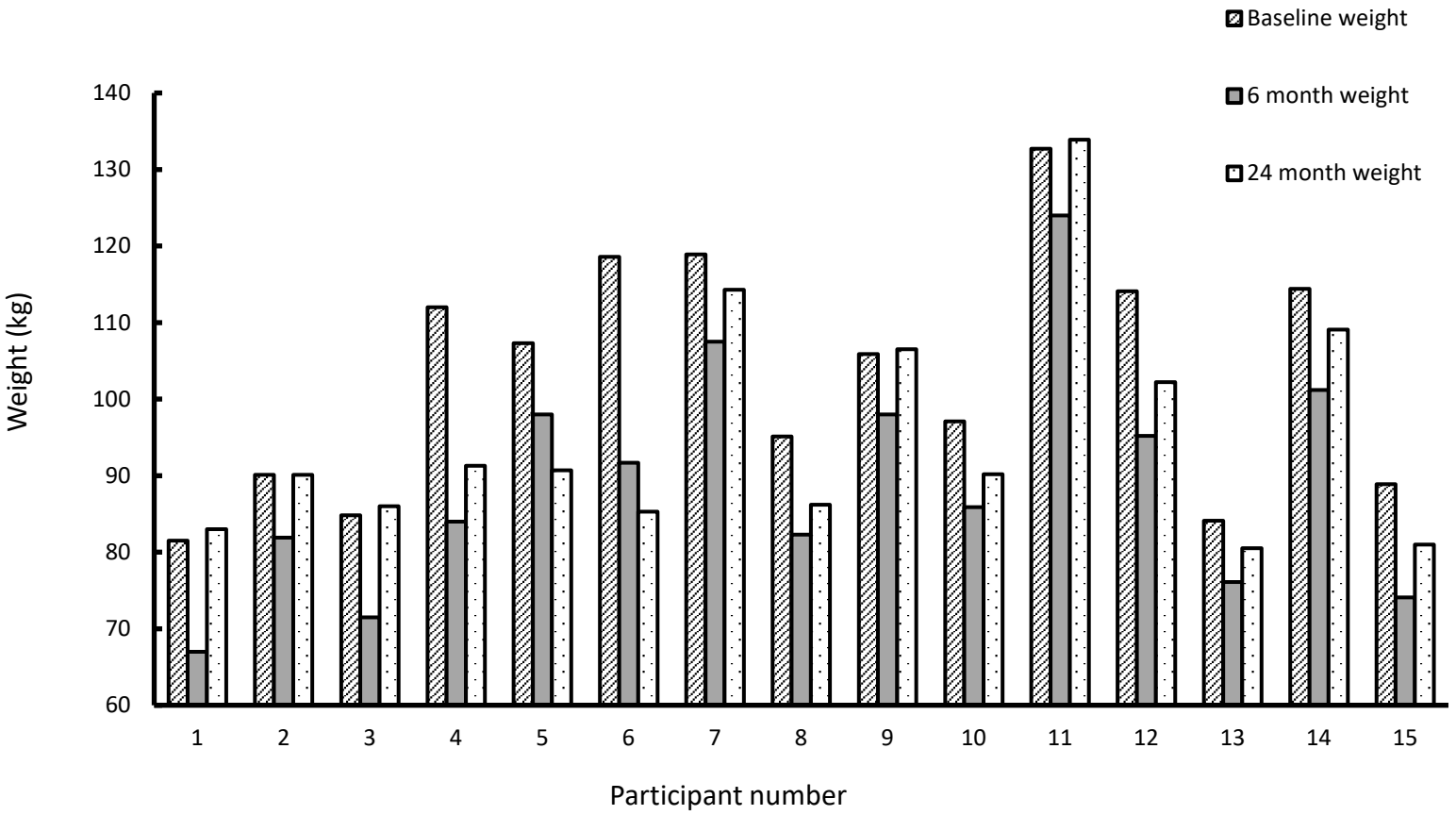



**Figure 2:** Body weight (kg) at baseline, 6 months and 24 months for each participant

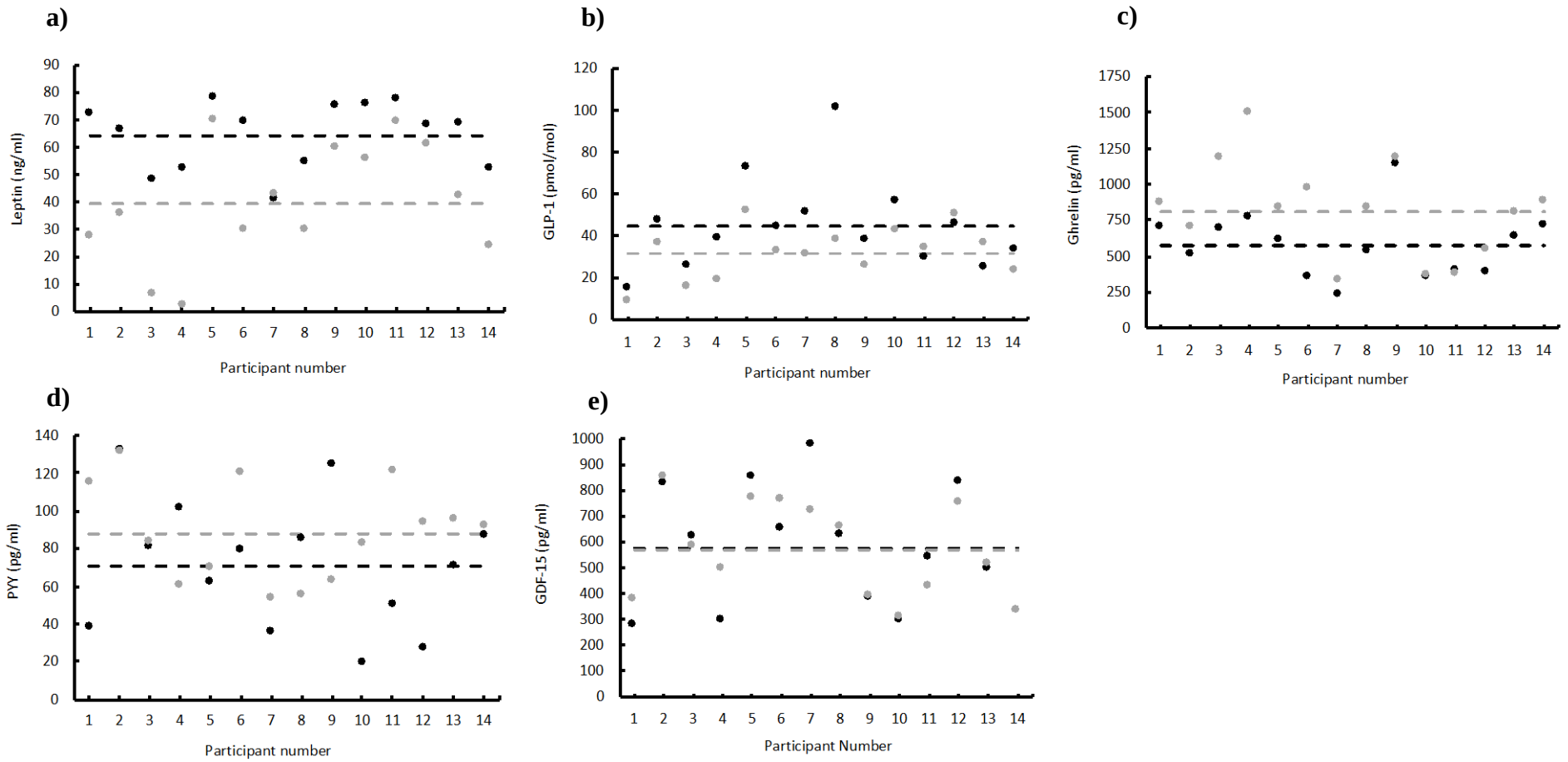



**Figure 3:** Individual plasma concentrations of a) Leptin, b) GLP-1, c) Ghrelin, d) PYY and e) GDF-15 measured before and after weight loss. Black circles indicate baseline values **(•)** and grey circles indicate post weight loss values **(•)** for each participant. Black dashed lines indicate mean value at baseline **(- - -)** and grey dashed lines indicates mean value after weight loss **(- - -)**

