Study of compensatory mechanisms of energy balance during and after weight loss

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ABSTRACT

A number of strategies to lose weight are available. However, a high inter-individual variability is commonly observed in terms of weight loss and its maintenance in individuals enrolled in different interventions. This high variability is mainly explained by individual differences in the activation of compensatory mechanisms triggered by energy deficits. Increases in appetite ratings as well as the rewarding effects of foods are some of the consequences commonly observed from weight loss induced by caloric restriction. On the other side of the energy balance equation, resting energy expenditure (REE) was also found to decrease as consequence of weight loss. Numbers might in fact decrease beyond what could be expected from changes in body weight and composition, highlighting an adaptation in thermogenesis in some individuals. These changes were previously found to be associated with the magnitude of weight loss. However, it is not clear whether different rates of weight loss have a different impact on the compensatory mechanisms described above. Moreover, other questions regarding weight loss maintenance deserve further investigations. For example, the role of exercise, more specifically resistance training (RT), on weight loss maintenance needs additional attention. Accordingly, the present thesis aimed to investigate the effects of caloric restriction on compensatory mechanisms that occur during and after weight loss. We first aimed to determine whether the rate of weight loss differently influence physiological and psychological variables related to energy balance. Secondly, we aimed to elucidate whether early changes in the above mentioned adaptations in energy expenditure (EE) and energy intake (EI) variables predict final outcomes (fat mass - FM and weight loss). Finally, we aimed to determine whether RT promoted greater weight loss maintenance. In Article I and II, we investigated whether different rates of weight loss play a role in EI and EE related-variables. We noted significant increases in fasting appetite measures, as well as increases in satiety measures. REE decreased over time, as did the relative reinforcing value of fruit. No significant group interaction was observed illustrating that different rates of weight loss has no impact on the magnitude of adaptations in EI and EE after weight loss. In article III we demonstrated that early changes in fasting and

postprandial appetite measures in response to caloric restriction were associated with greater body weight and FM loss in women. Indeed, greater increases in fasting appetite were associated with greater FM loss, contrary to our hypothesis. However, increases in postprandial appetite were associated with greater FM and body weight loss, independently of changes in eating behaviours. Taken together, articles I and III demonstrated that caloric restriction has a significant impact on increases in appetite and reduction in REE as soon as the in the first week of intervention. Those changes remain significant until the end of the program. In article IV it was shown that 1-year of resistance training (2x/ week) after 6-month of caloric restriction was not sufficient to promote better weight and FM loss in post-menopausal women. Furthermore, the results demonstrated that RT did not improve the differences between measured and predicted measures in REE observed as consequence of weight loss. The picture that emerges is that, increases in appetite and decreases in REE can be observed since the first week of caloric restriction and remain significant until the end of the program, independently of the rate of weight loss. Feeding-related variables such as fasting and postprandial appetite and RRV of a snack food are better predictors of final FM loss, even after adjusting for changes in eating behaviours. In addition, our study demonstrated that different rates of weight loss do not have an independent aspect on either physiological or psychological aspects related to energy balance.

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LIST OF ABBREVIATIONS

AUC: Area under the Curve

CCK: Cholecystokinin

CT: Computed Tomography

DLW: Doubly Labelled Water

EE: Energy Expenditure

EI: Energy Intake

Ereq: Energy Requirements

FFM: Fat Free Mass

FM: Fat Mass

GLP-1: Glucagon-like Peptide- 1

LCD: Low Calorie Diet

PA: Physical Activity

PAEE: Physical Activity Energy Expenditure

PCOS: Polycystic ovary syndrome

PFC: Prospective Food Consumption

PYY: Peptide YY

REE: Resting Energy Expenditure

RM: Repetition Maximum

RRV: Relative Reinforcing Value

RT: Resistance Training

SAT: Subcutaneous Adipose tissue

SQ: Satiety Quotient

TEE: Total Energy Expenditure

TFEQ: Three Factor Eating Questionnaire

VAS: Visual Analogue Scale

VAT: Visceral Adipose Tissue

VLCD: Very Low Calorie Diet

PART ONE: EMPIRICAL, THEORETICAL AND METHODOLOGICAL CONSIDERATIONS

CHAPTER I: INTRODUCTION

A number of strategies to lose weight are available. However, a high inter-individual variability response in terms of weight loss and its maintenance in individuals enrolled in different weight loss programs is commonly observed. Investigations on the effects of weight loss on Energy Intake (EI) and Energy Expenditure (EE) have been extensively described in the literature as an attempt to explain the reasons for high variability in weight loss responses and poor long-term results in dieting interventions. However, the effects of different rates of weight loss on EI and EE related variables, and how early changes in these variables could predict body weight and composition changes remains to be elucidated. What is more, strategies associated with effective weight loss maintenance deserve further investigations. The present thesis is an attempt to clarify some of these questions. First, we investigated whether different rates of weight loss alter the impact on EI and EE related-variables, as well as the timeline of those changes. Second, we determined whether different rates of weight loss impact psychological variables known to influence EI (*e.g.* impulsivity and reinforcement) and whether these variables were associated with changes in body weight and composition. Third, we investigated whether early changes in EE and EI variables predicted body weight and fat mass (FM) loss. Fourth, the last paper of the thesis studied the effects of resistance training (RT) on weight loss maintenance.

As mentioned above, a handful of studies reported the impact of caloric restriction on the central and peripheral nervous signalling, driving EI upward and decreasing EE (Greenway 2015a, Tremblay et al. 2013). Indeed, appetite sensations after long and short-term caloric restrictions periods, demonstrating changes in the feedback control of EI (Doucet et al. 2000b, Drapeau et al. 2007b). Those increases in appetite are normally accompanied by decreases in peripheral satiety-related peptides such as leptin, cholecystokinin (CCK), glucagon-like peptide- 1 (GLP-1) (Crujeiras et al.

2010, Doucet et al. 2000e, Wisse et al. 1999) and increases in orexigenic peptides such as ghrelin (Crujeiras et al. 2010, Mason et al. 2015). Not surprisingly, such changes in appetite ratings and in appetite-related peptides were found to be associated with weight loss and weight maintenance in women (Drapeau et al. 2007b, Gilbert et al. 2009a).

In addition, caloric restriction was found to increase motivation to eat (Cameron et al. 2008, Gilhooly et al. 2007) and the rewarding components of food (Cameron et al. 2012, 2014), which are supported by neuro-imaging studies (Jakobsdottir et al. 2016, Murdaugh et al. 2012). Briefly, the liking component of food reward is a subjective component that refers to the psychological process that produces pleasure, also called 'palatability'; whereas the wanting component of food reward refers to a conscious or subjective desire (Berridge & Robinson 2003). For instance, palatability is normally highest for high-calorie foods (Berridge et al. 2009, Rolls 2005), which might favour a positive energy balance over time leading to increases in body weight (Berthoud et al. 2011).

Associated with palatability, olfactory performance (*e.g.* threshold to detect an odor) also contributes influencing EI and food choices (Yeomans 2006). Previous evidence suggests that caloric restriction causes an increase in olfactory performance (Albrecht et al. 2009, Cameron et al. 2012), which might also increase EI. Even though a handful of studies reported the impact of weight loss on the compensatory mechanisms related to EI, it is not clear how different rates of weight loss affect food reward, olfactory performance, palatability, appetite and EI.

Considering the high concentration of cues related to palatable foods in our environment, as well as the abundance of those items, it seems relevant to understand from a psychological perspective, how people make food choices on a regular basis. Choices might differ in terms of timing (concurrent vs.

delayed) or in in terms of the alternatives involved (different quantities of a same item vs. different item) (Bickel et al. 2000, Epstein et al. 2007a). Concurrent choices are often conceptualized in terms of Relative Reinforcing Value (RRV), whereas delayed choices can be conceptualized in terms of delay discounting (Bickel et al. 2000), which is one of main domains to assess impulsivity behaviour (Meule & Kübler 2014). Both constructs were found be to be higher in individuals living with obesity (Epstein et al. 2014, Weller et al. 2008) and to increase after caloric restriction periods (Best et al. 2012, Raynor & Epstein 2003). Moreover, when high RRV for food and high impulsivity interact, this combination of traits provides a better prediction of obesity status than either construct alone (Appelhans 2009, Epstein et al. 2012, Meule & Kübler 2014). Accordingly, RRV and impulsivity were also included as measures to further our understanding of the variation in EI in individuals living with obesity undergoing caloric restriction conditions.

Caloric restrictions also have an impact on the other side of the energy balance equation. Total Energy Expenditure (TEE) and Resting Energy Expenditure (REE) commonly decrease during and after caloric restriction periods as reported by many classical and recent studies (Doucet et al. 2007, Dulloo et al. 1997, Leibel et al. 1995). In fact, studies involving individuals living with obesity after weight loss demonstrate a significant decrease in TEE and REE compared to baseline values (Leibel & Hirsch 1984, Ravussin et al. 1985, Rosenbaum & Leibel 2016) and to controls who have never lived with obesity (Leibel & Hirsch 1984). Those changes were found to be associated with Fat Free Mass (FFM) (Doucet et al. 2007, Menozzi et al. 2000) and FM loss (Goele et al. 2009, St-Onge et al. 2013). A portion of decrease in REE that is not accounted by changes in body composition has been coined as adaptive thermogenesis (Dulloo et al. 2004). This concept is helpful in understanding why during weight loss, participants commonly lose less body weight than expected (Byrne et al. 2012, Goele et al. 2009). The impact of different rates of weight loss in the magnitude of these metabolic adaptations has not been fully documented. Studies investigating this particular topic have observed

different weight loss between intervention groups (Martin et al. 2007, Siervo et al. 2015), which might be an important confounder when interpreting results.

All those changes in EI and EE regulation were found to start as early as the first few days of caloric restriction (Alajmi et al. 2016, Bray 1969, Clayton et al. 2016, Müller et al. 2016). What is more, feeding-related variables might increase in the first hours of caloric restriction whereas decreases in REE were previously reported to start in the third day of dieting (Bray 1969, Müller et al. 2016). Moreover, there is no evidence demonstrating that these early changes in EI and EE related-variables predict final outcomes. Accordingly, we also performed an investigation of how early changes in EI and EE related-variables might predict body weight and fat loss.

Despite those above cited metabolic adaptations, previous evidence suggests that exercise might be a useful strategy to promote weight loss maintenance (Saunders et al. 1999). More precisely resistance training (RT) could improve weight loss maintenance since it can contribute to preserving or increasing FFM (Dionne et al. 2004) and EE (Hunter et al. 2000, 2008). Given the association between REE and FFM, it is possible to speculate that a higher FFM maintenance would also provide a maintenance of REE and potentially better weight loss maintenance. As such, we also included in the manuscript an investigation on the role of exercising, more precisely RT, on body weight and fat loss maintenance. Furthermore, we aimed to elucidate whether RT is effective in offsetting the impact of weight loss on metabolic adaptations.

We opted to include only females since women were found to be more vulnerable to present obesity (Flegal et al. 2013). As such, women often make up most of the participants in clinical trials related to weight management (Pratt et al. 2009), due physiological and physiological sex-related differences in eating behaviours, which is a result from interactions between cultural, social and biological factors as

previously reviewed (Kanter & Caballero 2012). This greater proportion of women in weight loss treatment intervention is due not only to physiological and physiological sex-related differences in eating but also to What is more, the effects of menopause on fat distribution that may increase even more the risk of negative effects of obesity on health (Morita et al. 2006). Accordingly, all studies included in the present manuscript were performed in women living with obesity. The first three studies included females before menopause whereas the fourth study included only post-menopause women.

Significance of the study

Given the reported high rates of unsuccessful weight loss and weight relapse in individuals living with obesity (Kraschnewski et al. 2010, Maclean et al. 2011), it seems relevant to identify the factors associated with better outcomes in terms of body weight and body FM loss after dietary-induced interventions. Furthermore, strategies for better long-term maintenance of the outcomes deserve to be investigated.

Even though the ‘ideal’ rate of weight loss has been repeatedly discussed in the literature, there is still controversy regarding the clinical implications of choosing rapid *vs* a slow weight loss. In fact, some studies reported no changes in REE in either rapid or slow weight loss programs (Coutinho et al. 2017), whereas other studies demonstrated that individuals enrolled in a slow weight loss they have a more pronounced decrease in REE (Siervo et al. 2015). Along the same lines, there is still a controversy on how appetite ratings are affected by different rates of weight loss. Previous evidence demonstrated no difference in appetite ratings during weight loss (Purcell et al. 2014) whereas other study observed increase in fasting appetite only in the rapid weight loss (Coutinho et al. 2017).

These results point out to the necessity of further investigations on the effects of different rates of weight loss on EI and EE adaptations. Considering that feeding involves not only homeostatic needs, but also pleasure and satisfaction, it seems relevant to include more comprehensive variables related to EI, such as palatability, olfactory performance, as well as, psychological variables related to feeding, such as RRV and impulsivity. Moreover, the assessment of those measures at multiple time points during the intervention would be helpful to assess the timeline of compensatory mechanisms and might identify periods during weight loss that deserve closer attention.

Importantly, the first three studies included in the present thesis were designed to promote similar weight loss, as total weight loss is a relevant confounder for studies investigating the impact of the rate of weight loss on EI and EE related-variables. To our knowledge, none of the studies on rate of weight loss have incorporated all those variables related to homeostatic and non-homeostatic control of EI, and have performed assessments at several time-points during intervention, confirming the novelty of our study design (Papers I & II).

Furthermore, the present thesis investigated early responses of these above mentioned variables and whether they were associated with final body weight and FM loss (Paper III). Available literature reported predictors of weight loss by associating final outcomes (*e.g.* weight loss) to final responses (*e.g.* changes in REE) (Astrup & Rössner 2000, Pasman 1999) or have used baseline measures to predict better outcomes (Byrne et al. 2004, Pasman 1999, Vogels et al. 2005, Weiss et al. 2007). To our knowledge, no study has investigated whether early responses to a weight loss intervention is associated with final weight loss outcomes. This would seem pertinent since short-term caloric restriction affects appetite, oro-sensory variables such as palatability and olfaction and also decreases REE (Alajmi et al. 2016; Cameron et al. 2012, 2014; King et al. 2011), which collectively increase the drive to eat and compromise the maintenance of the negative energy balance needed for weight loss. These acute changes could thus potentially play a role in influencing post-intervention

weight and FM loss. Accordingly, identifying those early markers would also enable more effective and personalized interventions promoting better intervention outcomes for individuals engaged in weight loss programs.

Given all adaptations and changes promoted by weight loss in psychological, physiological variables related to EE and EI, it is relevant to investigate strategies that are helpful in maintaining their results in terms of body weight and FM loss. Accordingly, the second project (Paper IV) included in the present thesis aimed to investigate whether exercising would be effective in preventing weight and FM regain after a prolonged caloric restriction period. Previous evidence reported the effectiveness of a walking program in weight loss maintenance (Villanova et al. 2006), whereas RT were associated with better FM loss maintenance in man (Saunders et al. 1999). However, in post-menopausal women a little attention has been given to RT as a tool for weight loss maintenance. Accordingly, this fourth paper discusses the effectiveness of RT in preventing or attenuating the metabolic adaptations promoted by weight loss and consequently, the long-term weight maintenance in post-menopausal women.

Taken together, the above-mentioned evidence clearly demonstrates the difficulty for people living with obesity to lose weight and even more so to maintain lower adiposity over time. The present thesis discussed these compensatory mechanisms of energy balance during and after weight loss; including psychological and physiological variables related to EI and EE. Furthermore, it was discussed whether these compensatory mechanisms predict final outcomes. We also included a discussion of the effects of different interventions (*e.g.* slow vs rapid weight loss; inclusion of RT to weight loss maintenance) on final outcomes and their maintenance.

Definitions

1-Appetite: Appetite involves psychological events (hunger perception, cravings, and hedonic sensations), behavioural operations (meals, snacks, energy and macronutrient intakes) and peripheral physiology and metabolic events; and the level of neurotransmitter and metabolic interactions in the brain (Hopkins et al. 2016);

2-Reward: Psychological process that might reinforce stimulus. Food reward is a composite process that involves “liking” and “wanting” as major components (Fulton 2010);

3-Liking: Component of food reward is a subjective component that refers to the psychological process that produces pleasure, also called the hedonic impact. It might divide in *implicit liking,* which is measured by positive facial reactions to different food stimuli, and *explicit liking,* which is measured by the subjective rating using Visual Analogue Scales (VAS) (Berridge et al. 2009);

4) Wanting: The wanting component of food reward refers to a conscious or subjective desire, involving a psychological process that encourages the behaviour and the consumption, stimulating goals and expectations. It is commonly associated with food cravings and/or the motivation to obtain food (*explicit wanting*) and higher reaction time to food, or reinforcement (*implicit wanting)* (Berridge et al. 2009)*;*

5-Relative Reinforcing Value: Refers to the motivation to obtain food, how hard someone will work or how much time will be spent to obtain food *vs* other available items (Epstein et al. 2007a);

6-Satiation: Satiation refers to the physiological processes that lead to the termination of a meal (Green & Delargy 1997);

7-Delay of gratification or delay discounting: Refers to the preference for smaller immediate *vs* larger delayed rewards (Bickel et al. 2000);

8- Adaptive thermogenesis: Declines in EE following weight loss that go beyond the changes explained by changes in body composition (Keys 1950);

CHAPTER II - REVIEW OF LITERATURE

This review of literature is divided into four different sections. The first section is included in the form of peer-reviewed paper entitled: **“Weight loss and Appetite Control in Women”, published in Current Obesity Reports, volume 6, issue 3, pp: 334-351, 2017.** The paper describes and discusses weight loss-induced variations in appetite in women and factors that are related to those changes. The second section of this review describes the components of EE, how body weight fluctuations might affect them and the role of changes in EE in weight loss maintenance. The third section addresses issues around potential predictors associated with EI and weight management in women. Finally, the last section discusses the role of reinforcement and impulsivity and its relationship with EI, weight status and its management.

WEIGHT LOSS AND APPETITE CONTROL IN WOMEN

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ABSTRACT

Purpose of review: To describe and discuss weight loss-induced variations in appetite in women as well as factors responsible for these changes.

Recent findings: Studies have shown post-weight loss increases in fasting and postprandial appetite in individuals engaged in weight loss trials, especially in women. Similarly, appetite-related peptides associated with the homeostatic control of feeding such as leptin, ghrelin, PYY, were also found to be altered in way that promotes increased appetite after weight loss interventions. Sustained caloric deficits also drive increases in the frequency and strength of food cravings, food reward and seem to enhance oro-sensory sensations in women who lost weight. The menstrual cycle has also been to shown to influence caloric intake in women, more specifically food cravings. On the other hand, caloric-restriction seems to increase cognitive restraint, decrease habitual disinhibition and susceptibility to hunger among women engaged in weight loss trials. Neural analysis corroborates these results, showing increased activation in brain areas involved in food reward and self-control processing.

Summary: In conclusion, evidence supports that weight loss increases appetite sensations, and promotes changes in homeostatic and non-homeostatic control of feeding, that collectively seem to up-regulate appetite in women.

Key-words: weight loss; caloric restriction; appetite; energy intake

1. Introduction

Worldwide Body Mass Index (BMI) increased by 0.5 kg/m^2 per decade in women in recent history [1]. Non-surgical weight loss strategies are only effective over short period of times (3-6 months) [2]. Indeed, Kraschnewski *et al.* [3] reported that less than 20% of individuals attempting to lose a 10% weight loss were able to maintain this loss over a year. Moreover, systematic reviews have described extremely high weight recidivism with numbers ranging from 75 to 95% [3,4]. Evidence supports that the homoeostatic regulation of body weight exerts protective effects against weight loss more vigorously than against weight gain [5,6]. These defensive predispositions involve central and peripheral systems that promote decreases in energy expenditure and increases in energy intake. The changes in energy expenditure partly stem from adaptive changes in thermogenesis [7,8] while hunger and appetite centres simultaneously drive energy intake upward. In fact, many studies have reported increased appetite sensations following caloric restrictions, providing evidence of changes in the feedback control of energy intake, which results in a drive to eat exceeding that of pre-restriction levels [9]. Additionally, the small rates of success in conventional treatments (*e.g.* restricted caloric intake and increased energy expenditure) are likely not only due to increased hunger but can also be related to increased motivation to eat and to changes in rewarding components of food [10].

The resilience of obesity might present an even greater challenge to women as they are approximately twofold more vulnerable to present severe and morbid obesity [11]. Women also often make up most of the participants in clinical trials related to weight management and other obesity treatments [12,13]. This greater proportion of women in weight loss treatment intervention are not only due physiological and physiological sex-related differences in eating but also to interactions between cultural, social and biological factors as previously reviewed [14]. The present manuscript proposes a description of the changes in appetite sensations (hunger, motivation to eat, prospective food consumption - PFC and fullness) that arise from weight loss/weight maintenance strategies but

more specifically in women. The aspects presented and discussed include variations in appetite sensations during the weight loss; possible factors for altered appetite during the weight loss, including appetite-related peptides and changes in food reward and eating behaviour traits.

