Response to comments on “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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To the editor:

We thank Professor. Martins for comments on our paper (1). She is entirely correct concerning the description of Figure 4c: an oversight in the original manuscript was missed by all co-authors and reviewers. To clarify, following diet-induced weight loss, a *smaller* reduction in plasma GLP-1 concentration was weakly correlated with *greater* weight regain at 2-years. This should be reflected in the abstract, discussion and conclusions.

On re-examining these data, we also noticed that one data point was missed from the published Figure 4c, during redrafting of the manuscript and after receiving reviewers’ comments. We have provided a revised graph below (Figure 1) for the Results, with correlation r=0.5, and corrected p=0.05. This does not alter the main published messages from this mixed methods study which were: 1) Higher fasting GLP-1 concentrations both before and after diet-induced weight loss may form part of a favourable biological profile for long-term weight-loss maintenance; 2) Hunger/appetite was not reported by study participants to be difficult to manage after weight loss; and 3) Life stress and negative emotions were perceived as key factors interfering with self-regulation of eating behaviour and contributing to weight loss relapse.

We agree with Professor Martins, that most studies of appetite and GLP-1 have primarily been concerned with post-prandial values and meal-induced satiety. It is a novel feature of

our study to observe that baseline (and post weight-loss) fasting GLP-1 concentrations were associated with weight regain at 2-years. These findings may be valuable and should not be discounted without further investigation within larger, well-controlled trials. Studies in other contexts have suggested that fasting gut appetite hormones may also have relevance for energy homeostasis. For example, studies using functional MRI have indicated that activation of key reward-related areas of the brain is reduced in response to images of highly palatable foods, which seem to occur more so in the fasted than the fed state, and likely mediated by satiety hormones (2). Whether this is restricted to weight loss achieved by bariatric surgery is unclear, but it is plausible that higher (rather than lower) concentrations of GLP-1 after diet-induced weight loss could reduce the desire to eat during weight loss maintenance. Higher fasting GLP-1 concentrations have also been associated with higher resting metabolic rate and fat oxidation (3), so mechanisms attenuating weight regain may act on both sides of the energy balance equation.

At present, we lack reliable biomarkers from which clinicians or researchers can predict successful weight loss and weight loss maintenance following dietary intervention (4, 5), or identify individuals who may require additional support, e.g. GLP-1 agonist therapy. It was not possible within our study to evaluate postprandial appetite hormone responses. Appetite trials are lengthy (typically >3 hours), undertaken in specialist research settings, and burdensome to participants and staff. In the original manuscript, we highlighted the work of the biological domain subgroup of the ADOPT project (6). This group of international obesity experts have suggested a template of core biological tests to be undertaken within research studies so that in future, pooling of data from multiple studies could be used to understand treatment outcomes and predict response. Although it is not the ‘gold standard’, a collection of fasting gut appetite hormones is considered to strike an appropriate balance between value and feasibility.

We are not suggesting that fasting and postprandial GLP-1 values can be used interchangeably: the point that we were aiming to make in the original paper was that there is value in obtaining fasting measurements when it is not possible to undertake postprandial studies. Nonetheless, unpublished findings obtained in a study conducted within the Human Nutrition Unit at University of Glasgow (Rizou et al, in preparation) show significant correlation ($r=0.8$, $p<0.001$, Pearson correlation on logarithmically transformed data) between fasting and postprandial plasma GLP-1 concentrations. Study participants (n=30) were healthy overweight females, who conducted two identical experimental trials, separated by at least four months. During each trial they consumed a breakfast meal, and after four hours, a lunch meal. The test breakfast consisted of croissant, chocolate spread, whole milk, milkshake powder and sugar providing 1 g fat, 1.2 g carbohydrate, 0.25 g protein and 15 kcal energy per kg body mass. The test lunch consisted of white bread, mild cheddar cheese, butter, potato crisps, whole milk, milkshake powder and sugar providing 0.8 g fat, 1.1 g carbohydrate, 0.35 g protein, 13 kcal energy per kg of body mass. Postprandial blood samples were collected for a total duration of 7-hours at 1-hour intervals and plasma GLP-1 was analysed using commercially available ELISA kits (Merck, Millipore, Bioscience Division, UK). Because of word limits, this could not be described in detail in our original paper, but will be submitted for publication shortly.

We thank Professor Martins for bringing to our attention the misinterpretation communicated in the original manuscript, and for the opportunity to add to the published paper this correction and further information about our study and its limitations.

Conflicts of interest: none

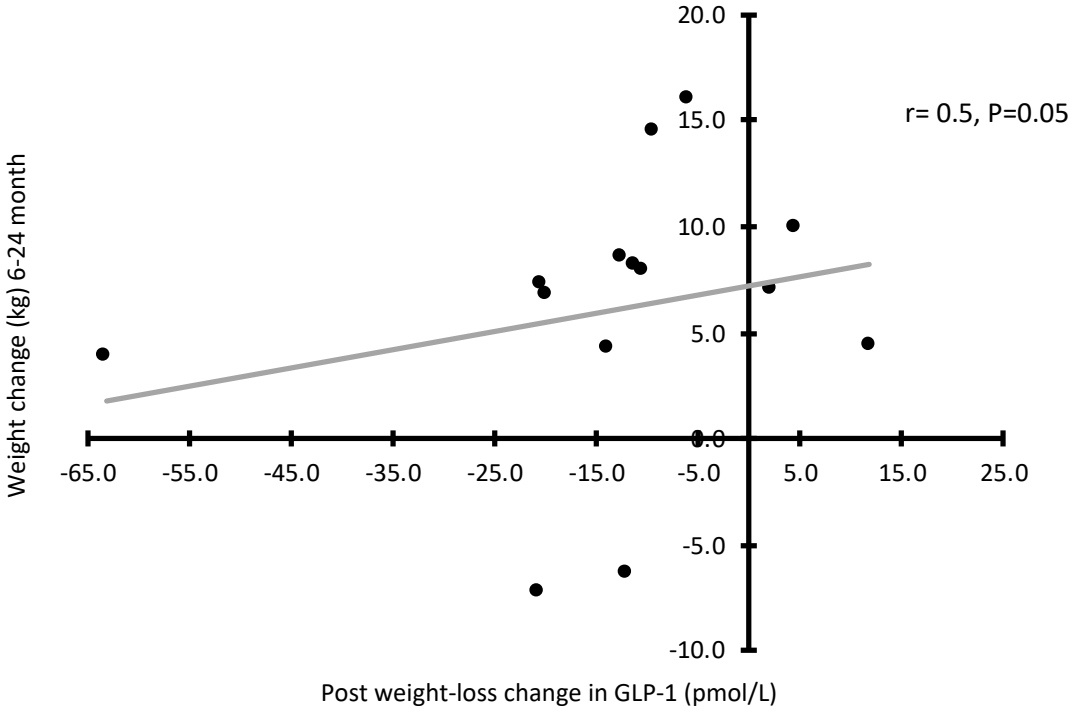

Figure 1. Association between weight regain (kg) between 6 and 24-months and change in GLP-1 from baseline to 6 months

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