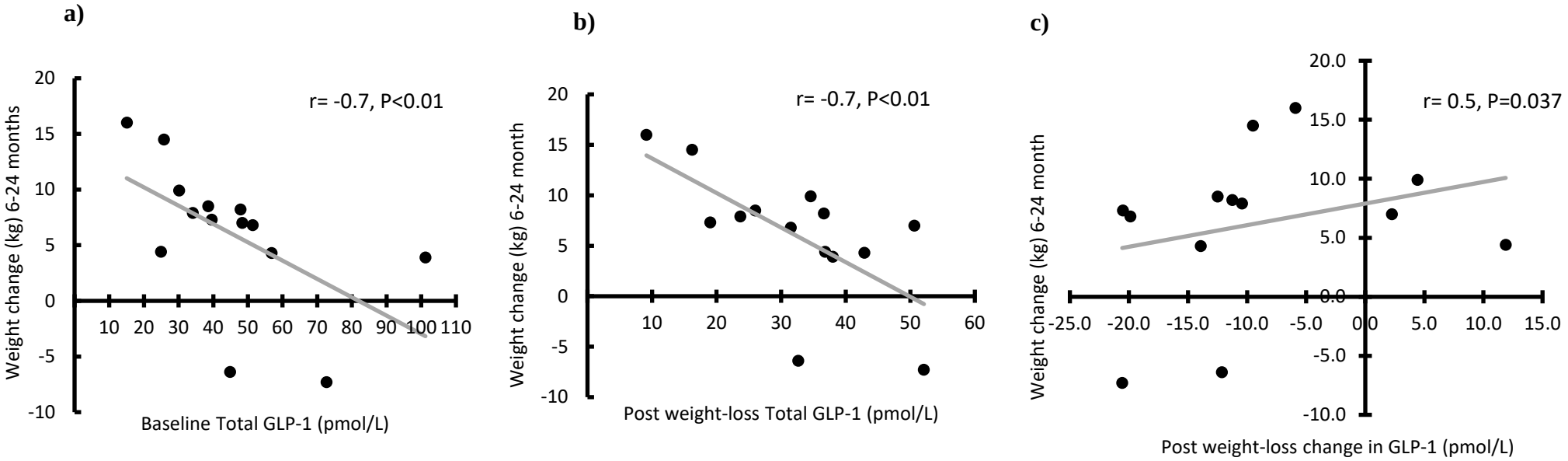



**Figure 4:** Associations between weight regain (kg) from 6 to 24 months and a) GLP-1 measured at baseline; b) GLP-1 measured after weight loss, and c) change in GLP-1 from baseline to maximal weight loss

**Table 1:** Weight and body composition, energy expenditure, and fasting plasma hormone and metabolite concentrations before and after weight loss. Values are means ± SD (n=15†)

| Participant characteristics | Baseline | 6 months | P value |
|---|---|---|---|
| Weight (kg) | 103.0 ± 15.5 | 89.2 ± 15.2 | <0.001 |
| BMI (kg/m$^2$) | 39.4 ± 4.3 | 34.1 ± 4.8 | <0.001 |
| Total adipose tissue mass (kg) | 54.6 ± 12.7 | 43.1 ± 13.2 | <0.001 |
| Skeletal muscle mass (kg) | 28.8 ± 4.0 | 28.4 ± 3.8 | 0.121 |
| RMR (kcal/day) | 1788 ± 349 | 1497 ± 225 | <0.001 |
| Measured–predicted RMR (kcal/day) | n/a | -150 ± 162 | 0.003 |
| Leptin (ng/mL) | 64.0 ± 12.2 | 39.5 ± 21.6 | <0.001 |
| Total Ghrelin (pg/mL) | 573.8 ± 232.0 | 814.5 ± 337.0 | 0.001 |
| Total GLP-1 (pmol/L) | 45.1 ± 21.9 | 32.1 ± 12.4 | 0.015 |
| PYY (pg/mL) | 70.7 ± 34.5 | 88.1 ± 26.1 | 0.157 |
| GDF-15 (pg/mL) | 573.7 ± 235.4 | 568.4 ± 184.2 | 0.861 |
| Insulin (µU/mL) | 12.9 ± 6.6 | 10.5 ± 6.1 | 0.110 |
| Glucose (mmol/L) | 6.4 ± 1.7 | 5.8 ± 1.4 | 0.861 |