2. Variations in Appetite during Weight Loss

It has been suggested that appetite it is one of the predictors of energy intake and of the efficacy of a weight loss intervention [15,16], as well as weight loss maintenance [15,17]. Furthermore, recent evidence has shown that changes in appetite offer a greater challenge to weight loss success than do metabolic adaptations [18]. The objective of the following section is to present and discuss results related to changes of appetite ratings after various weight loss interventions in women.

Effect of Caloric Restriction on Fasting Appetite Ratings

Caloric restrictions are commonly accompanied by changes in fasting appetite sensations. Several studies support this observation, showing increases in fasting hunger of 5 to 38%, in fasting motivation to eat of 10 to 51%, and decreases in fasting fullness in 14 to 60% after caloric restriction [15,19–21] (**Table 1**). Appetite markers have also been shown to remain unaltered after caloric restriction in women [15,22]. Specifically, Moran *et al.* [22] reported no significant changes in fasting appetite in women with and without Polycystic Ovary Syndrome (PCOS), and increased fasting desire to eat, hunger and PFC was reported only in men [15]. In contrast, some studies noted decreases in fasting hunger [23–25], desire to eat [23,24], together with an increase of fullness [24] after caloric restriction. However, it is important to note that one of the latter studies employed multivitamin and mineral supplementation [19,24] in an attempt to downplay the effects of caloric restriction on appetite sensations. In another study, the manipulation of macronutrient distribution has been shown to attenuate the increases in fasting appetite sensations among women [25]. In sum, from the studies

discussed in this section, it seems that caloric restriction *per se* increases fasting appetite. However, it seems that the use of calcium and vitamin D supplementation might and a high protein/low carbohydrate diet might attenuate those increases in fasting appetite sensations after intervention.

One of the difficulties when comparing studies is the varying magnitude of weight loss (see table 1 for details). In fact, there are many studies showing that participants who presented higher weight loss (4 to 9%) also reported increases in fasting hunger [15,19,21], whereas those reporting lower decrease in percentage weight loss (3 to 6%) reported decreases in fasting hunger. On the other hand, when participants were categorized according to their weight loss (first, second and third tertiles), the ones who presented greater weight loss, were the ones who had a lesser increased fasting appetite [20]. In this case, the smaller increases in appetite were related to higher weight loss in women, a factor which was considered to be a significant predictor of weight loss. Correspondingly, Gilbert *et al*. [21] reported a negative correlation between fasting desire to eat and changes in FM, and a positive correlation between changes in fasting fullness and changes in FM. As such, it remains uncertain whether women who lose more weight also have greater increases in appetite, or if women lost more weight because they presented smaller increases in appetite ratings. Indeed, it remains to be confirmed if higher weight loss is attributed to less important appetite changes, since it possibly facilitates tighter alignment with the dietary energy restriction.

Some studies have shown that the up-regulation of fasting appetite seems to remain during the weight maintenance phase following caloric restriction. Doucet *et al.* [17] reported a sustained increase in fasting desire to eat, hunger and PFC during an 18- week post-intervention follow-up. In parallel, after a 6-month follow up period, Jakubowicz *et al.* [26] reported a 16% increase in body weight in women, which was accompanied by a 15% increase in postprandial hunger. Similarly, Sumithran *et al.* [27] reported sustained increases in hunger after a 1-year follow-up during which a

slight rebound in body weight was also noted. These observations suggest that individuals living with obesity, and who have lost weight, are very likely to be hosts to multiple compensatory responses related to appetite, which in concert could likely favour weight regain.

Effect of Caloric Restriction on Postprandial Appetite Ratings

Postprandial appetite is also altered by prolonged caloric restriction. For instance, increases in Area Under the Curve (AUC) for hunger and desire to eat and a decreases in AUC for fullness and satiety were observed in several studies [17,19,20,24,28,29]. Similarly, two studies report sustained elevations in postprandial hunger after a 6-month [26] or even a 1-year follow-up [27]. In contrast, a 49% decrease of postprandial hunger was noted following a low-carbohydrate/high-protein dietary intervention [25]. As such, in addition to total weight loss as mentioned above, the macronutrient composition of diets employed to induce weight loss may also need to be considered when comparing appetite changes during and after weight loss.

To our knowledge, there are only a handful of dietary interventions that have demonstrated decreases while others demonstrated insignificant changes in postprandial appetite markers following weight loss. Specifically, a decrease of postprandial AUC for desire to eat, AUC for hunger and AUC for PFC [24], as well as an increase postprandial AUC for fullness, were seen after caloric restriction [23,24]. Hoddy *et al.* [23] have recently shown that after a 8-week alternating caloric restriction days, participants (n=59, 50 women), had a non-significant change in postprandial hunger and an increase in postprandial fullness. In contrast, Moran *et al.* [22] reported a non-significant difference in postprandial appetite markers following weight loss produced by a 8-week dietary intervention. Although a few papers have reported no increase or even a decrease in postprandial appetite in women after weight loss, it would seem that in sum, there are more studies supporting increased

postprandial appetite sensations post weight loss. Such increases could potentially lead to increased EI, thus compromising long-term weight maintenance among women [17,19–22,28] and men and women together [29].

Effect of Exercise on Appetite Ratings

Exercise-induced weight loss is generally less than that obtained through dietary interventions [30]. Whether this is caused by a greater challenge to appetite control under those conditions remains to be determined. Martins *et al*. [31] recorded greater postprandial AUC hunger and desire to eat, as well as fasting hunger, desire to eat and PFC after a 12-week intervention. Fasting fullness and satisfaction of appetite decreased even if these changes were not reflected by actual changes in energy intake. Similarly, other studies have shown modifications in fasting appetite, which were reflected through increased energy intake only in the non-responders to the exercise intervention [32,33] On the other hand, results from this set of studies also demonstrated that exercise intervention can improve meal-induced satiety in both responders and non-responders. The above-mentioned studies included both men and women in their sample, and no sex effects were reported. In sum, a trend toward an increase in fasting appetite seems to emerge after exercise-induced weight loss, an observation mostly apparent in participants who presented some form of resistance to slimming. The role of exercise in satiety remains to be fully elucidated.

Effect of Caloric Restriction and Exercise on Appetite Ratings

Interventions combining caloric restriction and exercise exhibit similar influence on appetite ratings, whereby appetite is stimulated. Anton *et al.* [34] led a 6-month weight loss study in four groups including men and women: control, caloric restriction, caloric restriction + exercise and very low-calorie diet (VLCD) also involving men and women. All groups had varying percentage weight loss

(see **Table 1** for details). Although the low-calorie diet (LCD) produced the greatest percentage weight loss, the caloric restriction group reported increases in hunger (13%) and desire to eat (23%), and decreases in fullness (26%) and satisfaction of appetite (37%). The exercise plus caloric restriction group presented the highest increase in PFC (+21%). Along the same lines, Keim *et al.* [35] reported increased AUC hunger, desire to eat and PFC, while decreased in fullness after 12-week of diet and exercise intervention in normal weight women. Overall, the studies combining caloric restriction and exercise that were reviewed also showed increased appetite ratings. However, whether this increase translates to increased free-living EI remains to be clearly established. In addition, it would seem that an energy deficit imposed through caloric restriction poses a greater strain to appetite regulation in men, at least in the short-term [36]. It is unknown at this point whether this would also be the case in women.

Sex-Related Effects

Even though some of the studies reviewed in this section included men and women, for the better part, these studies included a greater number of women in their samples. Correspondingly, a total of 883 women *vs* 456 men out 1339 individuals participated in the studies reviewed. Given that these weight loss studies included a majority of women, it is reasonable to conclude that sex does not play a major role in appetite variations upon energy deficits leading to weight loss.

Collectively, changes in appetite during weight loss interventions are highly variable and dependent on various factors such as the type of intervention, individual characteristics and percentage of weight and fat loss. Those changes in appetite, or the absence thereof, are very likely influenced by the interplay between central and peripheral signalling, which also fluctuate in response to perturbations of energy intake. The following section explores some of the appetite-related peptides and reward

driven behaviours, and how they could explain the modulations in the drive to eat that arise from weight loss interventions.

3. Possible Mechanisms for Altered Appetite along the Weight Loss

3.1) Appetite-related Peptides

Compensatory responses to energy deficits likely compromise weight loss and its maintenance. In this section, weight loss induced changes in appetite-related peptides will be discussed. Appetite-related peptides include, but are not limited to, leptin (long term signal mainly released from adipose tissue) and gut released ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) involved in short-term control of food intake and appetite regulation [37]. Briefly, short-term signals are modulated, at least in part, by meal size and composition, as well as by daily energy intake, while long-term signals mostly fluctuate in response to fluctuations in energy storage [38]. The central nervous system (mainly the hypothalamus and hindbrain) integrate short- and long-term signals in an attempt to regulate energy stores, food intake and energy expenditure. Collectively, these peptides exert a coordinated action to direct feeding. Most of these have been shown to fluctuate with changes in adiposity. In fact, there have been numerous reviews extensively covering the role of these peptides during and after weight loss [37,38]. The objective of the next section is not to present another similar review, but rather to highlight how these signals change during weight loss in women, and to discuss their role in influencing appetite responses. The studies reviewed in this section are presented in the **Table 2**.

Directors of Appetite and Food Intake

Several studies have investigated the relation between gut peptides and energy intake and appetite regulation in healthy subjects. Intravenous administration of ghrelin has been associated with immediate increases in appetite and food intake [39]. In contrast to ghrelin, fasting reduces leptin concentrations. Higher levels of adiposity are commonly accompanied by hyperleptinemia [40], however, it seems that appetite suppression is not effectively occurring in individuals living with obesity despite the anorexigenic effects of leptin [41], probably due to a potential leptin resistance in individuals chronically exposed to higher adiposity [40]. Intravenous administration of PYY causes reductions in appetite and EI together with a subsequent decrease in ghrelin levels [39]. Like PYY, both central and peripheral administrations of GLP-1 has been reported to reduced food intake [42] and appetite [39], and it would seem that these effects are enhanced when both PYY and GLP-1 are administered conjointly [39]. CCK also exerts suppressive effects on food intake [43]. Indeed, intravenous administration of CCK1 receptor antagonists is associated with decreased satiety and increased hunger and meal size [44]. Collectively, these peptides are associated with fluctuations of acute and chronic energy status.

Appetite-related Peptides after Weight Loss

Changes in the circulating levels of appetite-related peptides have been proposed to facilitate weight regain following weight loss in both overweight and obese women [45]. Energy restrictions trigger a more profound decrease in leptin concentrations during dynamic weight loss than during weight maintenance period [38]. In the first study of leptin after weight loss, Considine *et al.* in 1996 [46] reported that a 10% body weight reduction was associated with a 53% reduction in serum leptin. A few years later Wisse *et al*. [47] subjected 3 groups of women living with obesity to different degrees of caloric restriction, fasting, VLCD, and balanced-deficit diet (BBD). They reported that more severe restriction induced a greater decline in leptin during the first week. However, the difference was less

dramatic when all subjects showed comparable FM loss at the end of the fasting, VLCD and BBD interventions (76, 61 and 52% reduction in leptin levels, respectively). Similarly, other studies reported a reduction in leptin concentration of 26% by diet alone [48] and by 40% and 67%, respectively [35,49], from a moderate energy deficit in combined physical exercise. Moreover, administrating weight loss diets with different macronutrient compositions [50,51] reduced serum leptin concentrations in similar ways regardless of dietary pattern. Overall, most studies, have shown that weight loss induces reductions in leptin concentrations.

Similar to leptin, ghrelin is influenced by short and long-term energy imbalance. In the first documented report of the effects of weight loss on ghrelin, Cummings *et al.* [52] demonstrated that fasting leads to a sharp increase, while feeding contributes to its downfall. A 17% diet-induced weight loss in 13 obese individuals (8 women and 5 men) was associated with a 24% increase in AUC-ghrelin concentrations. Similarly, studies have reported lower circulating levels of ghrelin in people living with obesity compared to matched lean controls individuals, which may reflect a compensatory adaptation that contributes to a reduction hunger [53]. Weight loss following hypocaloric diets [54] or in combination with exercise [55] causes a significant elevation in ghrelin concentrations in overweight or women living with obesity by 18% and 72%, respectively. Weight loss induced by diet, exercise and drug therapy (Orlistat) in women with overweight was accompanied by a significant increase in ghrelin concentrations of 19% during 6 months of gradual weight loss but returned to baseline levels at subsequent 6 months of weight maintenance period [56]. In the same study, baseline ghrelin levels were also inversely correlated to the degree of weight reduction. In contrast, ghrelin concentrations remained unaltered following short-term energy-restricted diets for participants living with overweight or obesity (n=132, 77 women) [22,41]. The difference in results compared to other studies may be due experimental variations [41] or to the modest weight loss [22]. Collectively, available evidence supports a role for ghrelin in the regulation of long-term energy homeostasis.

Weight loss is also accompanied by reduced CCK response, which is associated with decreased leptin levels, an effect that could result in reduced satiety after meal consumption [44]. Weight loss induced by energy-restricted diet was significantly and negatively correlated with changes in AUC-CCK. However, weight loss caused no differences in fasting or postprandial CCK levels of women with and without PCOS. It is hypothesized that the low amount of protein or fat consumed by the participants may have not been sufficient to stimulate postprandial CCK release [22]. The studies investigating the effects of weight loss exclusively in women are few, but weight loss following a VLCD for 10 weeks was accompanied with a 29% reduction in CCK (fasting and postprandial) levels in a group of women living with overweight or obesity, which was not different from men in the study [27].

GLP-1 regulates the homeostatic control of feeding. It reduces the rate of gastric emptying, which in turn slows nutrient absorption, leading to the decrease in postprandial glycaemia and enhanced satiety [57]. There are discrepancies as far as the effects of weight loss on GLP-1 are concerned. GLP-1 levels were reduced by 15% in men and 8.4% in women following diet-induced weight loss [27,58]. In contrast, a VLCD induced 11% of body weight reduction in young women with obesity did not alter GLP-1 levels [59]. On the other hand, 8 weeks of low calorie, physical activity or Orlistat (or placebo) intervention increased pre- and postprandial GLP-1 by 45% in the Orlistat group [60]. That latter result should be interpreted in light of the fact that the greater increase of plasma GLP-1 levels in women receiving Orlistat could have resulted from the inhibition of the intestinal lipase activity causing increased intestinal fat content, thus likely contributing to greater stimulation of GLP-1 release.

Some studies have reported that individuals living with obesity have lower fasting and postprandial anorexic gut peptide concentrations due to reduction in PYY synthesis or releases. It has consequently been proposed that PYY deficiency could be involved in the pathogenesis of obesity [61]. Similar to GLP-1, there are inconsistencies regarding the weight loss-induced PYY response. In the first study of acute energy deprivation in adults, a reduction ranging from 11 to 50% of fasting and postprandial PYY levels was been reported during the two to four first days of energy intake reduction [62]. Energy restriction reduced PYY levels by 25% in a group of men and women with overweight or obesity [27]. However, a modest increase (non-significant) in PYY levels were found after weight loss in overweight/obese postmenopausal women [63] or women with PCOS [22]. The absence of significant changes in fasting or postprandial PYY following weight loss may be due to insufficient intervention duration, to the degree of weight loss, to increased central nervous system sensitivity to the effects of PYY or to other compensatory responses set in motion to restore energy balance[22]. In contrast, a low calorie diet and regular physical activity with or without Orlistat therapy was followed by significant increases in PYY concentrations but this elevation was about twofold higher in the group receiving Orlistat compared to placebo (105% vs 46%). The increases in PYY levels were independent of body mass changes [60]. In line with these results, PYY levels have also been shown to increase by 11.6% after both weight loss through low-energy density diet for 12 months and a weight maintenance period [64].

There are also several studies that have investigated appetite-related peptide profiles during a post-weight loss weight maintenance phase. In the first of these, persistent reductions in leptin, insulin, PYY and CCK concentrations and significant elevation in levels of ghrelin were shown after a 12-month weight maintenance phase [27]**.** These observations suggested compensatory persistent alterations in circulating mediators of appetite that could favour weight regain [65]. In a group of obese/overweight volunteers (men and women), a weight regain $\geqslant$10% after 32 weeks of initial

weight loss was associated with higher baseline fasting leptin and lower ghrelin levels [41]. In this study, ghrelin concentrations were significantly higher in women than men at all points of the study. Higher levels of leptin contributed to body weight regain, more so in women. In contrast higher levels of ghrelin were associated with less weight regain, especially in men. Findings from these suggest that weight regain following weight loss may be partly predicted from hormone levels at baseline.

As mentioned above, there are some discrepancies regarding the hormonal alterations following weight loss interventions in women. Those differences are likely due to the variety of interventions, the degree of weight loss, the duration, participant characteristics including pre- or postmenopause status and different responses in hormone regulations. Overall, it would seem that alterations in appetite-related peptides signalling are in a direction, which would favour weight regain. However, most of weight loss studies have not compared the effects of diet induced weight loss between men and women, so whether or not there are sex-related differences in those peptides signalling remain uncertain. Moreover, weight loss studies investigating alterations in levels of specific peptides following weight loss including; CCK, PYY, GLP-1 exclusively in women, are still necessary in order to clarify the effects of body weight fluctuations on appetite related peptides only in women. Considering the small number of studies that have reported changes in gastric inhibitory polypeptide, pancreatic polypeptide and amylin in women and the lack of evidence pointing to changes in these peptides following caloric restriction, we have not included them in the present review. There is also insufficient data to conclude that for similar weight loss, exercise interventions would promote changes in appetite-related peptides that would be different from that observed from caloric restriction.

Appetite Regulation Following Gut Peptide Alterations

To our knowledge, a handful of studies have investigated the effects of appetite-related-hormones alterations induced by weight loss on changes in appetite measures simultaneously and more particularly, in women (Table 2). In the study by Keim *et al.* [35] the decrease in leptin levels was accompanied by increases in hunger and desire to eat and it was associated with increased AUC hunger and PFC. While weight loss increased the sensation of fasting fullness in a group of overweight age- and weight-matched women with and without PCOS, postprandial appetite hormones were not associated with weight loss or with appetite scores [22]. However, a ⩾8% weight loss in subjects with obesity (men and women), followed by a 2- to 3-week weight stabilization period, was accompanied by lower levels of fasting GLP-1 and PYY along with increased appetite scores and hunger sensation [66]. Moreover, weight loss by VLED in 50 overweight or men and women with obesity resulted in reductions of leptin, PYY and CCK and to an increase in ghrelin levels. These appetite-related peptide modifications were accompanied by higher mean ratings of postprandial hunger, desire and urge to eat, of preoccupation with thoughts of food and PFC [27].

In general, most of the studies investigating appetite-related peptide alterations following weight loss have shown that prolonged energy deficits contribute to alterations in hormonal regulators of appetite in a manner that tends to increase appetite and decrease satiety. A condition that likely produces an overall promotion of food consumption and possibly overconsumption, which likely facilitates weight regain.

3.2 Reward Driven and Eating Behaviour Traits after Weight Loss

According to Berridge *et al.*[67], food reward is a composite process that involves “liking”, “wanting”, and learning as major components. The “liking” component of food reward is a subjective component

that refers to the psychological process that produces pleasure, also called the hedonic impact. The main brain regions involved are the amygdala, the primary and higher-order sensory cortical areas, including the insular and orbitofrontal cortex, which are responsible to form sensory representations of food [10,68]. The “wanting” component of food reward refers to a conscious or subjective desire, involving a psychological process that encourages the behaviour and the consumption; stimulating goals and expectations. It is largely mediated by cortical circuits, including mesolimbic dopamine projections [69,70] and commonly associated with food cravings and/or the motivation to obtain food. Finally, the learning component is comprised of the associations with and predictions about reward, which are mediated by different regions of the brain such as cortical and orbitofrontal areas, insular and other regions of cortex [71–73]. More specifically, “liking” and “wanting” can affect energy balance whereby they can promote overconsumption of specific food items and potentially weight gain. Both components of food reward are also affected by perturbations on energy balance. These effects are described in the following section.

For instance, food reward is normally highest for foods with high palatability, most often a characteristic of sweet and savoury foods. Increased motivation to eat, in conjunction with the types of food that are more frequently consumed under such circumstances, can favour positive energy balance and over time lead to increased levels of adiposity [74]. Similarly, perturbations of energy balance (*e.g.* calorie restriction and/or increased energy expenditure) have also been shown to influence the rewarding effect of food, potentially compromising weight loss and weight maintenance. A collection of studies that have measured food reward during weight loss is presented in the **Table 3.**

Impact of Caloric Restriction on Food 'Liking'

The liking component of food forward is commonly measured by ratings of the pleasantness of the taste of a mouthful, of eating these foods or by the brain activity in areas related to pleasure. Liking has been shown to increase in response to acute hunger state [75–77] and by chronic perturbations in energy balance leading to a reduction in body energy storage [78]. Indeed, a greater explicit 'liking' for sweet beverages was observed after 4 hours of caloric restriction [75], whereas an increase 'liking' for different food categories (savoury, sweet, high fat and low-fat) was noted in participants 24-hour fasting [76,77]. Those changes were also related to olfactory performance in women [77], potentially encouraging an acute compensatory feeding response among participants. Along the same lines, longitudinal studies have reported a 10% increase in liking for the participants' favourite snack after 8 weeks of caloric restriction (-700 kcal/day), while this increase was not observed after a standard meal [78]. The changes in hedonic ratings were not related to changes in body composition and no sex-related differences were reported.

It seems that acute and chronic caloric restriction impact on food liking, especially that of high-energy-palatable food items. This increase can lead to subsequent increases in energy intake, which can compromise weight loss and make weight loss maintenance more fragile. The studies discussed above included both men (n=50) and women (n=75). However, considering that women composed the greater part of this overall sample, and that no sex-related differences were reported, it is possible to speculate that liking in women and in men responds similarly to caloric restriction.

Impact of Caloric Restriction on Food 'Wanting'

Results pertaining to the wanting component of food forward have been reported in several different ways, such as from food cravings questionnaires, from food craving frequency, from desire to eat a

portion of a palatable item, as well as from functional imaging studies on brain areas related to craving and/or the motivation to obtain food. In the same way as the 'liking' component, the 'wanting' component of food reward can also be affected by acute and long-term caloric restriction, an effect that can lead to increased energy intake. In fact, randomized crossover design studies (fed state vs. fasting state) have shown increased motivation to respond to foods after 4h, 13h and 24 hours fasting [75,76,79]. Individuals under fasting condition (*vs* fed state) also presented increased reinforcing value of foods [75,76], causing them to work harder for food points during a computer task with the goal of earning a palatable food items. Greater explicit wanting for different food categories has also been reported in participants who were fasted for a 24-hour period [76]. This condition was associated with a 70% increase of energy intake measured in the laboratory. These studies again included both men and women, and no sex differences were reported.

Similar to acute energy deficits, cross-sectional [80] and longitudinal studies have reported increased wanting, promoting an increase in food craving frequency after longer periods of energy restriction in women [26,28,81,82]. Considering that most weight loss programs restrict not only energy intake but also the consumption of high-energy-density palatable food items, these interventions may compound the increase reinforcement value of the restricted food, which may be expressed as increased cravings for the restricted foods [75,81]. In fact, food-craving frequency was found to be a predictor of weight loss in women, whereas women who reported higher scores on Frequency Craving Questionnaire at baseline also had lesser weight loss [83]. Similarly, the reported percentage of time an individual gave in to food cravings was found to be a significant predictor of percent weight loss and weight maintenance. Conversely, women who presented a higher percentage of weight loss were also the ones who indicated a lower frequency of 'giving in' to their food cravings [81].

Collectively, these findings highlight that increases in food wanting measured by computer tasks, or measured through increased cravings may be part of the integrated appetite responses to caloric restriction in women. Furthermore, the strength and frequency of food cravings may mitigate the response to weight loss interventions and potentially weight loss maintenance.

Menstrual cycle, Caloric Restriction and Food 'Wanting'

The menstrual cycle seems to modulate total energy intake, craving frequency and energy expenditure as previously reported and reviewed [84]. In fact, during the follicular phase, it appears that women experience more frequent food cravings [85], particularly for chocolate [86] and increased explicit wanting for high fatty food [85], which could impact energy balance. More related to the context of this review, it was recently reported that permitting the ingestion of dark chocolate during the luteal phase, thereby increasing EI by 200kcal, enhanced the compliance to a weight loss diet [87]. Although it is likely that appetite control was improved as a result of the latter intervention because women lost more weight, appetite related peptides measurements were not actually performed in this study.

Effects of Weight Loss on Eating Behaviour Traits

The following section will describe the effects of weight loss on eating behaviour traits, as measured with the Three Factor Eating Questionnaire developed by Stunkard and Messink [88]. Results from weight loss studies commonly report significant increases in restraint [20,81,89,90] and decreases in disinhibition [20,90] and in the susceptibility to hunger [81,82,90]. Those results are also supported by functional neuroimaging analysis conducted in individuals who have lost weight and were able to maintain reduced body weight [91,92].

More specifically, the decrease in the susceptibility to hunger in women seems to be more apparent in those who have lost more weight [20]. Indeed, Gilhooly *et al.* [81] reported positive associations between susceptibility to hunger and food cravings frequency observed at baseline and after 6 months of caloric restriction in women. It was also recently reported that after controlling for sex and age in a model that included craving-trait and eating behaviours (restraint, disinhibition and susceptibility to hunger), only susceptibility to hunger was a predictor of weight changes after 20 weeks of caloric restriction [82].

Eating behaviours would thus seem to be influential mediators of diet-induced weight loss. In fact, increases in dietary restraint, in parallel to decreases in disinhibition and in the susceptibility to hunger have been reported to be positively associated with the magnitude of weight loss in women. Interestingly, these associations may be reflective of the fact that eating behaviour trait modifications may be necessary to oppose other adaptive appetite responses that are discussed in this paper.

Neural Studies in Food Reward

In order to locate brain areas involved in the perception of food-related stimuli, functional neuroimaging modalities are commonly used. fMRI is the method most commonly employed to evaluate the brain activity while participants are exposed to external stimuli (visual or sensory). For instance, analysis comparing brain activity in lean and individuals living with obesity revealed activation of different areas involved in food reward processing [93,94]. Along the same lines, longitudinal studies including subjects during and after weight loss, have noted increased activation in food reward brain circuit (insula, amygdala, ACC, middle occipital cortex areas) among weight losers [95,96].

Investigations of post weight loss neural activity have revealed increased activity in parts of food reward brain circuit (insula, amygdala, ACC, middle occipital cortex areas) when exposed to high caloric food *vs*. neutral images [96]. Results from 21 women with obesity exposed to high-calorie food *vs.* control pictures revealed associations between weight loss and neural activation of brain regions mediating motivational and attentional salience of food cues implicated in reward-system processes, such as the nucleus accumbens, anterior cingulate, and insula [95]. The study also reported that at the onset of the caloric restriction, higher levels of glucose were associated with lower levels of activity in brain regions related to food reward processing (hippocampus and insula). However, these effects were no longer observed after the caloric restriction period, which could be an indicative of changes in satiety signalling [95].

Activity patterns in brain areas such as the insula, hippocampus and amygdala are altered not only during and after weight loss but also seem to persist after the weight loss. Cross-sectional analyses have shown increased activation in anterior cingulate, left middle frontal gyrus in historical dieters women compared to non-dieters [91]. Historical dieters also exhibited elevated response of the bilateral occipital regions, right middle insula, left middle, and posterior insula, IFG, postcentral gyrus, and putamen when exposed to a highly palatable food item [93,97]. Using evidence of the implication of leptin in the control of feeding, Rosenbaum *et al*. [98], reported that subcutaneous injections of leptin in a small sample of weight maintainers (4 women and 2 men) was sufficient to reverse the effects of weight loss on brain areas responsible for emotional, and cognitive control of energy intake.

There is evidence to support that successful weight-losers present greater activation in reward circuitry. There is also data showing that those individuals present greater visual attention and great inhibitory control in response to food cues [97]. Greater activation in the dorsal prefrontal cortex,

dorsal striatum and anterior cerebellar lobe in response to meal consumption has been noted in successful dieters when compared to non-dieters. Considering that the dorsal prefrontal cortex is responsible for the control of inappropriate behaviour, it may explain the high level of cognitive restraint normally observed in successful dieters. In fact, the stepwise regression models dietary restraint was the only variable associated with changes in neural activity after a standard meal (compared to 36-h fasting) in the dorsal prefrontal cortex and in the anterior cerebellar lobe [92]. Again, evidence presented in this section reflects the elevated reward circuitry activation in response to highly palatable food in weight-reduced women. Furthermore, these adaptations seem to persist after weight loss, and could seemingly be compensated by a greater engagement of inhibitory control of certain brain regions, a modification that could partly explain how some individuals afford to maintain weight loss.

Taken together, studies presented herein point out to a neurophysiological response in individuals who are exposed to acute or chronic caloric restrictions. Such responses could in turn increase their susceptibility to overeat when exposed foods of higher hedonic value. Individuals exposed to calorie restriction present increased reward driven behaviours, reflected by increased liking and wanting, observations that are supported by functional neuro-imaging studies. Considering none of these studies reported the results separately for men and women, it is not possible at this time to ascertain whether or not these increases are more pronounced in women. Individuals who are more successful at maintaining weight loss also seem to display increased cognitive restraint and decreased susceptibility to hunger. Again, these observations are supported by increased activation in brain areas responsible for self-control among women who have maintained their weight loss. This could be interpreted as an attempt to counteract weight loss induced increases in food reward among other appetite changes that occur with weight loss.

4. Conclusion

Most of the evidence presented and discussed points out to increased fasting and post prandial appetite after weight loss in women. Those changes are supported by alterations in hormonal regulators of appetite in a manner that tends to increase appetite and decrease satiety after caloric-restriction periods. Similarly, weight loss seems to increase food reward driven behaviours such that it results in increased liking and wanting, observations that are supported by functional neuro-imaging studies. Associations between magnitude of weight loss and increase in dietary restraint in parallel to decreases in disinhibition and in the susceptibility to hunger may be reflective of the fact that eating behaviour trait modifications are necessary to oppose other adaptive appetite responses to weight loss. Sex does not seem to play a major role in appetite variations after weight loss since no sex-related differences were reported in the studies included in this review. Studies comparing neuro-imaging responses to caloric deprivation in men *vs* women are necessary in order to clarify if sex plays any role in the neurobiology of energy regulation. Furthermore, most of the changes presented throughout this review seem to persist after the weight loss. As illustrated in Figure 1, collectively these demonstrations illustrate the inherent challenge that prolonged negative energy balance impose on appetite control, which very likely impedes both desired weight loss and long-term maintenance of lower body adiposity.

Table and Figure Legends

Table 1. Variations on appetite along weight loss

EI: Energy Intake, PCOS: Polycystic ovary syndrome, VAS: Visual Analogue Scale, SQ: Satiety Quotient, AUC: area under the curve, PFC: Prospective Food consumption, CHO: carbohydrates, PROT: protein.

Table 2: Peptides-hormonal changes after weight loss

EI: Energy Intake; PCOS: Polycystic ovary syndrome, LED: low energy density, VLED: very low energy diet, CHO: carbohydrates, PROT: protein, CCK: cholecystokinin, PYY: peptide YY

Table 3. Reward and eating behavior traits after weight loss

EI: Energy Intake, SQ: satiety quotient, CHO: carbohydrates, PROT: protein, TFEQ: Three Factor Eating Questionnaire, fMRI: functional magnetic resonance imaging

Figure 1. Changes in subjective appetite, food reward, behavioural traits, peptides, and hormones in obese and weight reduced women after weight loss

Table 1

Study	Intervention	Sample size	Weight change	Results
Drapeau *et al.* [15]	Study 1: Drug (Topiramate) 12 months Study 2: Drug (Rimonabant) 4 week Study 3: Diet + fenfluramine/placebo N/A duration Study 4: Diet + PA approximately 30 weeks, Study 5: Diet + Ca^{2+} + vitamin D/placebo 15 weeks Study 5: Diet + supplement/placebo N/A duration	315 obese participants (139 women)	All studies: Men: ↓4.8 kg Women: ↓4.5 kg -no initial body weight reported	↑ Fasting desire to eat ↑Fasting hunger ↑ Fasting PFC: in men, not in women ↓ Lower satiety quotient in men
Doucet *et al*. [17]	Phase 1: 15 weeks caloric restriction (-700 kcal/day): Group 1: placebo + caloric restriction Group 2: 60 mg/d fenfluramine + caloric restriction Phase 2: 18 weeks: low-fat diet + aerobic exercise (65-70% VO2 max 3-5 x /week, 45-60 min/ session)	17 overweight and obese (7 women)	Phase 1: men: ↓11.4% women: ↓ 8.4% Phase 2: men: ↓13.7% women: ↓10.5%	Phase 1 (baseline *vs* post-intervention): ↑4%AUC desire to eat, ↓3.5%AUC hunger, ↑9%AUC fullness, ↓27%AUC PFC Phase 2 vs Phase 1: ↑3% AUC desire to eat, ↓1% AUC hunger, ↑8% AUC fullness, ↓15% AUC PFC (in women)
Gilbert *et al.* [19]	6 months: caloric restriction (-600 kcal/day) Intervention: caloric restriction +calcium supplementation Control: caloric restriction + Placebo	Intervention: 20 obese women Placebo: 21 obese women	Intervention: ↓9.1% Placebo: ↓6.7%	Intervention: ↑10.5% Desire to eat, ↑5% Hunger, ↑12.5% Fullness, ↑14% PFC Placebo: ↑51% Desire to eat, ↑21% Hunger, ↓59% Fullness,

				↑12% PFC
Tremblay *et al.* [20]	12 to 16 weeks: caloric restriction: (-500 to 700 kcal/day)	75 women	Body weight: ↓3.7%	↑9% Fasting hunger ↓ 14% Fasting fullness
Gilbert *et al*. [21]	4 months to 6 months: caloric restriction (-700 kcal/day)	54 overweight women	Body weight: ↓4.7% Body fat: ↓ 4.6 %	VAS Fasting: ↑ 13 % Desire to eat ↑ 6% Hunger, ↓ 15 % Fullness, ↑ 2.5% PFC SQ: ↑20% Desire to eat, ↑ 11.5% Hunger, ↑ 8.5% Fullness, ↑ 11% PFC AUC: ↓ 7.5% Desire to eat, ↓ 8.5% Hunger, ↑ 4% Fullness, ↓17% PFC
Moran *et al.* [22]	8 weeks: caloric restriction: (- 30% total energy expenditure) EI: approx. 1200 kcal	PCOS: 14 women Control:14 women	Intervention ↓2.8% Control: ↓5.9%	↑ Fasting fullness in PCOS and control, ↓Postprandial fullness in PCOS and control No numerical baseline data provided
Hoddy *et al.* [23]	8 weeks: caloric restriction (-25% baseline energy expenditure) + ad libitum intake on each alternating feed day	59 obese participants (50 women)	Body weight ↓4.2% Fat mass↓ 5.3%	↓Fasting hunger, ↑ Postprandial fullness, ↑ AUC Fullness No numerical baseline data provided
Major *et al.* [24]	15 weeks: caloric restriction (-700 kcal/day (non-macronutrient-specific) Intervention: caloric restriction + calcium supplement Control: caloric restriction + placebo	Intervention: 19 (11 women) Placebo: 21 (11 women)	Intervention : ↓2.8% Control: ↓5.8%	Intervention: Fasting: ↓35% Desire to eat, ↓7% Hunger, ↑ 83% Fullness, ↓ 19.3% PFC, AUC:

				↓42% Desire to eat, ↓ 35.5% Hunger, ↑24 % Fullness, ↓49 % PFC
Nickols-Richardson *et al.* [25]	6 weeks caloric restriction (EI: 1,500 - 1,700 kcal/day): Low-CHO/high-prot (LCHP) & High-CHO/low FAT (HCLF)	LCHP: 13 women HCLF: 15 women	LCHP: ↓5.7 % HCLF: ↓3.3 %	LCHP: ↓49% Self-rated Hunger HCLF: ↓17% Hunger
Jakubowicz *et al.* [26]	16 weeks: EI: 1,400 kcal to 1,700 kcal/day Low CHO diet (LC) High CHO + breakfast dessert (HCP) 32-wk follow up	HCP: 97 overweight and obese participants (44 women) LCb: 96 overweight and obese participants (42 women)	Intervention: HCP: ↓14.9% LC: ↓16.8% Follow up: HCP ↓9% LC: ↑15.6%	Intervention: HCP: ↓0.2% AUC Hunger, ↓1% AUC Satiety LC↑14.5% AUC Hunger AUC ↑5% AUC Satiety Follow-up: HCP ↑3% AUC Hunger AUC, ↑2% AUC Satiety LCb ↓0.03% AUC Hunger, ↓3.5% AUC Satiety
Jakubowicz *et al.* [28]	12 week: caloric restriction EI: 1,400 kcal/day High-calorie breakfast (HCB): 50% Daily calorie intake in their breakfast High-calorie dinner (HCD): 50% Daily calorie intake in their dinner	HCB: 38 overweight and obese women HCD: 36 overweight and obese women	HCB ↓11% HCD ↓4%	Fasting: Hunger HCB < Hunger HCD Satiety HCB > Satiety HDC Post prandial: Hunger HCB < Hunger HCD Satiety HCD < Satiety HCB
Parra *et al*. [29]	8 weeks caloric restriction -30% of total energy expenditure (50-55% CHO, 16-20% PROT, 30-25% FAT) 1. control: no seafood (6 placebo capsules/d),	Low n-3 FA intake 112 (68 women) high n-3 FA	↓ 5.9 % No specified info per	Analysis: diet 1 & 2: low FA intake diet 3 & 4: high FA intake 0h postprandial: Fullness high FA >

	2. lean fish (150 g cod 3 times/wk), 3. fatty fish (150 g salmon 3 times/wk), 4. fish oil capsules (6 caps/day)	intake 121 (67 women)	group provided	Fullness low FA Hunger high LC FA < Hunger low FA 2h postprandial: Fullness high LC FA > Fullness low FA, Hunger high FA < Hunger low FA
Martins *et al.* [31]	12 weeks: exercise program (500 kcal energy expenditure at 75% max heart rate, 5 days/week)	15 (7 women)	Weight loss: ↓ 3.7%	Fasting: ↑ 58.5% Hunger, ↑ 33.5% Desire to eat, ↑ 18.5% PFC, ↓46 Fullness Postprandial: ↑36% AUC Hunger, ↑32% AUC Desire to eat
King *et al.* [32]	12 weeks exercise program (500 kcal energy expenditure at 70% max HR, 5 days/week)	58 overweight and obese participants (39 women)	Responders ↓5.7% Non-responders ↓1%	Responders: ↑24% Fasting hunger, ↑10%AUC Hunger, ↓8.5% AUC Desire to eat, ↑1%AUC Fullness Non-Responders: ↑38% Fasting Hunger ↑43%AUC Hunger, ↑6.5% AUC Desire to eat, ↓10%AUC Fullness
King *et al.* [33]	12 weeks exercise program (500 kcal energy expenditure at 70% max HR, 5 days/week)	35 overweight and obese participants (25 women)	Non-compensators: ↓6.9% Compensators: ↓1.6%	AUC Compensators: ↑26% Hunger Non-compensators: ↑1.4% Hunger
Anton *et al.* [34]	6 months: Control: weight maintenance diet; Caloric restriction (CR): -25% baseline energy requirements;	Control: 11 (6 women) CR: 12 (6 women)	Control: ↓1% CR: ↓10.4%	Fasting Appetite Control: ↑8% Hunger ↓26% Fullness ↑14% Desire to eat ↓22%

	Caloric restriction + exercise program (CR + EX; ↓ 12.5% baseline energy requirements + ↑12.5% total energy expenditure); Low-calorie diet (LCD): EI: 890 kcal/ day	CR+EX: 12 (7 women) LCD: 11 (5 women)	CR+ EX ↓10% LCD: ↓14 %	Satisfaction of appetite ↑13% PFC CR: ↑13% Hunger ↓14% Fullness ↑23% Desire to eat ↓37% Satisfaction of appetite ↑13% PFC CR+EX: ↑11% Hunger ↓12% Fullness ↑12% Desire to eat ↓30% Satisfaction of appetite ↑21% PFC LCD: ↑13% Hunger ↓15% Fullness ↑14% Desire to eat ↓12% Satisfaction of appetite ↑15% PFC
Keim *et al.* [35]	12 weeks caloric restriction & exercise program Nutrition: 23 to 28 kcal/body weight kg/day (60%CHO , 18% PROT, 22% FAT) + Exercise: (5day/week, at 65% VO2max+ 3days/week resistance training	12 women	Body weight: ↓ 9% Fat mass ↓ 21%	AUC: ↑31.5% Hunger, ↓7.5% Fullness, ↑39.5% Desire to eat, ↑20.5% PFC