BMI, body mass index; eFFM, estimated fat free mass; eFM, estimated fat mass; RMR, resting metabolic rate
†Biochemical data (leptin, ghrelin, GLP-1, PYY, GDF-15 insulin and glucose) is based on 14 participants

**Table 2:** Examples of verbatim quotes relevant to hunger, stress and coping during weight loss maintenance

| Perspective | Verbatim quotes |
|---|---|
| Hunger / appetite | *"I actually feel as if I eat more now than I did before, but obviously it's healthy choices […] whereas before I always felt hungry..."* (P-8, 24-months)<br>*"…I don't finish dinners as I used to. I used to finish my whole plate […] I assume that my stomach has got smaller, it can only take so much food..."*(P-15, 24-months)<br>*"I am conscious of feeling really full, much much quicker now."* (P-12, 14 months)<br>*"…It was really clear to me that it [overeating] actually wasn't about hunger […] I think that was one thing I realised, that my issues aren't actually to do with hunger."* (P-11, 15-months)<br>*"I don't really eat because I am hungry, I know that I am eating for something else."* (P-10, 24-months) |
| Stress and coping | *"When I'm stressed and tired I lose the focus. I don't want to be restricting myself […], I don't want to punish myself any further, I want to enjoy something nice and think oh well I have had a shit day, I deserve something good..."* (P-10, 24-months)<br>*"…If it's only maybe one kind of stress, kind of work-related or home related I am fine [...] but if it's more than one area of my life I find it difficult.* (P-4, 24-months)<br>*"…I think I have got that much else going on in life to think about, food as an added thing, it's just too much for me."* (P-13, 24 months)<br>*"…I had my PDR [personal development review] recently and my colleague was saying to me, you managed to survive a stressful time at work without chocolate, and I said could I put it on my PDR, like my goal!"* (P-4, 24-months)<br>*"…the way I would have been normally would have been oh poor me I am going through all this stress […], that would have been a trigger to say, do you know what, I don't need to cook, I am just going to get a takeaway, […] and just open a bottle of wine. I have not done any of that at all."* (P-8, 24-months)<br>*"…you think it's going to be a stress reliever, but in actual fact after I've done it I think to myself oh why did you do that, why did you do that, you have blown it […] and then you get mad with yourself and you beat yourself up…"* (P-12, 12-months)<br>*"I think my mood did really dip, and I think I was probably drinking and eating because I was probably feeling a wee bit depressed."* (P-6, 16-months)<br>*"I get low, I do because that's life, you have your up and down days. It might be a crap day at work, and you do get low, and yeah I probably would on a low day turn to chocolate…"*(P-13, 24-months) |

Weight loss and maintenance data of each participant in the qualitative study (abbreviated as 'P' and identified by participant number):

| | | |
|---|---|---|
| P-4, Start weight: 110kg | Lowest weight: 81.7kg | 24-month weight: 91.3kg, 18.5% body weight loss |
| P-6, Start weight: 118kg | Lowest weight: 75kg | 24-month weight: 85.3kg, 28.1% body weight loss |
| P-7, Start weight: 118.9kg | Lowest weight: 104.2kg | 24-month weight: 114.3kg, 3.9% body weight loss |
| P-8, Start weight: 95.1kg | Lowest weight: 82.2kg, | 24-month weight: 86.2kg, 9.4% body weight loss |
| P-9, Start weight: 105.9kg | Lowest weight: 96.2kg | 24-month weight: 106.5kg, 0.6% body weight gain |
| P-10, Start weight: 97.1kg | Lowest weight: 85.7kg, | 24-month weight: 90.2 kg, 7.1% body weight loss |
| P-11, Start weight: 132.7kg | Lowest weight: 118.2kg | 24-month weight: 133.9kg, 1.2% body weight gain |
| P-12, Start weight: 114.1kg | Lowest weight: 94.5kg | 24-month weight: 102.2kg, 10.4% body weight loss |
| P-13, Start weight: 84.1kg | Lowest weight: 73.9kg, | 24-month weight: 80.5kg, 4.3% body weight loss |
| P-14, Start weight: 118kg | Lowest weight: 100.2kg | 24-month weight: 109.1 kg, 7.5% body weight loss |
| P-15, Start weight: 88.9kg | Lowest weight: 71.9kg | 24-month weight: 81kg, 8.9% body weight loss |