Table 2

Study	Intervention	Sample size	Weight changes	Results
Moran *et al.* [22]	8 weeks: caloric restriction EI: 1240 kcal/day	PCOS: 14 Control: 14 (only women)	Weight loss: PCOS: ↓4.1% Control: ↓ 5%	No change in ghrelin, No changes in fasting and postprandial CCK and PYY;
Sumithran *et al.*[27]	8 weeks: VLED EI: 500 -550 kcal/day 62-wk- follow up	34 overweight or obese participants (23 women)	Week 10 Weight loss: ↓14% Fat loss: ↓ 9.8% Week 62 (vs baseline) ↓Weight loss: 8.2%: , ↓Fat loss: 5.3%	Week 10 ↓ 65% Leptin, ↓ 25% PYY, ↓ 29% CCK ↓15% GLP-1 , ↑ 45% Ghrelin Week 62 (vs baseline) : ↓ 36.5% Leptin, ↓24% PYY, ↓6% CCK, ↓ 8% GLP-1, ↑ 20% Ghrelin
Keim *et al.* [35]	12 months: caloric restriction (-478 kcal/day + ↑energy expenditure 191 kcal/day)	12 women BMI: 23-37 kg/m^2	Weight loss ↓9%	↓ 67% Leptin
Crujeiras *et al.*[41]	8 weeks: caloric restriction (-30% total energy expenditure) 32-wk Follow-up	104 participants (49 women)	Week 8: weight loss ↓4.5% (women) ↓5.9% (men) Week 32: (25 women and 30 men) maintained the weight loss 49 subjects (24 men and 25 female) regained at	Weight loss > 5% ↓ 51% Leptin ↑ Ghrelin 5.3% Weight loss <5% ↓ 28% Leptin ↓ 5% Ghrelin

			least 10% of the lost weight	
Considine *et al.* [46]	8 to 12 weeks :caloric restriction EI: 800 kcal/ day (liquid diet)	7 obese participants (6 women)	Weight loss of 10 % of the initial weight	↓ 53% Leptin
Wisse *et al.* [47]	4 weeks: caloric restriction Total fasting; VLED: EI approx. 454 kcal/day LED: EI approx. 1.300 kcal/day (53% CHO, 30 % PROT, 17 % FAT) + 2-week refeeding	Total Fasting: 8 VLED: 6 LED: 7 Only women (BMI>30 kg/m^2)	At week 1: Fat loss: Fasting: ↓3.2 % VLED: ↓2.8 % LED: 1.9 % fat loss The rates of loss remained constant in each subsequent week, up to week 4	Fasting: ↓76.5 % Leptin at week 2 VLED: ↓61 % Leptin at week 2 LED: ↓52.5% Leptin at week 4
Doucet, *et al.* [48]	15 weeks: caloric restriction Group 1: placebo + caloric restriction (-700 kcal/day) Group 2: 60 mg/d fenfluramine + caloric restriction	17 overweight and obese (7 women)	Men: ↓11.4% Women: ↓ 8.4%	Phase 1: ↓ Leptin 26% (women) ↓ Leptin 34% (men)
Mason *et al*. [49]	12 months: Caloric restriction: EI 1200-2000 kcal/day (30% FAT) Exercise: (45 min/day, 5x/wk) Caloric restriction +exercise Control	Caloric restriction: 118 exercise: 117 Caloric restriction +exercise: 117 control: 87 Only postmenopausal women (BMI > 27 kg/m^2)	Body weight : Caloric restriction: ↓8.5% Exercise : ↓2.4% Caloric restriction +exercise : ↓10.8%	Only among women who lost ≥10% of body weight: Caloric restriction: ↑ 11 % Ghrelin ↓ 27% Leptin Caloric restriction + Exercise: ↑ 9% Ghrelin ↓ 40% Leptin

Miller *et al.* [50]	12 weeks: Low-carbohydrate high-protein (LCHP): EI aprox.1400 kcal/day (20 -60 g/d CHO + PROT+ FAT) High-carbohydrate-low-fat diet (HCLF) EI :1500 -1700 kcal/day (60% CHO 15% PROT, 25% FAT)	LCHP: 13 HCLF: 12 Only women (BMI > 27 kg/m^2)	Weight loss: LCHP: ↓ 8.5 % HCLF: ↓ 7.8% Fat Loss: LCHP: ↓14.4% HCLF: ↓ 16.6%	LCHP : ↓ 42% Leptin HCLF : ↓44.3% Leptin
Thompson *et al.* [51]	6 months: caloric restriction (-500kcal/day) Low CHO - (32% CHO) Low FAT – (17% FAT) Control	192 overweight/obese women Low CHO: 66 Low FAT: 73 Control: 53	Weight Loss Low CHO: ↓ 13% Low FAT: ↓ 12% Fat loss: Low CHO: ↓ 27.4% Low FAT: ↓ 27%	Low CHO: ↓ 59% Leptin Low FAT: ↓ 62% Leptin
Cummings *et al.* [52]	3 months: EI 1000 kcal/day (low-fat, high-protein) + multivitamin-minerals 3-mo: solid diet (55 % CHO, 15 % PROT, 30% FAT)	13 obese subjects (8 women)	Weight loss ↓17 %	↓ 38% Leptin ↑ 24% Ghrelin
Becker *et al.* [54]	12 weeks: control Low glycemic index diet (LGI) GI < 55 , (50% CHO, 20% PROT, 30% FAT) - 20 kcal/kg BW .	LGI: 14 Control: 12 Only infertile women (BMI >27 kg/m^2)	Control: ↑1% weight gain LGI: Weight loss: ↓5.8% Fat loss: ↓ 3.7 %	LGI: ↓ 26 % Leptin ↑ 18% Ghrelin
Leidy *et al.* [55]	3 months : Control Isocaloric diet: (55% CHO, 15% PROT, 30% FAT) +Exercise (5days/week, at 70–80% max heart rate)	Exercise weight stable: 5 Exercise weight- loss: 10 Control: 7 Normal weight	Weight loss Control ↓0.3% Exercise weight-stable: ↓0.8% Exercise weight loss: ↓5.3%	Exercise weight loss: ↑72% Ghrelin

		women (BMI 18.5 - 24.9 kg/m^2)		
Garcia *et al.* [56]	12 months: caloric restriction (-500 kcal/day) + exercise (30-150 minute, 5x/ weeks) + orlistat (120 mg) Control (no intervention)	Treatment: 25 Control: 23 Only women	Treatment: Weight loss: ↓8.5% Control: no reported	Intervention compare to baseline ↑ 19% Ghrelin at 6 months ↓ 8% Ghrelin at 12 months ↑35% Leptin at 12 months
Due Luis [58]	3 months: caloric restriction EI: 1520 kcal (52% CHO, 23% PROT, 25% FAT) + exercise program (3 x/week for 60 min).	Weight gain: 14 (12 women) Weight loss 75 (67women)	Weight gain: ↑3.2% Weight loss: ↓ 5%	Weight loss: ↓ 8.5 % GLP-1
Svendsen *et al.* [59]	8 weeks: caloric restriction EI:500-600 kcal/day	17 obese women	Weight Loss: ↓ 11%	No changes in GLP-1
Olszanecka-Glinianowicz *et al*.[60]	8 weeks: caloric restriction EI: 1200–1400 kcal) + exercise (5x/week /30–40 min) + G1:120 mg of orlistat G2: placebo	40 obese women G1: 20 G2: 20	Weight loss: G1: ↓ 9% G2: ↓6% Fat loss: G1: ↓22 % G2: ↓7.4%	G1: ↑ 94.11% PYY ↑92.4%GLP-1 G2: ↑ 68%PYY ↑51.1%GLP-1
McNeil *et al.* [63]	6 month: Group 1(G_1): caloric restriction (-800 kcal/day) Group 2 (G_2): caloric restriction +resistance training.	G1: 65 G2: 28 Only post-menopausal women BMI > 30 lg/m^2	Weight loss: G1: ↓ 5.7% G2: ↓ 8.2% Fat loss : G1: ↓10.3% G2: ↓16.1%	G1: ↓ 19% Leptin ↑5% PYY G2: ↓ 29% Leptin ↑ 4% PYY
Hill *et al.* [64]	12 month: caloric restriction: ↓fat intake and ↑water-rich foods intake	71 obese women	Weight loss: ↓7.8%, Fat loss: ↓13.5%	Month 6: ↑14% Ghrelin Month 12 ↑11.5 % PYY

				↑9% Ghrelin
Sloth *et al.* [66]	Phase 1: 8 weeks: 1000 kcal/day Randomization phase 2 Phase 2: isocaloric isoenergetic diet Moderate-fat (35-45% FAT) Low-fat (20-30% FAT) Control (35%)	Phase 1: 131 overweight/obese participants Phase 2: 42 overweight/obese participants Moderate-fat:15 (8women) Low-fat:18 (10 women) Control: 9 (4 women)	Phase 1: at least ↓ 8% Phase 2: Moderate-fat: ↑ 4.2% Low-fat: ↑ 3% Control: ↑ 4.7%	Phase 1: ↓ GLP-1; PYY↓ Numbers no specified Phase 2: Moderate-fat: ↑ 47% GLP-1 ; ↑ 26% PYY Low-fat: ↑ 14.5% GLP-1; ↑ 9.5% PYY Control: ↑ 51% GLP-1; ↑20% PYY

Table 3

Study	Intervention	Sample Size	Weight changes	Variables	Methods to measure	Results
Cameron *et al*. [78]	8 weeks: caloric restriction (-700kcal/day)	15 obese adults (9 women)	Weight loss: ↓ 5.2 % Fat loss: ↓8.2 %	Food liking Food reinforcement	Visual Analogue Scale Progressive ratio computer task	No difference in the food reinforcement; ↑10% Liking favourite snack
Massey & Hill [80]	Prospective quasi-experimental	52 dieters 40 weight-maintainers 37 non-dieters (only women)	Data no-shown	Food craving frequency Food craving strength	7-day food record questionnaires Visual Analogue Scale	Dieters presented stronger cravings and more difficult to resist (compared with non-dieters and maintainers)
Gilhooly *et al*. [81]	6 months: caloric restriction High glycemic diet (60% CHO, 20% PROT, 20% FAT) Low glycemic diet (40% CHO, 30% PROT, 30% FAT)	32 overweight women	Weight loss: ↓8.8% Fat loss: ↓14.44%	Food cravings: Dietary restraint Disinhibition Susceptibility to hunger	Food Craving Questionnaire TFEQ	↑18.5% Dietary restraint ↓ Food craving
Batra *et al*. [82]	20 weeks: caloric restriction EI: 500 to 1000kcal/day (48% CHO 26% PROT, 26% FAT)	Intervention: 74 (54 women) Control: 21 (18 women)	Weight loss: Intervention: ↓9.2% Control: ↑1%	Food craving (frequency & intensity) Dietary Restraint, Disinhibition, Susceptibility to hunger	Food Craving Questionnaire Food craving Inventory TFEQ	↓Cravings frequency and intensity intervention group
Jakubowiz	16 weeks:	HCP: 97	Weight	Cravings	Cravings score	Intervention: all

et al. [26]	caloric restriction EI: 1,400 kcal to 1,700 kcal/day Low CHO diet (LC) High CHO + breakfast dessert (HCP)	(44 women) LC: 96 (42 women)	loss: HCP: ↓15% LC: ↓17% Follow up: HCP: ↓9 % LC: ↑15.5%	frequency for sweet, carbohydrates, fast foods, high fat food items	Questionnaire	cravings scores (sweets, high fats, CHO/starches and fast foods) LC > HCP
Tremblay *et al.*[20]	12 to16 weeks caloric restriction: (-500 to 700 kcal/day)	75 women	Weight loss: ↓3.7%	Dietary restraint Disinhibition Susceptibility to hunger	TFEQ	↑42% Dietary restraint ↓23% Disinhibition ↓39% Susceptibility to hunger
Bas & Donmez [90]	20 weeks caloric restriction: EI: 1400 to 1800 kcal/day	96 overweight and obese individuals (76 women)	Weight loss: Men: ↓11% Women:↓ 11.5%	Dietary restraint Disinhibition Susceptibility to hunger	TFEQ	Men ↑30% Dietary restraint ↓24% Disinhibition ↓ 34% Susceptibility to hunger Women: ↑ 30% Dietary restraint ↓33% Disinhibition ↓ 39%Susceptibility to hunger
Ely *et al.*[91]	Cross sectional study	10 historical dieters 10 non dieters 10 dieters (only women)	Data no-shown	Dietary restraint Disinhibition, Susceptibility to hunger Activity in brain areas	TFEQ fMRI (high palatable food images/neutral food images/ neutral	↑ Dietary restraint in Dieters and Historical dieters Historical dieters *vs* Non-dieters*:* ↑Right anterior cingulate, ↑Left

				related to food reward processing during visual food cues	images)	middle frontal gyrus Historical Dieters vs. Current dieters: ↑Right middle frontal gyrus, ↑Insula, ↑ Caudate, ↑Pallidum
DelParigi *et al.* [92]	Cross sectional study	9 obese reduced individuals 20 obese individuals	Data no-shown	Brain activity response after consuming liquid meal	fMRI	Obese reduced *vs* Obese ↑Dorsal prefrontal cortex ↑Anterior cerebellar lobe
Sweet *et al*. [93]	Cross sectional study	44 participants 17 successful weight loss maintainers 15 obese 12 never obese	Data no-shown	Brain activity during 1-min orosensory presentation	fMRI	↑ Bilateral occipital regions ↑ Left posterior, left middle and right insula ↑ Left inferior frontal and left post central gyrus, ↑Left putamen
Jakobsdottir *et al.* [95]	4 week caloric restriction (-1000 kcal/day)	18 healthy post-menopausal women	Weight loss: ↓ 4.8%	Brain activity during visual food cues	fMRI and food images/ landscape images	↑Left anterior insula ↑Left hippocampus ↑Amygdala ↑Right cingulate gyrus
Murdaugh *et al.* [96]	12 week: psychosocial weight loss program 9 months follow up	21 obese participants (19 women)	Weight loss: ↓3.46% (total n) ↓3.64% (women) Follow up	Brain activity during visual food cues	fMRI and food images/landscape images	Weight loss: ↑Insula, amygdala, ACC insula, ACC, middle occipital cortex, postcentral gyrus,

			period: ↑ 0.75%			inferior temporal gyrus
McCaffery *et al.* [97]	Cross sectional study	17 weight maintainers 16 obese 18 never obese	Data no-shown	Brain activity during visual food cues	fMRI and high fat food, low fat food and neutral pictures	Weight maintainers: ↑Central gyrus Obese ↑Left anterior cingulate

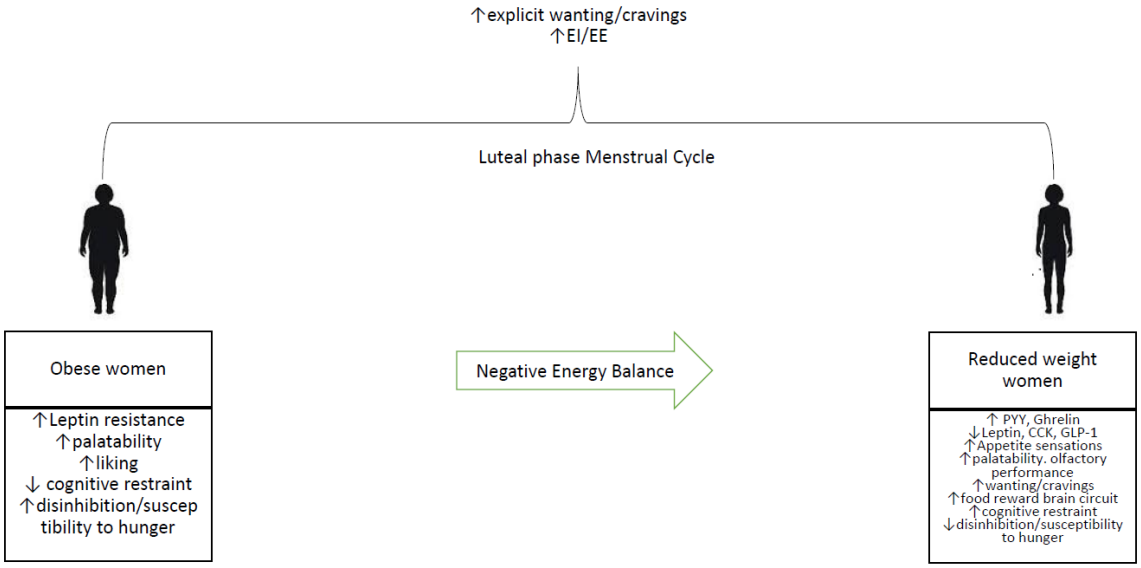
↑explicit wanting/cravings
↑EI/EE
Luteal phase Menstrual Cycle
Obese women
↑Leptin resistance
↑palatability
↑liking
↓ cognitive restraint
↑disinhibition/susceptibility to hunger
Negative Energy Balance
Reduced weight women
↑ PYY, Ghrelin
↓Leptin, CCK, GLP-1
↑Appetite sensations
↑palatability. olfactory performance
↑wanting/cravings
↑food reward brain circuit
↑cognitive restraint
↓disinhibition/susceptibility to hunger

Figure 1

5. References

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CHAPTER II - REVIEW OF LITERATURE CONTINUED

1. Energy expenditure and its components

TEE is accounted for by cellular and organ functions related to the resting state, postprandial metabolism and non-resting EE. On average, REE is responsible for about 55 - 75% of TEE and it represents the energy cost to maintain the cellular and the cardiorespiratory activity in humans (Ravussin et al. 1986a). Postprandial EE accounts approximately 10% of the TEE and involves the metabolic cost of digestion, transport and storage of nutrients. Non-resting EE is the component that most varies between individuals and is mainly explained by Physical Activity (PA). On average, represents 25% to 40% of TEE (Ravussin et al. 1986a).

All these components depend on different factors such as age, sex, and body composition (Astrup et al. 1990, Ravussin & Bogardus 1992, Ravussin et al. 1986b). Women present lower TEE compared to men (Dionne et al. 1999, Doucet et al. 2000e, Ferraro et al. 1992, Jones et al. 1996), mainly due the differences in body composition and adipose tissue distribution (Dionne et al. 1999, Jones et al. 1996). Aging is also associated with decreases in TEE (Elia et al. 2000, Roberts & Dallal 2005). This decline is related to changes in body weight and body composition (Roberts & Dallal 2005), as well as by reduced mobility and higher prevalence of chronic disabilities in the elderly population (Elia et al. 2000). A large analysis of doubly-labeled water measurements involving a sample of healthy subjects with different age ranges, suggests that there is a decrease of 0.69 in men and 0.43 MJ/day/decade in women. Physical Activity Energy Expenditure (PAEE) and REE accounted for 46% and 44% of the decrease in TEE, respectively (Elia et al. 2000).

Body composition plays an important role in the inter-individual variability of TEE. Indeed, FFM is the major predictor of REE, its decrease causes a reduction of REE and non-resting EE (Astrup et al. 1990, Ravussin & Bogardus 1992, Ravussin et al. 1986a). FFM loss can even play a role on EI, possibly promoting a hyperphagic response after a caloric deficit period (Dulloo et al. 1997). On the other hand, even though FM is not considered a highly metabolically active tissue *per se*, it can

explain a biologically meaningful part of the variation in EE (Ferraro et al. 1992). Higher adiposity in the abdominal area has been found to promote increases in the sympathetic system activity, which partially account this association between FM and EE (Jones et al. 1996).

Even though current obesity therapies mostly focus on decreasing FM storages and preserving FFM in order to maintain a higher TEE, it seems that this by itself may not be sufficient to prevent individuals from weight regain. Indeed, decreases in EE that go beyond the decreases predicted by FFM loss are commonly reported in the literature. Of note, we are using the term 'metabolic adaptations' to refer to the decreases in EE that are not explained by changes in body composition. The following sections will discuss the decreases in EE following caloric restriction, as well as the decreases in REE that are not accounted for changes in body composition.

1.1 Changes in components of EE following weight loss

Total energy expenditure

TEE has been shown to be decreased during and after caloric restriction periods. Classical and current studies involving individuals living with obesity after weight loss demonstrate a decrease in the absolute and relative values of TEE compared to baseline values (Leibel & Hirsch 1984, Ravussin et al. 1985, Rosenbaum & Leibel 2016) and to never-obese controls (Leibel & Hirsch 1984). Leibel & Hirsch (Leibel & Hirsch 1984) reported a 40% reduction in the absolute daily Energy requirements (Ereq) and 28% reduction for surface area in a group of weight-reducers (average 35% weight loss). The values were 24% below those observed in the control group, even if the latter presented a 60% lower body weight.

Ravussin *et al.* (Ravussin et al. 1985) conducted one of the first studies that investigated all components of TEE following 10% and 20% weight loss. The authors noted a reduction of 16% in TEE (24-h EE measured in respiratory chamber) after a 12% weight loss. Surprisingly, the fall was not accounted by changes in REE, but by the decreases in Thermic Effect of Food (TEF) and PAEE.

These results are similar to those by Weigle *et al.* (Weigle et al. 1988), wherein participants were found to spent 75% of the total calories predicted them to spend after a 20% weight loss. Again, changes were only accounted by decreases in non-resting EE.

Another landmark study (Leibel et al. 1995) evaluated the changes in EE after manipulating body weight in subjects living with obesity and in controls who had never been living with obesity. The results demonstrated a 15% decrease in TEE after a 10% weight reduction and a 16% increase in TEE after a 10% weight gain. The changes were similar in weight-reducers and normal weight controls. Individuals who were at 10% below their initial body weight were spending 10% less energy than what was accounted by changes in body composition. TEE decreases were explained by both the resting and non-resting components of EE. No differences in REE were noted comparing when individuals were at 10% and at 20% of weight reduction, demonstrating that the maximum metabolic adaptation in individuals who are losing weight should occur at 10% of their weight loss. However, these findings were questioned in prospective studies involving individuals who presented massive weight loss (~35%). Accordingly, a study involving participants of a TV show competition demonstrated that metabolic adaptations were continually increasing even after 3, 6 and 7 months of weight loss (Knuth et al. 2014). Along the same lines, a recent study noted decreases in absolute and relative TEE at 20% of body weight reduction. Nonetheless, the additional decrease was smaller than that noted after 10% weight loss (Rosenbaum & Leibel 2016).

Accordingly, a handful of weight loss studies have demonstrated significant decreases in TEE following caloric restriction (Delany et al. 2014, Heilbronn et al. 2006, Hunter et al. 2015, Redman et al. 2009, St-Onge et al. 2013, Weinsier et al. 2000). Studies comparing different weight loss methods have highlighted that participants who lost weight through either moderate caloric restriction (-25% their Ereq) or Low Calorie Diet (LCD) (890 kcal/day) presented significant decreases in TEE in both absolute and corrected by FFM values, after 3 months and 6 months of intervention (Heilbronn et al. 2006, Redman et al. 2009). The studies still showed a decrease in TEE

varying from 6 to 10% beyond the fall in EE explained by changes in FFM and FM, which was linearly correlated to plasma thyroid hormones (Heilbronn et al. 2006, Redman et al. 2009).

Although for the most part studies report a significant decrease in TEE following weight loss, there is still controversy as to whether exercising could attenuate this decrease. A recent study (Hunter et al. 2015) noted a decrease in TEE only in the non-exercising group (*vs.* RT & *vs.* aerobic training groups), whereas another study (Redman et al. 2009) found no difference in absolute TEE after 6 month weight loss program in the group who were losing weight combining caloric restriction and exercising (-12.5% energy restriction & -12.5% exercising EE). Delany *et al.* (2014) observed a significant decrease in the calorie restriction + exercising group; however, those changes were significantly smaller than the ones observed in the diet only group. In contrast, another study (Heilbronn et al. 2006) demonstrated a similar decrease in TEE following weight loss in the caloric restriction+exercising group compared to the only caloric restriction groups. Along the same lines, RT was found to not protect post-menopausal women against metabolic adaptations in TEE following weight loss (St-Onge et al. 2013).

Collectively, evidence demonstrates that TEE is affected by caloric restriction; however, there is still controversy regarding which components of EE are more closely associated with these said changes. Moreover, it remains uncertain whether exercising can represent a strategy to attenuate metabolic adaptations once participants are energy deprived. The following sections will discuss the components of EE and their changes following weight loss.

Resting Energy Expenditure

REE is the largest component of TEE, accounting for approximately 70% of the daily Ereq in somewhat sedentary individuals. Reductions in this component of EE can offset the expected weight loss and potentially compromise weight loss maintenance (Pasman 1999). Likewise, it partially explains why during weight loss, participants commonly lose less weight than what could be predicted from the prescribed energy deficit (Byrne et al. 2012, Goele et al. 2009).

Among the first studies investigating REE after weight loss, decreases of approximately 15% in REE after weight loss were noted (Bray 1969, Leibel et al. 1995). Those decreases were mainly explained by declines in oxygen consumption in patients living with obesity after 24 days of Very Low Calorie Diet (VLCD) (450 kcal/day). There is increasing evidence that support the falls in REE following weight loss (Byrne et al. 2012; Camps et al. 2013b,a; Doucet et al. 2000e, Goele et al. 2009, Heilbronn et al. 2006, Hunter et al. 2015, Martin et al. 2007, Menozzi et al. 2000, Wang et al. 2008), a fall associated with FFM (Doucet et al. 2007, Menozzi et al. 2000) and FM (Goele et al. 2009, St-Onge et al. 2013) loss. In fact, FFM was found to be a better predictor of REE reductions in men (Doucet et al. 2000e), whereas FM was found to be a predictor of REE decreases in women (Doucet et al. 2000e, Goele et al. 2009). In a study involving men and women, FFM was found to explain 80% of the variance in REE following a small (-3%) weight loss (Menozzi et al. 2000), whereas FM was found to explain 14% of the decreases in REE in pre-menopausal women (Goele et al. 2009).

It seems that exercising, when combined with a caloric restriction does not attenuate the adaptations in REE (Heilbronn et al. 2006, Hunter et al. 2015, Keim et al. 1990, Martin et al. 2007, St-Onge et al. 2013) that accompany body weight fluctuations. Even though this is not unanimous (Hunter et al. 2008), a good proportion of the studies comparing different types of weight loss interventions have noted that neither RT (Hunter et al. 2015, St-Onge et al. 2013), nor aerobic (Hunter et al. 2015, Martin et al. 2007) training protected weight reducers from decreases in REE, even when the FFM was maintained (Johannsen et al. 2012).

As previously mentioned, FFM is one of the best predictors of REE. However, it is commonly observed that declines in REE following weight loss might go beyond changes in body composition (Bosy-Westphal & Kossel 2009, Camps et al. 2013a, Doucet et al. 2007, Dulloo et al. 1997, Goele et al. 2009, Heilbronn et al. 2006, Martin et al. 2007, Müller et al. 2015). For instance, the classical Minnesota study (Dulloo et al. 1997) noted a 39% decline in REE in the participants, wherein approximately 35% could not be explained by changes in FM and FFM, but due to metabolic

adaptions. A replication of this classical study has been recently published confirming some of the evidence provided in the seminal work (Müller et al. 2015). The replication included 32 young non-obese man and their dietary interventions involved 1-week of overfeeding (+50% of EEreq) followed by 3-week of caloric restriction (-50% of EEreq) and a subsequent 2-week of refeeding (+50% of EEreq). The results also reported a significant decrease in REE during caloric restriction and a significant difference between measured *vs* predicted values during the weight loss phase (-7.5% initial weight). Subsequently, during the refeeding phase, REE values adjusted for FFM were back to baseline values after a 4.5% weight regain.

The differences between predicted *vs* measured values of REE might be associated with the degree of caloric restriction (Knuth et al. 2014) and the magnitude of weight loss (Camps et al. 2013a, Tremblay et al. 2015). Indeed, a strong and positive correlation between metabolic adaptation and weight loss has been reported (Camps et al. 2013a). Subjects who lost more weight also presented the highest metabolic adaptations, in accordance with other studies involving individuals following massive weight loss (Fothergill et al. 2016, Johannsen et al. 2012, Knuth et al. 2014).

In a previous study (Tremblay et al. 2015) involving only women, they classified weight loss posteriori in tertiles and noticed that the highest tertile also presented the greatest decrease in REE. However, no significant differences were observed between the measured and predicted REE in this particular study. In contrast, another study demonstrated that greater differences between measured and predicted values of REE were associated with lower weight loss (Bosy-Westphal & Kossel 2009).

The start and duration of those metabolic adaptations has been widely studied since longer periods of metabolic efficiency are associated with poorer long-term weight loss. Those adaptations could be observed from the first days of caloric restriction (Bray 1969, Müller et al. 2016) until years following weight loss (Camps et al. 2013a, Fothergill et al. 2016, Knuth et al. 2014, Rosenbaum et al. 2008a, Wang et al. 2008). Indeed, Bray (Bray 1969) noted that more than half of the total decreases in REE

was seen in the first 8 days of weight loss, whereas Muller *et al.* (Müller et al. 2016) noted that changes in REE were significantly lower even earlier, at 3-day of caloric restriction.

Other evidence also support that the effects of caloric restriction on energy metabolism are still apparent in the weight maintenance phase for as long as the reduced body weight is also maintained (Camps et al. 2013a, Johannsen et al. 2012, Rosenbaum et al. 2008a, Tremblay et al. 2015). Rosenbaum *et al.* (2008a) compared the TEE and REE in individuals who just had completed a weight loss intervention (-10%) and compared the values to a control group who lost the same amount of weight and were able to maintain for at least 1 year. The results showed no difference between groups, suggesting that the adaptations in TEE and REE promoted by weight loss seemed to persist when the weight loss is maintained. In another study, the adaptations were sustained only in men, differences between measured and predicted were reported to be attenuated in women when they were no longer energy-deprived (Doucet et al. 2007).

The duration of metabolic adaptations is another topic that has been addressed in the landmark study (Leibel et al. 1995). They suggested that the maximum degree of REE adaptation should occur at 10% weight loss, given that no differences in REE values measured at 10% and 20% weight loss were noted. On the other hand, more recent evidence (Camps et al. 2013a) does not support this finding. Differences between predicted and measured values during caloric restriction were found to be correlated with weight loss up to 25% in a linear way. Along the same lines, differences between measured and predicted values of REE were significantly different even after 6 years of massive weight loss in men and women (Fothergill et al. 2016). Taken together, these adaptations clearly create a challenge for the long-term maintenance of weight loss among weight-reducers.

Thermic Effect of food

TEF is another component of TEE defined as increased REE after meal ingestion. It accounts approximately 10% of the TEE (Ravussin & Bogardus 1992) and were found to be associated with

FFM (Leibel et al. 1995, Rosenbaum et al. 1996). There is evidence that this variable is reduced in subjects living with obesity (Leibel et al. 1995, Weinsier et al. 1995), however, whether or not TEF remains decreased in reduced-weight individuals is still controversial. Previous evidence (Schutz et al. 1987) states that smaller absolute TEF is maintained even after subjects achieve an ideal body weight, whereas other studies have shown that caloric restriction might affect absolute TEF, accounting for up to 40% of the decrease in TEE noted following weight loss in sedentary individuals (Ravussin et al. 1985, Weigle et al. 1988). Along the same lines, other study demonstrated significant decrease in TEF expressed as an absolute value or as kilocalorie of energy consumed after 5% weight loss (Luscombe et al. 2002). On the other hand, different evidence has shown that absolute TEF remains unchanged after 10% weight loss (Leibel et al. 1995, Rosenbaum et al. 1996). Whereas, increases in body weight of 10% was found to increase TEF up to 24% (Leibel et al. 1995; Rosenbaum et al. 1996, 2003).

Overall, studies have demonstrated that there is a decrease in absolute TEF following weight loss, which is mainly explained by positive association between EI and TEF (Reed & Hill 1996). Whether TEF has impact in the variability in weight loss response in individuals living with obesity remains to be investigated.

Physical Activity

PAEE is one of the most controversial components of EE when it comes to discussing its role in weight loss and weight loss maintenance. Because this component of EE is more easily manipulated (King AC et al. 1989) and is under voluntary control (Donnelly et al. 2004), exercising has been reviewed as a potential strategy for weight loss and its maintenance, even though its efficacy for such a purpose is still somewhat debated.

In fact, several studies that investigated PAEE after weight loss and have shown significant decreases in both: PA (Camps et al. 2013b, Martin et al. 2007, Redman et al. 2009, Wang et al. 2008) and the cost of PA (adjusted for FFM) following weight loss by caloric restriction (Camps et al.

2013b, Martin et al. 2011, Redman et al. 2009). Other evidence also demonstrated that prolonged periods of caloric restriction can lead subjects to become apathetic and less active as previously reviewed (Drenowatz 2015, King et al. 2012), decreasing absolute and relative (per kg in FFM) PAEE and TEE. One of the first studies highlighting the magnitude of non-resting EE in decreases in TEE was conducted by Weigle *et al.* (Weigle et al. 1988). The authors noted that PAEE explained 71% of decreases in TEE following a 20% weight loss. More recent studies have shown significant decreases in PA levels and PAEE in individuals who were engaged in only caloric restriction to lose weight; however, it was not observe in individuals who combined exercising and caloric restriction for weight loss (Hunter et al. 2015, Martin et al. 2007, Redman et al. 2009). Along the same lines, Camps *et al.* (Camps et al. 2013b) noted a significant decrease in both PAEE and PA measured by triaxial accelerometer only during the caloric restriction period. Values were found to be back to baseline values after weight loss. A more recent study reported that PA measured by a triaxial accelerometer and 7-day recall did not change after weight loss in any of the groups included in the study. However, significant decreases in relative PAEE measured by doubly label water were noted in the low-caloric intake and caloric restriction groups, demonstrating the occurrence of compensatory mechanisms in these groups (Martin et al. 2011).

Accordingly, other studies using doubly label water measures also reported lower relative PAEE following caloric restriction (Leibel et al. 1995, Redman et al. 2009), measured values were significant below than those predicted to the participants following a 10% and a 20% weight loss (Leibel et al. 1995). For instance, Doucet *et al.* (Doucet et al. 2003) noted that measured values were below predicted values for the net cost of standardized exercise in reduced-obese participants during a 15-week weight loss program (net exercise calculated by subtracting the sitting EE from the total exercise EE of walking on a treadmill, 65% FC max.). In other words, metabolic adaptations in PAEE might also be a consequence of caloric restriction.

Changes in muscle work efficiency were also found to explain the changes in PAEE after a weight reduction (Crescenzo et al. 2006, Goldsmith et al. 2010, Rosenbaum et al. 2003). A particular study

(Rosenbaum et al. 2003) noted 25% increase in skeletal muscle efficiency during an exercising on a graded cycle ergometry in individuals in weight reduced state (at 10% weight loss). On the other hand, participants who were maintaining +10% body weight, presented a decreased muscle work efficiency (-18%) during the same exercise. In sum, changes in muscle work efficiency at altered body weight accounted for 35% of the changes in PAEE. Not surprisingly, all those changes in PA levels and PAEE during and after weight loss were associated with weight relapse and weight maintenance after a follow-up period (Catenacci et al. 2011, Delany et al. 2014, Donnelly et al. 2004, Klem et al. 1997, Swift et al. 2014, Wang et al. 2008).

Another topic that remains controversial is the effectiveness of PAEE in weight loss and weight maintenance and its impact in EI. Some studies demonstrated a higher EI in active subjects, suggesting a compensatory behavior among them (King et al. 2007, 2009). Indeed, there is evidence suggesting the association between diet compliance and PA levels. PA measured by accelerometer was found to be higher only in participants who presented lower compliance to the diet (Jimenez Jaime et al. 2015) demonstrating the compensatory effects of PA on EI. It should also be noted that when exercise is used to produce weight loss, it generally results in lower body weight changes at the end of the intervention when compared to diet alone (Miller 1999).

Taken together, all those factors contribute to the high variability in weight loss response and EE adaptations following caloric restriction and might compromise long-term weight loss maintenance. Different strategies for better weight loss maintenance remain to be investigated, the combination of different therapies (*e.g.* inclusion of medications; closer behavioral follow up; use of ketogenic diets) might be helpful to elucidate these remaining questions.

1.2 Rate of weight loss and compensatory mechanisms of EE

The ‘ideal’ rate of weight loss and its clinical implications in weight management has been the focus of much discussion in the literature (Astrup & Rössner 2000). The belief that a slower rate of weight

loss is associated with a better weight loss maintenance has been recently questioned (Casazza et al. 2015, Nackers et al. 2010, Purcell et al. 2014, Vink et al. 2016). A landmark study (Purcell et al. 2014) involved 200 subjects living with obesity who were assigned to either a gradual (-400 to 500 kcal/day for 36 weeks) or rapid (450-800 kcal/day for 12 weeks) weight loss intervention. Participants who achieved a minimum of 12.5% weight loss were reassessed after a 144-week follow-up. Results demonstrated that a higher percentage of individuals engaged in the rapid weight loss (81% vs 62% of the gradual weight loss) were able to achieve the target goal for the maintenance phase. By the end of the maintenance phase, the percentage of weight recovery (~71%) was similar for both groups. Accordingly, other studies demonstrated that similar weight loses promoted at different rates do not seem to affect weight regain after 9-month (Vink et al. 2016) and 1-year (Nackers et al. 2010) differently.

As mentioned in previous sections of the thesis, the high rates in weight relapse are commonly noted in weight reducers and are mainly attributed to compensatory mechanisms related to EI and EE. The existence of those compensatory mechanisms following weight loss seems be well established in the literature. However, very few studies have investigated whether different types of diet and/or degrees of caloric restriction exert some influence over the magnitude of those compensatory changes (Coutinho et al. 2017, Purcell et al. 2014, Siervo et al. 2015). Previous evidence (Siervo et al. 2015) noted significant decreases in TEE and in REE following 10% of weight loss in two groups who were losing weight using a VLCD (approximately 600 kcal/day) or a LCD (approximately 1200 kcal/day). In this particular study, the metabolic adaptation (significant difference between predicted and measured values) for TEE were similar in both groups (VLCD = −6.2%; LCD = −6.8%), however the changes in REE was greater in the LCD (− 5.3%) compared to the VLCD (−1.4%) group, which puts into question the initial hypothesis that slower weight loss would promote smaller metabolic adaptation. Indeed, the rate of weight loss was inversely associated with changes in REE ($r = 0.-42$, $p = 0.01$).

Along the same lines, Coutinho *et al.* (Coutinho et al. 2017) did not observe any difference in REE in individuals engaged in either VLCD (550 and 660 kcal/day for women and men, respectively) or LCD (1200 and 1500 kcal/day for women and men, respectively). Both groups presented similar weight loss (~9%) and similar decreases in REE. On the other hand, participants who were engaged in the rapid weight loss group, presented a higher exercise efficiency (pedaling at 60 rpm against graded resistance to generate 10W and 25W) after weight loss and they spontaneously increased their PA (measured by accelerometer) (Purcell et al. 2014).

Studies that have investigated the effects of different rates of weight loss on appetite and appetite-related peptides report inconsistent results. Serum Ghrelin concentrations (measured in different time points) were found to increase after weight loss and to remain elevated after 144-week follow-up period (Purcell et al. 2014), and the rate of weight loss was not associated with those changes. Other evidence demonstrated that only the rapid weight loss seemed to increase in postprandial active ghrelin, even if it was not reflected in the final weight loss (Coutinho et al. 2017). The decrease in fasting leptin was more pronounced in the rapid weight loss (*vs.* slow weight loss group) group after the weight loss phase, while no differences between groups were noted in the end of the follow-up periods (Purcell et al. 2014). Along the same lines, basal PYY and insulin presented significant and similar reduction in both groups. No differences within or between groups were noted when comparing baseline and the end of the maintenance phase (Coutinho et al. 2017).

Hunger ratings (measured by VAS) were found to be significantly higher during follow-up only in the rapid weight loss group (Purcell et al. 2014). On the other hand, another study noted that individuals subjected to rapid weight loss presented a significant decrease in fasting Prospective Food Consumption (PFC), postprandial fullness and hunger after weight loss, while no differences were noted in the slow weight loss group (Coutinho et al. 2017). After the maintenance phase, no differences were noted between groups. At the end of the study, both groups presented a similar increase in fasting hunger comparing baseline to maintenance phase (Coutinho et al. 2017).

Collectively, available evidence might put into question the superiority of slower weight loss rates in final outcomes and its maintenance. However, the discrepancy in the effects of different rates of weight loss on EE and EI variables demonstrates the need of further investigations in these aspects. The inclusion of more comprehensive variable panels such as EI, as well as palatability, olfactory performance as well as psychological variables related to feeding behavior could contribute in the understanding of how different rates of weight loss affect final outcomes. Given that palatability and olfaction might interact to influence the drive to eat differently under varying levels of caloric restriction, different impacts in these variables could lead to different weight loss between groups. Moreover, none of the previous studies on the rate of weight loss assessed REE and appetite at multiple time points during intervention to assess the timeline of metabolic adaptations. Finally, most part of the studies these studies above mentioned did not produce similar weight loss, which is an important confounder for studies investigating the impact of the rate of weight loss on metabolic adaptations.

2. Predictors of weight loss success

Available literature has extensively described variables that are associated with successful or non-successful weight loss. Previous evidence suggested that maximum lifetime body weight (Byrne et al. 2004, Weiss et al. 2007), dieting frequency (number of previous periods under caloric restriction to lose weight) (Pasman 1999, Vogels et al. 2005), baseline body weight (Byrne et al. 2004, Weiss et al. 2007), and pre-intervention REE (Vogels et al. 2005) are significant predictors of the outcome of weight loss intervention at varying degrees. In the case of prospective predictors, it has been reported that poorer initial weight loss response (weight loss at 2-4 weeks) predicted smaller weight loss as previously reviewed (Astrup & Rössner 2000), whereas more pronounced decrease in REE after 8 weeks of VLCD was associated with higher weight loss relapse (Pasman 1999).

Given the low rates of success in weight loss interventions, it seems important to identify variables that are related to improved outcomes. Accordingly, the following sections discuss the significant

predictors of weight loss. However, we aimed to review only prospective predictors that are related to feeding behavior and EE. This was done because the present thesis focused on these specific variables, as they are known to largely influence energy balance.

The effects of weight loss on REE, appetite, motivation to eat and oro-sensory variables (palatability and olfactory performance) were extensively discussed in the previous sections of this review of literature. The following sections will concentrate on the description of the effects of short-term caloric restriction on these variables, as well as their predictive power for longer-term weight management.

2.1 Do acute changes in appetite, food reward and energy expenditure predict long-term weight loss?

Appetite ratings have been suggested to be strong predictors of EI under laboratory (Drapeau et al. 2007b,a; Parker et al. 2004, Sadoul et al. 2014) and free-living conditions (Drapeau et al. 2007b, Sadoul et al. 2014). More specifically, fasting and postprandial AUC for desire to eat, hunger, PFC and fullness were found to be strong predictors of *ad libitum* EI measured at the laboratory settings, as well as of a 3-day self-reported EI (Drapeau et al. 2007b). In the long-term, fasting appetite measured at baseline was found to predict weight loss in adults (Drapeau et al. 2007b). Indeed, a handful of studies investigated the association between appetite and weight loss, suggesting that long-term caloric restriction might increases appetite and potentially EI as we previously reviewed (Hintze et al. 2017a). These increases in appetite and EI can be observed even after short-term caloric restriction periods (Alajmi et al. 2016, Cameron et al. 2016, King et al. 2011). Previous studies noted that participants who were calorie deprived by 25% of their Ereq also presented appetite and increased EI (Cameron et al. 2016), mainly explained by fat and protein intake (King et al. 2011). Particularly in women, higher overall appetite rates were noted in the caloric restriction conditions, reflected in increased EI, protein, fat and carbohydrate, after 8-hour testing period (Alajmi et al. 2016).

Taken together, available evidence demonstrates that compensatory mechanisms in EI start in the beginning of caloric restriction periods. However, whether these short-term increases affect long-term changes in body weight and body composition remains to be investigated.

2.2 Short-term caloric restriction and changes in oro-sensory components

Oro-sensory variables are highly influential in motivating food selection (Mela 2006, Rolls 2005), suggesting the important role of those variables in determining eating behavior. In fact, palatability was found to be strongly associated with EI as previously reviewed (Johnson & Wardle 2014, Sørensen et al. 2003). Under an evolutionary perspective, our taste preferences are consequences of the need of high-energy density when energy sources were scarce (Krebs 2009). It partly explains the preference for high-fat and sweet items and also contributes to understanding the effects of caloric restriction on those variables (Krebs 2009). Indeed, previous evidence demonstrates that palatability ratings are higher in a hungry state (Finlayson et al. 2007, 2008), as well as during caloric restriction periods (Cameron et al. 2008, Umabiki et al. 2010). Given the association between palatability and EI, it is possible to consider that increases in palatability might be a protective mechanism against weight loss (Johnson & Wardle 2014). These increases are noted after only 4-h fasting (Epstein et al. 2003), whereas twenty-four fasting period also increased olfactory performance in women (Cameron et al. 2012), an increase that was significantly correlated to changes observed in palatability. Along the same lines, men subjected to a 25% caloric restriction for 4-days presented increased olfaction threshold (Cameron et al. 2016).

Overall, this evidence demonstrates that short-term caloric restriction seems to enhance oro-sensory variables, which might drive the increase in EI under such circumstances. The role of the association between olfaction, palatability and EI in long-term weight management deserves further investigations.

2.3 Short-term caloric restriction and changes in EE

Long-term weight loss studies have demonstrated the association between REE and weight loss (Doucet et al. 2007, Heilbronn et al. 2006, Redman et al. 2009). However, evidence supporting changes in REE as early response of caloric restriction have shown some controversial results. A recent study conducted only in men demonstrated no impact of a severe-caloric-restriction day (-75% energy needs) on the resting EE in the subsequent 48-hours (Clayton et al. 2016). Similar to observed in men living with obesity after 4-day of caloric restriction (-800kcal/day) (Doucet et al. 2004) and in women after 1-day of fasting (Antoni et al. 2016). After periods of complete fasting, no differences in REE were noted after 48-hour in women living with obesity (Bergman et al. 2007) and 72-hour in normal weight men (Horton & Hill 2001). Conversely, another study noted increases in REE after 36-h of fasting in normal weight men and women (Webber & Macdonald 1994).

Overall, REE did not present a short-term response to caloric restriction. Among the studies that presented significant impact, it is uncertain the onset of these potential changes. There is evidence showing that 3 days of caloric restriction might be sufficient to promote decreases in REE in individuals living with obesity (Bray 1969), whereas more recent studies did not observe any significant differences (Bergman et al. 2007, Doucet et al. 2004).

In sum, results from short-term caloric restriction studies demonstrated that few hours are already sufficient to increase appetite rating in adults, whereas a few days are necessary to decrease REE. There is enough evidence demonstrating the effect of these changes in short-term EI. The role of these acute changes on long-term weight management deserves to be further investigated.

3 Reinforcing value, impulsivity and obesity

The Behavioral choice theory or behavioral economics may contribute to understanding some of the factors that influence food choices and EI among the population (Epstein et al. 2010, Stojek & MacKillop 2017). The theory is a combination of findings from economics, psychology and neuro-science, having as an objective to understand how people decide to spend time, efforts or resources among available alternatives (Bickel et al. 2000). More precisely in the nutritional field, this theoretical approach might provide an understanding of how different factors influence everyday choices, which in the end could lead to positive energy balance and potential weight gain (Epstein et al. 2007a, 2010; Stojek & MacKillop 2017).

Choices might differ in terms of timing (concurrent vs. delayed) or in in terms of the alternatives involved (different quantities of a same item vs. different item) (Bickel et al. 2000, Epstein et al. 2007a). Concurrent choices are often conceptualized in terms of RRV, whereas delayed choices can be conceptualized in terms of delay discounting (Bickel et al. 2000). RRV of food refers to the motivation to obtain food, how hard someone will work or how much time will be spent to obtain food *vs* other available item (Epstein et al. 2007a). Delay of gratification or delay discounting refers to the preference for smaller immediate *vs* larger delayed rewards (Bickel et al. 2000, Epstein et al. 2010) and it is one of main domains to assess impulsivity behavior (Meule & Kübler 2014). Accordingly, the following section will describe how RRV and impulsivity influence food choices and EI, as well as how both factors interact to predict EI and body weight.

3.1 Reinforcement and energy intake

Reinforcement is a fundamental determinant of choice, it can shape and strengthen the development of many aspects of our behavioral repertories, including the ones related to EI (Epstein et al. 2010). In fact, food is considered one of the most powerful reinforcers since it is an indispensable condition

for survival (Epstein et al. 2007a), and might also serve other functions such as meeting needs of pleasure and satisfaction (Appelhans 2009).

Particularly in studies involving eating behaviors, RRV of food characterizes how valuable energy-dense food item is to the individual in comparison to an alternative item available (Epstein et al. 2007a). In other words, it is measured by evaluating by the amount of work an individual would be willing to engage in order to obtain the reinforcing item (*e.g.* chocolate bar) *vs.* another available commodity (*e.g.* banana). RRV is commonly measured by progressive ratio tasks, utilizing high-palatable food item as a reinforce item *vs* an alternative healthy food item or sedentary activity (Goldfield & Epstein 2002). In the measurement of RRV, the amount of work (*e.g*. Pressing bottom repeatedly) to gain access to the more reinforcing item increases over time, increasing also the difficulty in earning the preferable item. A greater amount of work (*i.e.* button presses) to obtain the reinforcer reflects a high amount of reinforcement, while a lower amount of work indicates the person does not find that food reinforcing (Epstein et al. 2007a).

The amount of work in order to obtain a reinforcing food item seems to be higher in adults living with obesity compared to lean individuals (Epstein et al. 2007a,b, 2011; Goldfield et al. 2011, Temple & Epstein 2011). Similar results were observed in studies involving only women (Clark et al. 2010, Giesen et al. 2010, Saelens & Epstein 1996, Temple et al. 2009). Women living with obesity were found to work harder for high-calorie snack *vs.* low-calories foods, when both are equally liked (Giesen et al. 2010). When consumed daily, the RRV of a palatable snack was found to increase in obese women, and to decrease in normal weight-women after 14-days (Clark et al. 2010, Temple et al. 2009). In these two particular studies, increased RRV of snack was not reflected in increased EI, as measured with 24-h dietary recalls.

On the other hand, other evidence demonstrated the association between RRV food and EI in adults (Brace & Yeomans 2016; Epstein et al. 2004, 2007b, 2011). Previous results observed that the RRV for food was positively related to laboratory-measured (Epstein et al. 2004, 2011) and free-living EI

(Epstein et al. 2011). In addition, it was found to predict sugar (Epstein et al. 2011) and snack (Brace & Yeomans 2016) intake but not total carbohydrate, fat, or protein intake (Epstein et al. 2011). This evidence supports that RRV is may be a predictive measure of short-term EI, which should play a role in body weight regulation. In fact, RRV of food was found to predict BMI increases after 12-months of follow up in both adults (Carr et al. 2014) and children (Feda et al. 2015, Hill et al. 2009).

Particularly in situations where food or reinforcing item are not available, such as fasting and dieting periods, the deprivation seems to increase the RRV, making it more difficult to resist over time (Epstein et al. 2007a). In this case, the motivation to obtain food may gain strength over time and people may allocate more and more resources to obtain and consume these reinforcing items. Accordingly, there is evidence suggesting that after short (Epstein et al. 2003, Polivy et al. 2005, Raynor & Epstein 2003) and long caloric restriction periods (Best et al. 2012), individuals have an increased RRV of food; which could also lead to an acute increase in EI, thus compromising their weight loss and weight loss maintenance.

Overall, those results highlight the difficulty of people living with obesity to control the consumption of high-palatable items and consequently EI. Considering that energy deprivation is one of the most common paths to lose weight, evaluating the effects that deprivation has on the RRV and its association to EI and weight loss in women undergoing weight loss intervention is important to assess.

3.2 Impulsivity, delay reward discounting and energy intake

Impulsivity is a complex personality construct defined as the tendency to act without premeditation, a lower ability to control inappropriate behaviors and its consequences, as well as higher difficulty in delaying rewards (Dawe & Loxton 2004, Patton et al. 1995). Measures of impulsivity in these studies included computer tasks (such as delay discounting tasks) (Leitch et al. 2013, Meule & Kübler 2014)

and multi-dimension self-report scales (*e.g.* Barratt Impulsiveness Scale) (Patton et al. 1995), indicating consistent findings with self-report and objective measures of impulsivity.

One of the constructs of impulsivity is defined by the ability to voluntarily postpone an immediate gratification and persist in goal-directed behavior to achieve later outcomes defined as delay discounting (Bickel et al. 2000). For instance, higher delay discounting characterizes preferences for smaller immediate rewards ($10 dollars now) over larger future rewards ($20 dollars two weeks later). From a clinical perspective, it might be associated with lower ability to self-regulate actions or behaviors (Stojek & MacKillop 2017). This paradigm has been studied in individuals living and not living with obesity, in order to assess if the ability to delay rewards might translate to EI habits (Bonato & Boland 1983, Geller et al. 1981). What is more, the inability to delay gratification could present long term implications. In fact, a recent evidence has shown that difficulty in delaying gratification during childhood predicts increases in BMI 30 years later (Schlam et al. 2013).

Along these lines, higher delay reward discounting is also associated with weight management in previous studies. Participants with a higher BMI presented higher delay discounting (Price et al. 2016) and impulsive behavior (Schag et al. 2013). Particularly in women, studies demonstrated that women living with obesity presented more discounting of future rewards compared to leaner counterparts (Manwaring J., Green L., Myerson J, Strube M. 2011, Schiff et al. 2016, Weller et al. 2008). Those results might also play a role in EI. Recent evidence indicated that women living with obesity and presenting higher impulsive traits, tend to choose away-from-home foods with a higher energy density (kcal/g), in a higher quantity (Appelhans et al. 2012).

Furthermore, impulsivity and more specifically delay discounting towards food was also found to be greater in subjects who were energy and water deprived (Kirk & Logue 1997, Manasse et al. 2017), predicting subsequent weight gain in individuals who lost weight (Brockmeyer et al. 2017, Kishinevsky et al. 2012, Weygandt et al. 2015). Accordingly, in a study involving participants who underwent to at least 8% of body weight loss, higher delay reward discounting for food items

measured at the end of the 12-week program was predictive of greater weight regain 12 months later (Weygandt et al. 2015). Along the same lines, other study observed that participants who were able to maintain a minimum 10% weight loss demonstrated less impulsive choices in a computer task (Brockmeyer et al. 2017).

Taken together, those findings demonstrate the contribution and impulsivity, more specifically delay discounting, to the etiology and maintenance of the obese state; pointing out to the importance of management of this personality trait to influence EI and in individuals seeking weight loss treatment.

3.3 Food Reinforcement, impulsivity, EI and BMI

RRV of food represents how hard one is willing to work to obtain food relative to another rewarding stimuli, RRV of food is an important factor in the drive to obtain and consume food, while impulsivity is important for decisions around resisting palatable food for better health in the future. Both of these constructs exert their effects from separate neural pathways (Appelhans 2009, Appelhans et al. 2011) and their possible their interaction influence EI more than either one alone (Epstein et al. 2012). For example, individuals who find palatable foods more reinforcing may also find it more difficult to delay gratification to consume these energy dense foods (Appelhans 2009). Along the same lines, another study demonstrated that impulsive reactions to high-calorie food-cues seem to be more pronounced when both impulsivity and food craving are high (Meule & Kübler 2014). One important study found a significant interaction between RRV and delay of gratification such that RRV food was found to predict EI only when participants were more impulsive characterized by having difficulty in delaying monetary gratification (Rollins et al. 2010).

Overall, the evidence demonstrates that among individuals living with obesity, who tend to present higher RRV of food and higher impulsivity, the more energy deprived they are, the greater the difficulty they probably will have resisting consumption of palatable food items. Losing weight requires sustained energy deficits, and that may result in increases in the RRV of food, which could

interact with impulsivity. Together, these could enhance the difficulty to delay gratification, which might pose additional challenges for to achieve weight loss outcomes and long term weight maintenance. However, whether different degrees of caloric restriction impact RRV and impulsivity differently remain to be investigated. Moreover, it is still uncertain whether the baseline values or changes in either construct will predict weight loss outcomes better than their interaction, and whether these relations will differ in women under different degrees of caloric restriction.

Summary points:

- Fasting and postprandial appetite has been found to increase after weight loss in women, which was supported by alterations in hormonal regulators of feeding;
- Evidence supporting increases in food reward driven behaviors such as liking and wanting after weight loss is also available, which was supported by functional neuro-imaging studies;
- TEE, REE and PAEE have been found to decrease during and after caloric restriction periods, which might go beyond the changes explained by changes in body composition;
- Most of the changes in feeding-related and EE variables presented throughout this review seem to persist after the weight loss;
- Short-term and long-term caloric restriction promotes increases in appetite, palatability and olfaction, which increases the drive to eat and compromises weight loss;
- RRV and impulsivity are higher in individuals with higher BMI and were both found to predict EI and weight loss;
- The impact of different rates of weight loss on appetite rates, oro-sensory (palatability and olfaction) and REE remains controversial and it remains to be investigated;
- No studies in rate of weight loss including impulsivity and RRV of food were performed indicating the need of further investigations;
- It remains uncertain whether exercising could attenuate decreases in EE and metabolic adaptations after weight loss;

- The present thesis aims to elucidate these remaining questions related to the rate of weight loss as well as the role of exercising on metabolic adaptations;

PART ONE CONTINUED: OBJECTIVES AND HYPOTHESES

Objectives and Hypotheses

The first and second original papers included only women living with obesity randomized in two distinct groups after chronic deprivation periods of 10 or 20 weeks. In the first paper (Original I) we investigated whether different rates of weight loss would affect REE, appetite measures, olfactory performance, food palatability. In this paper we quantitatively assessed, using a psychological systems approach, how appetite, olfaction, food reward, and *ad libitum* feeding respond to two degrees of energy deprivation. The second paper (Original II) we investigated whether different rates of weight loss would affect differently psychological variables (RRV of food and impulsivity) of EI. We also investigated whether changes in RRV and its interaction with impulsivity would predict final outcomes after weight loss. The following paper (Original III) studied whether changes in appetite and oro-sensory variables in the first week of caloric restriction predict final outcomes in our participants. Finally, the fourth paper (Original IV) investigated the role of RT in the maintenance of weight loss and EE parameters in post-menopausal women. Due to the fact that this thesis is composed of two separate studies (and four original research papers), the objectives and hypotheses will be presented accordingly.

Article I**— The rate of weight loss does not affect resting energy expenditure and appetite sensations differently in women living with obesity**

Objective: The objective of the study was to investigate the changes in REE, appetite sensations, olfaction, palatability and EI in pre-menopausal women who lost a similar amount of body weight while engaged in either a slow (-500 kcal/ day, 20 weeks) or a rapid (-1000 kcal/day, 10-week) weight loss program.

Hypothesis: We hypothesized that both slow and rapid weight loss would lead to similar REE and appetite changes following weight loss in premenopausal women living with obesity.

Article II— **The effects of different rates of weight loss on the relative reinforcing value of food and impulsivity in women living with obesity**

Objective: The objective of the study was to investigate the changes in RRV and impulsivity in pre-menopausal women engaged in either a rapid (-1000 kcal/ day, 10 weeks) or in a slow weight loss (-500 kcal/day, 20-week) programs. Secondly, to investigate whether RRV and impulsivity independently or interactively predict final outcomes (weight and FM loss). Finally, to investigate whether changes in RRV and impulsivity would be associated with final body weight and FM loss.

Hypothesis: We hypothesized impulsivity and RRV would significantly increase after the intervention, however no differences between groups would be noted since the study was designed to promote similar weight loss.

Secondly, we predicted that the interaction between impulsivity and RRV (baseline and delta changes) would predict final weight and FM loss.

Finally, we predicted that greater increases in RRV and impulsivity would be associated with poorer weight and fat loss.

Article III**— Appetite changes after 7-day of caloric restriction predict final weight and fat mass loss in pre-menopausal women living with obesity**

Objective: The objective of the present study was to identify whether early changes in variables related to energy balance would be predictive of successful weight loss in women living with obesity.

Hypothesis: We hypothesized that increases in appetite, oro-sensory variables (olfaction and palatability) and decreases in REE measured in the first week of caloric restriction would be

associated with lower fat and body weight loss in women living with obesity subjected to diet-induced weight loss.

Article IV**— A one-year resistance training program following weight loss has no impact on body composition and energy expenditure in postmenopausal women living with overweight and obesity**

Objective: The objective of the study was to investigate the effects of a 1-year RT program on weight loss maintenance and measures of EE following a 6-month dietary weight loss intervention in postmenopausal women.

Hypothesis: We first hypothesized that RT would lead to better body weight loss and FM loss maintenance in postmenopausal women than a diet only intervention. Second, we also hypothesized that RT would be associated with higher resting EE when compared to a diet only intervention.

Assumptions, Limitations and Delimitations

The major limitations of the first study is regarding the sample size, which is limited to 30 pre-menopausal women, and this study was composed of relatively "healthy" individuals which delimits the finding for this specific population. Secondly, even though we tailored the EI and the macronutrient proportions for each participant according to their individual choices, the minimum EI pre-set was 1200 kcal in order to avoid micro-nutrients deficiency. Accordingly, some of the participants in the rapid weight loss were not deprived by 1000 kcal/day, the average of caloric restriction for this specific group of -816.50 (175.73) kcal/day. Although we noted significant correlations between appetite changes in the first week and changes in FM, these correlations presented in the study cannot infer causality.

The major limitation of the second study is the adherence to the RT program during weight maintenance which was only moderate. Second, even though the RT intervention was designed according to the American College of Sport Medicine recommendations for elderly (>65 years) people, the EE achieved might have been too low, either because of low total duration intensity and/or frequency, to observe significant improvement in body composition. We recognize that the volume of training could be other limitation of this study. However, considering our sample was composed of postmenopausal women living with overweight or obesity, the intervention prescribed and performed was realistic for the population studied. Thirdly, our sample size was limited to 54 postmenopausal women, and this cohort was composed of relatively “healthy”, non-diabetic postmenopausal women living with overweight or obesity.

CHAPTER III—METHODS

Methods used for the data collection in each of the studies conducted are presented in article format in four separate original research articles. To also include them here in a separate section would be redundant for the reader, and it was therefore deemed appropriate to describe the methods within each corresponding article.

PART TWO: RESULTS OF THE STUDY AND DISCUSSION

RESULTS AND DISCUSSION

Chapters IV, V, VI and VII present the results and discussions of each of the original studies in article-style format. Overall there are 2 separate studies that compose the original work of my thesis.

Chapter IV, Article I, 'The rate of weight loss does not affect resting energy expenditure and appetite sensations differently in women living with obesity' (Luzia Jaeger Hintze, Gary Goldfield, Ryan Seguin, Aleck Damphousse, Alexandre Riopel, Éric Doucet), is currently submitted to the Journal **Physiology Behaviour**.

Chapter V, Article II, titled 'The effects of different rates of weight loss on the relative reinforcing value of food and impulsivity in women living with obesity' (Luzia Jaeger Hintze, Éric Doucet, Gary Goldfield), is currently being prepared for submission the journal **Appetite.**

Chapter VI, Article III, titled 'Appetite changes after 7-day of caloric restriction predict final weight and fat mass loss in pre-menopausal women living with obesity', (Luzia Jaeger Hintze, Gary Goldfield, Ryan Seguin, Aleck Damphousse, Alexandre Riopel, Éric Doucet) is currently being prepared for submission.

Article VII, titled 'A one-year resistance training program following weight loss has no impact on body composition and energy expenditure in postmenopausal women living with overweight and obesity', is published in **Physiology Behaviour** (Luzia Jaeger Hintze, Virginie Messier, Marie-Ève Lavoie, Martin Brochu, Jean-Marc Lavoie, Denis Prud'homme, Rémi Rabasa-Lhoret and Éric Doucet), **volume 15, issue 189, pp:99-106, 2018.**

CHAPTER IV: Article I

Running Head: The rate of weight loss does not affect resting energy expenditure and appetite sensations differently in women living with obesity

This article is currently submitted to the Journal Physiology Behaviour

The rate of weight loss does not affect resting energy expenditure and appetite sensations differently in women living with overweight and obesity

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ABSTRACT

Background: The impact of different degrees of caloric restriction on the magnitude of those compensatory changes in response to weight loss in human remains to be investigated. Accordingly, the purpose of the study was to investigate the changes in resting energy expenditure (REE), appetite, olfaction, palatability and energy intake (EI) in women who were engaged in either a slow (-500 kcal/day, 20-week) or in a rapid (-1000 kcal/ day, 10 weeks) weight loss program. **Methods:** Thirty-six women with obesity were randomized to a slow or to a rapid weight loss group. Body composition (DXA), REE (indirect calorimetry), olfactory performance (Sniffin' Sticks), appetite (Visual Analogue Scale) were assessed at multiple time points during the intervention. **Results:** A total of 30 participants completed the study (slow group n=14; rapid group n=16). Body weight decreased by -4.46 (3.99) % ($P<0.001$) and -6.23 (3.06) % ($P=0.001$) in the slow and rapid groups, respectively. No differences in % weight loss were noted between groups ($P=0.175$). Significant decreases in body fat ($P=0.008$), REE ($P=0.035$), total EI ($P=0.001$) were observed over time from both groups. However, no significant differences emerged between groups for any of the outcomes. The satiety quotient (SQ) at time 180 min significantly increased for desire to eat ($P=0.01$), hunger ($P=0.011$) and PFC ($P=0.002$), while the area under the curve for postprandial appetite rates were not changed. No differences in palatability and smell performance were noted after the intervention. **Conclusions:** Our results suggest that different rates of weight loss exert similar effects on REE, appetite, satiety, and EI when weight loss are comparable.

Keywords: rate of weight loss; energy expenditure; appetite; visual analogue scale

1. Introduction

The ‘ideal’ rate of weight loss as well as its clinical implications in weight management have been discussed repeatedly in the literature [1,2]. The belief that a slower weight loss is associated with a better weight loss maintenance has been investigated and recently questioned [3–6]. In fact, there is evidence that a higher percentage of individuals engaged in the rapid weight loss (81% vs 62% of the slow weight loss) were able to achieve the target goal for the maintenance phase [3]. Along the same lines, individuals enrolled in a rapid weight loss group were found to be five times more likely to achieve 10% weight loss at 18 months compared to the individuals enrolled in a slow weight loss group [5]. Furthermore, results have demonstrated that individuals who engaged in weight loss interventions with different degrees of caloric restriction presented similar weight regain after 9-month [4], 1-year [5] and 144-week [3] follow-up period.

The high rates of weight relapse commonly observed after weight loss are mainly attributable to compensatory mechanisms that relate either to energy intake (EI) or to energy expenditure (EE) [7–9]. The existence of metabolic adaptations following weight loss seems to be well established in the literature; however, many studies have not investigated whether different types of diet and/or degrees of caloric restriction impact the magnitude of those compensatory changes [3,10,11]. Available literature on the rate of weight loss also reveals group differences as far as the final weight loss is concerned [11,12]. Considering the existence of an association between the magnitude of weight loss and the extent of metabolic adaptations [13–16], studies aiming to investigate whether the rate of weight loss influences metabolic adaptations need to control for the differences in total weight loss.

Siervo *et al.* [11] observed significant decreases in TEE and REE following 10% of weight loss in groups under very low-calorie diet (VLCD- rapid weight loss) and low-calorie diet (LCD – slow weight loss); TEE decreases were similar in both groups whereas changes in REE were greater in the slow

weight loss arm [11]. Of note, the first study [11] was only performed in men, and participants from different groups presented different weight loss, which is an important confounder of the changes in these variables. In contrast, Coutinho *et al*. [10] did not report any differences in REE after 10% weight loss in individuals engaged in either rapid or slow weight loss groups.

Results related to the effects of different weight loss rates on appetite are also incongruent. Another study reported that after reaching a minimum of 12.5% weight loss, only participants in the rapid weight loss presented significant increases in hunger ratings (measured by Visual Analogue Scale-VAS) at 44 and 144-week of follow-up period [3]. On the other hand, another study demonstrated that only slow weight loss promoted significant increases in fasting Prospective Food Consumption (PFC), whereas greater decreases in postprandial fullness and hunger after the intervention period were noted in the rapid weight loss group [10]. It is important to note that some of these studies differ in terms of design. Purcell *et al.* [3] excluded results of participants who did not reach the minimum predicted weight loss (-12.5%), which resulted in a higher proportion of participants from the rapid weight loss group (*vs.* slow weight loss) being included in the analyses.

Taken together, findings point out to the necessity of further investigations on the effects of different rates of weight loss on EI and EE adaptations. Such studies should include more comprehensive variable panels including EI, as well as palatability and olfactory performance as available literature demonstrates that caloric restriction increases palatability and olfaction, potentially driving increases in EI [17–20]. Accordingly, palatability and olfaction might interact to influence the drive to eat differently under varying levels of caloric restriction, potentially leading to different weight loss between groups. Moreover, the assessment of REE and appetite need to be done at multiple time points during intervention to assess the timeline of metabolic adaptations. Finally, these studies should produce similar weight loss to experimentally control for total weight loss as this is an

important confounder for studies investigating the impact of the rate of weight loss on metabolic adaptations.

To our knowledge, no study has investigated the effects of different rates of weight loss on palatability and olfactory performance together with measures of REE, fasting and postprandial appetite. Furthermore, more information is needed in terms of the trajectory of those adaptations in EI and EE during weight most in order to identify 'critical' time-points that might deserve closer observation during weight loss. As such, a recent publication [21] demonstrated that significant decreases in REE are observed after 5% weight loss (obtained at 3-wks in a VLCD) whereas more significant metabolic adaptations were significant at 10% weight loss. However, this particular study did not include appetite measures and participants were under similar degrees of caloric restriction. Accordingly, the purpose of the study was to investigate the changes in REE, appetite sensations, olfaction, palatability and EI in pre-menopausal women who lost a similar amount of body weight while engaged in either a slow (-500 kcal/ day, 20 weeks) or a rapid (-1000 kcal/day, 10-week) weight loss program. We hypothesized that both slow and rapid weight loss would lead to similar REE and appetite changes following weight loss in premenopausal women living with obesity.

2. Methods

2.1 Subjects

A total of 36 overweight and obese pre-menopausal women enrolled the program; however, only 30 completed the intervention. The inclusion criteria were as follows: 27≥BMI≥40 kg/m^2, 18 years and older, waist circumference >88 cm, weight-stable (±2 kg last 6 months), be sedentary (less than 150 minutes per week), no history of alcohol or drugs abuse, no food allergies, non-smoker, pre-menopausal with a regular menstrual cycle, not pregnant, not taking any medication that can interfere in EI and EE (*e.g.*, psychiatric medications, appetite suppressants), normal scores in Binge

Eating [22] and depression symptoms [23]. Furthermore, participants who self-reported having any history or evidence of: 1) cardiovascular disease, peripheral vascular disease, or stroke, 2) diabetes (75g oral glucose tolerance test), 3) known renal and liver disease, 4) asthma requiring therapy, plasma cholesterol > 8 mmol/L, 5) systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, 6) previous history of inflammation disease, or cancer, 7) untreated thyroid or pituitary disease, 8) medications that could affect cardiovascular function and/or metabolism, 9) food allergies, could not be included in the study (n=12). All participants gave their written informed consent to participate in this study, which was approved by the University of Ottawa, Research Ethics Board.

2.2 Study design and procedures

All women were initially screened for enrolment by email and/or by phone and scheduled for a 3-hour visit at the laboratory (preliminary visit). The preliminary visit included measures of height, weight, waist circumference and questionnaires that confirm their eligibility for the study. During this session, participants were asked to choose which items they desired for breakfast from a validated food menu [24]. They were instructed to eat ‘as much or as little you want’ and the quantities for each item were standardized as their breakfast for all other experimental sessions over the course of the study (baseline, 7-day, post-intervention).

Participants were also able to select from the same food menu the items they desired for the remainder of the day as well as for the following day. Briefly, participants received two lunch boxes containing all food items that they had selected and were instructed to eat ‘as much or as little you want’; however, they were instructed to eat only items contained in their lunch boxes during those 2 days. We have used this method to assess *ad libitum* EI under free-living conditions as previously reported [25,26].

The macronutrient composition obtained at baseline from the analysis of the intake from the lunch boxes was used for the prescription of the macronutrient distribution during the weight loss intervention. The participants were also asked to wear a biaxial accelerometer (Sense Wear Pro 3 Armbands©, Health Wear Bodymedia, Pittsburgh, PA, USA) during 7 days to evaluate their physical activity EE and to confirm the sedentary eligibility criterion.

Participants who met all inclusion criteria and completed all measures of the preliminary session were then randomized in two distinct groups: slow weight loss (-500 kcal/day) and rapid weight loss (-1000kcal/day). The total duration of the program was thus 20 and 10 weeks for the slow and rapid groups, respectively. Thus, the prescribed total energy deficit was the same for both groups. This was done in an attempt to match the total weight loss for the two groups. Both groups were assessed at baseline, 5 to 7 days after starting the program and post-intervention (at week 10 or 20) for body composition, REE, fasting and postprandial appetite sensations, olfactory performance, palatability and *ad libitum* EI. In addition, REE, body weight, fasting appetite were also measured at 3 times points throughout the intervention period. The rapid weight loss group was assessed every two weeks, while the slow weight loss group was assessed every four weeks. In order to minimize the effects of the participant's menstrual cycle on the main outcomes measures, all participants were tested during their follicular phase (between days 1 and 5 of their menstrual cycle) in the preliminary, baseline and post-intervention sessions.

2.3 Nutritional intervention

The nutritional interventions consisted of caloric restrictions of -500 kcal/day and -1000 kcal/day, for the slow and rapid weight loss, respectively. These restrictions were calculated from individual daily EE requirements (Ereq). Total EE was estimated from a combination of measures of REE and

biaxial accelerometer placed around the upper arm (mid-distance between the acromion and the olecranon). The SenseWear Professional software (version 7.0, Bodymedia, Pittsburgh, PA, USA) was used to retrieve the data once the accelerometer was returned to the laboratory as previously described [25]. The minimum amount of caloric intake was pre-set in 1200 kcal for the both groups, as suggested by the Academy of Nutrition and Dietetics [27]. The diet macronutrient composition was personalized for each participant based on the results of 2-day EI at preliminary session, as discussed above. To achieve and maintain the dietary energy restriction, the Food exchange system from the Canadian Diabetes Association [28] was used. In this system, foods are categorized into the seven following groups: milk and dairy products; meat and substitutes; vegetables; fruits; bread and cereals; fats (including oils, margarine, butter, nuts and seeds); and items with unlimited consumption (*e.g.* condiments, seasonings, tea, coffee no sugar added). This nutritional intervention allows participants to select foods that they enjoy during the weight loss; however, in smaller quantities.

2. 4 Body composition

Body weight was measured to the nearest 0.1 kg on a calibrated balance (HR-100; BWB-800AS, Tanita Corporation, Arlington Heights, IL., USA) and standing height was measured using a wall stadiometer (Tanita HR-100, Tanita Corporation of America, Inc, Arlington Heights, IL). Fat Free Mass (FFM) and Fat Mass (FM) were measured using dual energy X-ray absorptiometry – DXA (Lunar Prodigy, General Electric, Madison, WI, USA). In our laboratory, the coefficient of variation and correlation for body fat percentage measured by DXA scanner in 12 healthy participants were 1.8% and r=0.99, respectively [29]

2. 5 Resting Energy Expenditure

REE was assessed by indirect calorimetry using the ventilated hood technique and the Vmax Encore 29 N metabolic cart (SensorMedics Corporation, Yorba Linda, CA, USA). The metabolic carts were calibrated against 95% O2/5% CO2 reference gas at the beginning of each day. Concentrations of CO_2 and O_2 were measured during 30 min (5 min of acclimatization and the average of the following 6^{th}-25^{th} min were included in the analysis) and Weir's equation [30] was used to determine absolute 24-hour resting EE. Measurements were taken between 7:00 and 9:30 AM after 12-hour fasting period. This measurement was always done in same room, which was kept dark and at an ambient temperature of 21° Celsius. After a 20 to 30-minute resting period in the supine position, 30 minutes of measurements were accomplished, whereas only the last 20 minutes were used in the calculation of resting EE. Ethanol burning tests were performed along the intervention in order to control quality of the measurements, as previously described [31,32]. Tests demonstrated -5% and 4.76% difference in CO2 and O2 measures, respectively.

2. 6 Appetite

Appetite ratings were measured fasting, at 0, 30, 60, 90, 120, 180 min after a standardized breakfast using a 100-mm computerized VAS [33]. Desire to eat, hunger, fullness and PFC were rated using the following questions: 1) "How strong is your desire to eat?" (Very weak- Very strong); 2) "How hungry do you feel?" (Not hungry at all- As hungry as I have ever felt); 3) "How full do you feel?" (Not full at all- Very full), and 4) "How much food do you think you could eat?" (Nothing at all- A large amount). The trapezoid method was used to calculate AUC for each appetite sensation, as previously described [34]. The satiety quotient (SQ) for each appetite sensation (AS) was calculated with the following formula, as proposed by Green *et al.* [35]:

$$SQ(mm/100kcal) = \frac{(fasting\ AS - mean\ 60\ \text{min}\ postmeal\ AS)x100}{energy\ content\ of\ the\ test\ meal\ (kcal)}$$

Of note, the SQ calculation for the fullness is reversed (*i.e.* mean 60 min post-meal fullness - fasting fullness). Higher SQ score is an indicator of greater satiety response to the meal [35]. In the present study, breakfast was standardized and personalized across sessions. The differences in SQ observed over the trial were dependent on the changes in appetite sensations as a result of the standardized breakfast.

2. 7 Olfaction and palatability

Olfactory performance was measured with Sniffin' Sticks (Burghart Instruments, Wedel, Germany). The assessment consisted in a 3-test battery of 16 odorized markers that measure odor detection threshold, odor discrimination, and odor identification as previously described [36]. The total score was calculated with the sum of these 3 tasks. The order of each test was the same for all participants and they were administered at 90min after a standard breakfast. Palatability was measured using a 100mm VAS [37], taken right after a standard breakfast.

2. 8 Energy intake

Ad libitum lunch energy and macronutrient intakes were measured at 180min after a standard breakfast at baseline, 7-day and post-intervention sessions. Briefly, participants were invited to select items that they would like to have for lunch from a validated food menu. They were instructed to consume 'as much or as little you want' from these items. All selected food items were prepared and measured according to the guidelines previously described previously [24]. The macronutrient composition of foods and beverages consumed was determined and analysed with Food Processor SQL software (version 9.6.2; ESHA Research).

2.9 Degree of energy compensation

The degree of energy compensation was calculated from the total caloric deficit prescribed (kcal) and body composition changes (kg converted to kcal) over the intervention. Changes in body composition were calculated by subtracting body composition values (FM and FFM) obtained post-intervention from those measured at baseline. We considered equivalents of 9500 kcal and 1200 for every kg lost in FM and FFM, respectively as previously suggested [38]. The degree of energy compensation (%) was calculated using the following equation:

$$\%\ Compensation = \frac{(\Delta FM\ Kg * 9500) + (\Delta FFM\ Kg * 1200)}{Total\ energy\ deficit\ kcal\ - Thermogenic\ adjusment\ kcal} * 100$$

Accordingly, 0% is indicative of the fact that body composition changes were exactly the values predicted by the prescribed deficit. In contrast, a compensation of 100% indicates that body composition remained the same despite the nutritional intervention. Finally, negative compensation values indicated that body energy stores reduced beyond what was expected from the amount of energy deficit prescribed in the intervention.

2.10 Statistical Analysis

All data were analyzed with Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). Results with a parametric distribution are presented as mean ± standard deviation. Two-way repeated measures ANOVA were performed for changes in body weight, body composition, REE, appetite, olfactory performance and EI variables at baseline, after 7-days and post-weight loss within each group and between groups (*time x group* interaction). Effects were considered significant at $P < 0.05$. Moreover, in order to assess the magnitude of potential observed differences, the effect size was computed (eta squared, η2). The values of 0.0099, 0.0588, and 0.1379 were considered benchmarks for small, medium, and large effect sizes [39]. We also

performed secondary data analyses by comparing results for the main outcomes (body weight, FM, FFM, REE, appetite sensations) in participants who presented >5% weight loss.

To assess the presence of adaptive thermogenesis in our sample across the trial, values of the 36 women who started the trial were then used to compute a prediction equation to estimate REE at baseline and post-intervention. Linear multiple regression analyses were used to identify the best predictors of REE (probability to enter the model was set at $P<0.05$). The independent variables entered into the model were age, height, FM and FFM. All variables met the entry criteria of $P<0.05$. The following equation was then computed: Predicted Resting EE=840-(108.976×height) + (15.96×FFM) + (7.546 x FM) – (4.61 x age); R=0.919, R^2=0.835, Standard error: 126.181 kcal/day.

3. Results

During the intervention period, 6 participants (or 16.7%) quit the study. Reasons included lack of motivation (3), lack of time (2), and personal/health problems not related to the trial (1). As such, 30 participants completed the intervention and were included in the analyses (slow: n=14; fast: n=16).

Physical and demographic characteristics of participants from both groups are displayed in the **Table 1**. No differences were noted between groups for any of the variables, confirming that both groups started the intervention under the same conditions. Furthermore, no differences were noted when comparing completers and non-completers, for any of the variables (data non-shown).

Table 2 presents the changes in body weight, body composition and REE in completers from the slow and rapid weight loss groups. Overall, a significant time effect with a large effect size was observed for all variables. Weight loss after dietary intervention was -4.46(3.99) % ($p<0.001$) and -6.23 (3.06) % ($p=0.001$) in the slow and rapid groups, respectively. No differences in % weight loss were noted between groups ($P=0.175$). No time*group effects were observed for any of the

variables, and only small effect sizes were noted. We also calculated the % of energy compensation in both groups. Because the data presented a non-parametric distribution, variables are presented in median and interquartile range. The values obtain were 49.76 (67.74)% and 50.29 (87.19)% in the slow and rapid groups, respectively. No significant differences between groups were observed (P=0.430).

Figure 1 shows the changes in body weight and REE at three time points during the intervention. Body weight and REE decreases were significant overtime ($p<0.01$ and 0.027, respectively) and a large ($\eta2=0.693$) and a medium effect size ($\eta2= 0.083$) was noted for body weight and REE, respectively. No time*group interactions were noted for these variables. We compared the rates of weight loss for both groups by dividing the total weight loss by the number of weeks. As designed, a significantly lower rate of weight loss was noted in the slow *vs.* rapid weight loss group (-0.21 (0.18) *vs.* -0.52 (0.25) kg/week ($p<0.001$), respectively).

Figure 2 displays changes in fasting appetite rates throughout the intervention. Fasting desire to eat (A), hunger (B) and PFC (C) ($P<0.01$) significantly and progressively increased overtime in a similar way in both groups. No significant time*group interactions were noted.

Table 3 shows the measures SQ, smell performance, palatability and EI before and after intervention. Overall, we observed a 17% increase in smell threshold in our sample; however, this increase was not statistically significant. The time*group analysis for smell threshold revealed no significant differences between groups over time, although a trend toward significance was noted ($P=0.08$, ($\eta2=0.083$). Similarly, a significant group*time interaction ($P=0.012$) and a large effect size ($\eta2=0.147$) was noted the smell identification score, where the rapid weight loss group showed an

increase in smell identification and the slow weight loss group showed a decrease. No group or group*time effects were noted for palatability.

Measures of SQ at time 60 and 180min for desire to eat, hunger and PFC were found to significantly increase after the intervention. Large effect sizes were observed for all variables. No time*group interactions were noted, demonstrating that changes were similar in both groups over the course of the intervention. Accordingly, *ad libitum* EI decreased by the end of the trial ($p=0.001$, $\eta2=0.214$), which was explained by decreases in protein ($p=0.024$, $\eta2=0.124$) and carbohydrate intake ($p=0.002$, $\eta2=0.204$). No significant time x group interactions were noted for macronutrient outcomes. No significant time or time*group differences were observed for AUC postprandial appetite after intervention (data not shown).

We also calculated the expected REE at baseline and post-intervention and we compared the results to the measured REE in both groups. As previously described, measured REE significantly decreased over time ($p<0.001$, $\eta2=0.33$); however, no differences between predicted and measured REE values were noted either over time ($p=0.844$; $\eta2=0.001$) or between groups ($p=0.668$, $\eta2=0.007$).

4. Discussion

Only a handful of studies have evaluated the impact of different rates of weight loss on REE [10,11] and appetite ratings [3,10] and we are unaware of any study that investigated changes in EI, palatability and smell capacity under these conditions. To our knowledge, the present study is also the first one to investigate changes in REE and fasting appetite at multiple time points during the intervention in groups under different rates of weight loss who were prescribed the same total energy deficit. The findings partially support our hypotheses that both slow and rapid weight loss leads to

similar changes in REE and appetite when weight loss is comparable between groups. In fact, our results demonstrated that REE decreased significantly over time, whereas fasting desire to eat, hunger and PFC all increased, with none of these changes seemingly influenced by the rate of weight loss.

Decreases in REE are a well-known consequence of weight loss [12,16,40,41]. In fact, we noted a decrease in this component of EE as early as the first week and it declined steadily until the end of the intervention. Accordingly, other studies observed a decline in REE from the first days of caloric restriction [42,43]. Bray [42] noted that more than half of the total decreases in REE happened in the first 8 days of weight loss whereas Muller *et al.* [43] noted that changes in resting EE started to become significant even earlier, at only 3-day of caloric restriction.

In our study, the fall in REE accompanied changes in body weight in both groups and the degree of caloric restriction did not influence these changes. In line with our results, other studies have shown a significant decrease in REE in participants involved in both: slow [10,12] and rapid [10,16,42,44] interventions. More precisely the study conducted by Coutinho *et al.* [10] presented very similar results to those observed in our study. The authors observed similar decreases in REE over time, no differences were observed between groups engaged in either rapid (550 and 660 kcal/day for women and men, respectively) or slow (1200 and 1500 kcal/day for women and men, respectively), after 8 weeks of intervention and comparable weight loss [10].

Given we noted significant decreases in REE over time in our study, we analysed whether those changes in REE were beyond to the values predicted based on body composition changes as we have previously documented [45]. No significant differences between measured and predicted values were observed, contrary to the observed in other studies [11,12] discussing different rates of weight loss. In the study conducted by Martin *et al.* [12] participants were divided in two groups: 25% caloric restriction group (slow weight loss) and in group having a VLCD (890 kcal/day – rapid weight

loss). Both groups presented significant metabolic adaptations (significant differences between predicted and measured values); however, no differences in the extension of the adaptation were detected between groups, even if participants from both groups presented different weight loss (10.4% *vs.* 13.9%). In contrast, another study demonstrated that slower weight loss seems to trigger a higher degree of metabolic adaptation compared to a fast weight loss [11], given the rate of weight loss was inversely correlated with changes in REE ($r = 0.-42$, $p = 0.01$). It should be noted that only men were included in this particular study [11].

Accordingly, Camps *et al.* [16] has shown a strong and positive correlation between metabolic adaptation and weight loss, which seems be more evident in studies involving individuals after massive weight loss [13–15]. Indeed, a very recent study observed after 5% weight loss, significant decreases in REE were observed; however, only after 10% weight loss mark these decreases in REE were beyond the changes explained by body composition, characterizing the occurrence of metabolic adaptation in their participants [21]. These findings coincide with our results given we observed 5% weight loss as well as a significant decrease in REE overtime; however, no differences between measured and predicted values were noted.

Our study indicated constant and progressive increases in fasting desire to eat, hunger, and PFC during intervention. In fact, as previously reviewed [46], there are several reports indicating increases in fasting appetite following caloric restriction [34,47–49]. On the other hand, the impact of different rates of weight loss on fasting appetite rates is not well documented. We noted similar increases in fasting desire to eat, hunger and PFC in both groups, which contrasts with results previously reported. Coutinho *et al.* [10] noted that fasting hunger only increased significantly in the slow weight loss group, while fasting PFC significantly only decreased in the rapid weight loss group. Anton *et al.* [48] indicated similar increases in fasting desire to eat and PFC in both: individuals deprived in 25% their total EE (slower weight loss) and in individuals under LCD (890 kcal/day –

rapid weight loss). However, in this second study [48] participants had different weight loss following the intervention, which could have potentially influenced the results.

Postprandial appetite ratings were not significantly different after weight loss in our study, contrary to previous evidence [50,51]. Coutinho *et al.* [10] noted significant decrease in postprandial PFC and hunger only in the rapid weight loss group. In other study, hunger ratings were not different between groups during weight loss; however, at 44-wk and 144-wk of follow up phase higher appetite ratings were observed in only in the rapid weight loss group[3].

These increases in appetite were not reflected in increased EI measured in the laboratory (data not shown). A recent meta-analysis stated that a minimum change of ≥15–25mm on a 100mm VAS was necessary to observe significant changes in subsequent EI [52]. Although we noted significant increases in postprandial appetite, they were not sufficient to trigger increases in EI in a subsequent *ad libitum* laboratory condition. On the other hand, % nutritional compensation data in our study suggest that in free-living conditions, the increased appetite rating might have led to increased EI [53] and/or our participants decreased their physical activity EE [54] since the degree of energy compensation was approximately 50% in both groups.

SQ significantly increased after intervention in our study measured at time 60min and 180min, similar to what was observed by other studies [49,55,56]. These results suggest that a higher sensitivity to food-induced satiety signalling after the caloric restriction in our participants, which was previously suggested [57]. Whether this increased sensitivity remains in the maintenance phase of weight loss deserves further investigation.

The present study has some limitations. First, our sample size is limited to 30 pre-menopausal women, and this study was composed of relatively “healthy” individuals which limits the generalizability of the findings for this specific population. Secondly, even though we tailored the EI and the macronutrient proportions for each participant according to their individual choices, the minimum EI pre-set was 1200 kcal in order to avoid micro-nutrients deficiency. Accordingly, some of the participants (n=6) in the rapid weight loss were not deprived by 1000 kcal/day, the average of caloric restriction for this specific group of -816.50 (175.73) kcal/day. On the other hand, the results confirmed that groups had significant different rate of weight loss and the data suggested that both groups presented a similar degree of compensation. Our results are strengthened by its design (randomized clinical trial), as well by the number of follow ups and assessments performed during intervention. Other aspects of the methods of our study such as the use of gold-standard techniques in the measures of EE and body composition, the personalized breakfast and control for the phase of the menstrual cycle are other aspects that provide to strength our results. Finally, both groups lost a similar amount of weight, which decreases the impact of the magnitude of the weight loss on the variables of interest in the study.

In conclusion, our results suggest that the impact of rapid *vs* slow rates of weight loss on REE, fasting appetite and satiety in women is comparable when final weight loss are comparable between groups. Taken together, the evidence presented questions the superiority of slower weight loss rates in final weight loss and its adaptations. Both, slow and rapid weight loss approaches might be suitable options for patients seeking weight reduction treatment, as they do not seem to exacerbate other energy balance factors differently.

Table and Figure Legends

Table 1. Baseline characteristics of the slow and rapid weight loss groups

Data presented as mean ± SD; Categorical variables present as frequency (percentage); BW: Body weight; BMI: Body Mass Index, WC: Waist Circumference; BF: Body Fat; REE: Resting Energy Expenditure; TEE: Total Energy Expenditure; EI: Energy Intake

Table 2. Changes in body composition and resting energy expenditure at baseline, 7 days and post dietary intervention loss

Data presented as mean ± SD; FM: Fat Mass; FFM: Fat Free Mass; REE: Resting Energy Expenditure; effect size was assessed using eta squared; **significant differences**

Table 3. Changes in Satiety Quotient, olfactory performance and energy intake at baseline, 7 days and post dietary intervention

Data presented as mean ± SD; AUC: Area under the curve; PFC: Prospective Food Consumption; SQ: Satiety Quotient; effect size was assessed using eta squared**; significant differences**

Figure 1. Body weight (A) and Resting Energy Expenditure (REE) during dietary intervention in the slow and fast weight loss groups, * represents a significant change overtime; no significant time & group interaction.

Figure 2. Fasting Appetite Rates for Desire to eat (A), Hunger (B), Prospective Food Consumption-PFC (C) and Fullness (D) following dietary intervention in the slow and fast weight loss groups, *represents a significant change over time

Table 1

	Slow (n=14)	Rapid (n=16)	P
Age (years)	29.8 (8.9)	35 (8.8)	0.120
BW (Kg)	87.29 (11.65)	92.18 (16.54)	0.364
BMI (kg/m2)	32.11 (3.12)	33.53 (4.39)	0.329
WC (cm)	94.21 (6.78)	95.94 (9.75)	0.584
%BF	47.02 (3.49)	47.32 (2.66)	0.789
Attempts to lose weight	3.93 (3.27)	4.63 (2.19)	0.494
Highest BW lifetime (Kg)	90.13 (13.22)	94.44 (16.45)	0.440
REE (kcal/day)	1499.76 (198.01)	1550.47 (205.79)	0.499
Estimated TEE (Kcal)	1973.93 (185.74)	2091.06 (267.87)	0.288
EI Breakfast (Kcal)	500.94 (146.05)	490.46 (168.34)	0.858
EI Day 1 (Kcal)	1590.22 (560.72)	1829.84 (637.87)	0.288
EI Day 2 (Kcal)	2037.51 (631.77)	2227.69 (575.64)	0.396
Ethnicity (n, %)			
Caucasian	8(26.67%)	12(40%)	
Black	3 (10%)	0 (0%)	
Others	3 (10%)	4 (13.33%)	0.458
Education (n, %)			
High school	4 (13.33%)	2 (6.67%)	
Some college, no degree	2 (6.67%)	2 (6.67%)	
Associate's degree	1 (3.33%)	1 (3.33%)	
Bachelor's degree	2 (6.67%)	5 (16.67%)	
Master's degree	5 (16.67%)	5 (16.67%)	
Professional degree	0	1 (2.8%)	0.487

Table 2

	Slow (n=14)			Rapid (n=16)				
	Baseline	7 days	Post Intervention	Baseline	7 days	Post Intervention	time	time* group
Body Weight (Kg)	87.29(11.65)	86.1 (11.41)	83.36 (11.16)	92.18 (16.54)	90.6 (16.54)	86.69 (17.26)	**<0.01**	0.21
FM (Kg)	42.28 (7.81)		40.52 (7.76)	43.21 (7.57)		40.46 (8.55)	**<0.01**	0.311
FFM(Kg)	44.10 (5.38)		42.10 (5.74)	47.09 (8.35)		45.03 (8.62)	**<0.01**	0.936
REE (kcal/day)	1502.5 (191.1)	1432.04 (192.23)	1359.25 (416.43)	1517.54 (143.39)	1495.85 (121.98)	1355.75 (393.73)	**0.035**	0.862

Table 3

	Slow (n=14)			Rapid (n=16)				
	Baseline	7 days	Post Intervention	Baseline	7 days	Post Intervention	P	time* group
SQ at 60 min Desire to Eat (mm/100 kcal)	10.60 (6.22)	14.32 (5.85)	16.16 (9.03)	11.40 (11.46)	12.91 (8.3)	15.21 (8.60)	**0.004**	0.688
SQ at 180 min Desire to Eat (mm/100 kcal)	5.67 (5.51)	11.48 (5.68)	13.18 (7.33)	7.62 (10.36)	9.84(7.76)	11.15(5.88)	**0.001**	0.333
SQ at 60min Hunger (mm/100 kcal)	11.35 (7.43)	14.90 (7.07)	14.34 (8.51)	11.30 (11.22)	13.12 (8.99)	15.28 (8.22)	**0.009**	0.488
SQ at 180min Hunger (mm/100 kcal)	7.39 (5.53)	12.09 (6.71)	11.57 (7.53)	7.47 (10.42)	9.20 (6.63)	11.13 (5.32)	**0.011**	0.502
SQ at 60min Fullness (mm/100 kcal)	14.15 (7.36)	17.28 (6.62)	15.25 (6.59)	15.97 (11.07)	14.24 (7.95)	16.81 (7.13)	0.711	0.086
SQ at 180min Fullness (mm/100 kcal)	10.85 (5.90)	13.61 (5.80)	12.59(6.49)	11.88 (9.90)	10.31 (7.33)	11.69 (4.98)	0.833	0.278
SQ at 60min PFC (mm/100 kcal)	7.06 (6.13)	8.80 (7.76)	11.61 (8.53)	10.32 (8.86)	12.48 (10.30)	13.35 (7.05)	**0.001**	0.258
SQ at 180min PFC (mm/100 kcal)	3.34 (5.23)	9.86 (5.54)	8.73 (9.29)	6.51 (7.78)	8.60 (8.40)	9.49 (4.57)	**0.002**	0.234
Smell Threshold	9.80 (2.58)	11.32 (2.28)	10.80 (2.64)	9.69 (2.03)	8.92 (2.33)	10.78 (2.32)	0.215	0.08
Smell Discrimination	12.29 (1.73)	12.29 (2.05)	12.57 (1.72)	12.38 (1.5)	12.44 (1.96)	12.44 (1.55)	0.854	0.902
Smell Identification	13.14 (2.14)	12.86 (2.48)	12.2 (1.73)	12.50 (1.92)	13.5 (1.86)	13.31 (1.40)	0.326	**0.012**
Smell Total Score	35.04 (4.71)	36.46 (4.85)	35.68 (3.13)	34.56 (3.70)	34.92 (4.70)	36.28 (4.14)	0.284	0.383
Palatability (mm)	84.55 (15.15)	85.87 (14.24)	83.84 (16.66)	82.52 (17.15)	82.28 (14.81)	71.64 (31.57)	0.216	0.391

Energy Intake Lunch (Kcal)	538.99 (171.53)	518 (193.09)	504.33 (225.79)	644.08 (250.63)	475.35 (122.44)	415.11 (199.60)	**0.001**	**0.019**
CHO (Kcal)	303.81 (103.91)	261.12 (104.70)	276.15 (139.19)	337.82 (167.06)	260.37 (97.30)	219.15 (107.68)	**0.002**	0.093
Protein (Kcal)	111.01 (37.57)	94.17 (42.91)	100.41 (48.46)	114.60 (58.24)	93.84 (19.85)	75.11 (38.30)	**0.024**	0.246
Fat (Kcal)	124.21 (65.93)	155.80 (117.40)	127.76 (71.06)	183.82 (89.59)	125.64 (63.36)	129.54 (85.40)	0.38	**0.05**

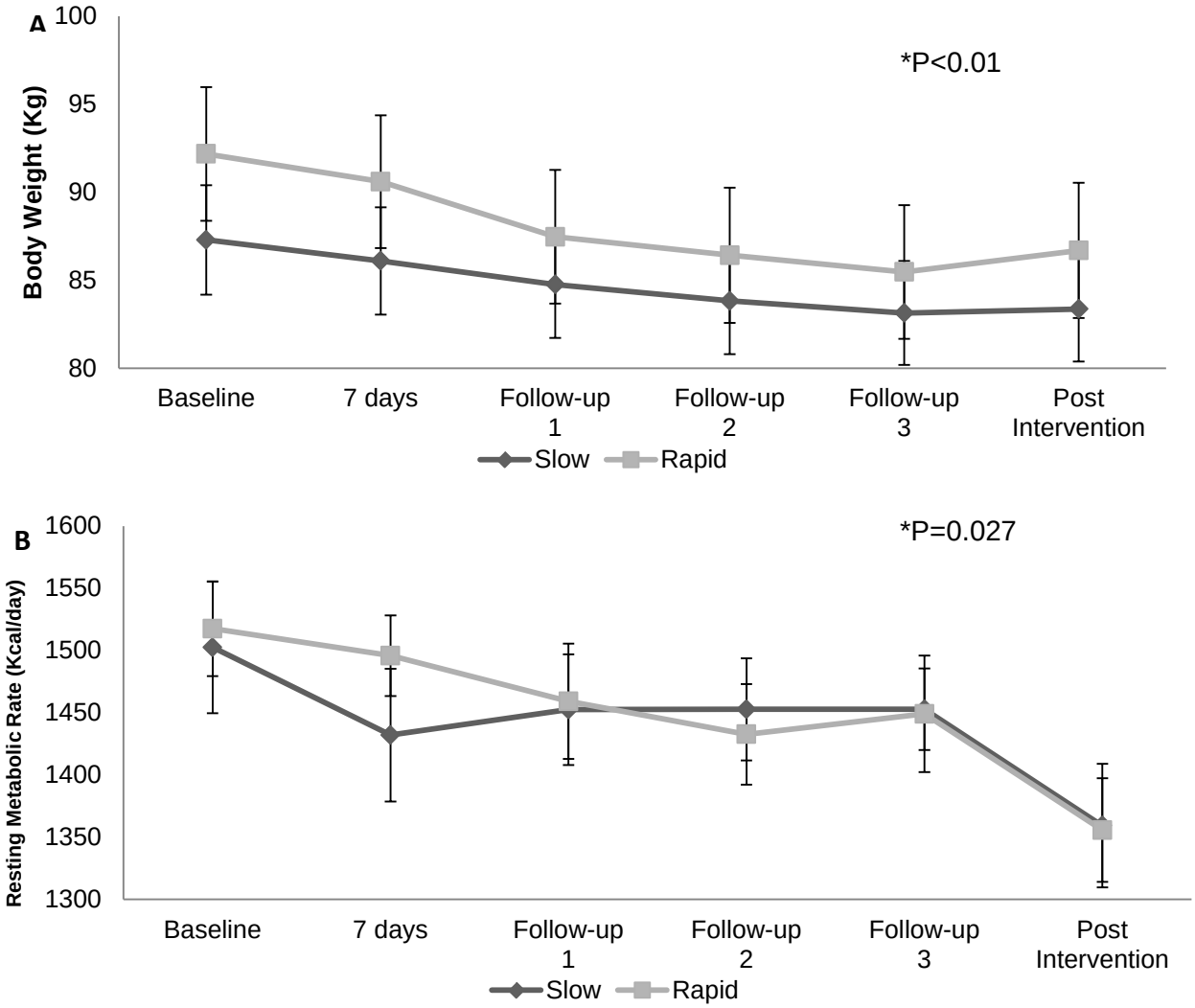
A
100
95
90
85
80
Body Weight (Kg)
*P<0.01
Baseline
7 days
Follow-up 1
Follow-up 2
Follow-up 3
Post Intervention
Slow
Rapid
B
1600
1550
1500
1450
1400
1350
1300
Resting Metabolic Rate (Kcal/day)
*P=0.027
Baseline
7 days
Follow-up 1
Follow-up 2
Follow-up 3
Post Intervention
Slow
Rapid

Figure 1

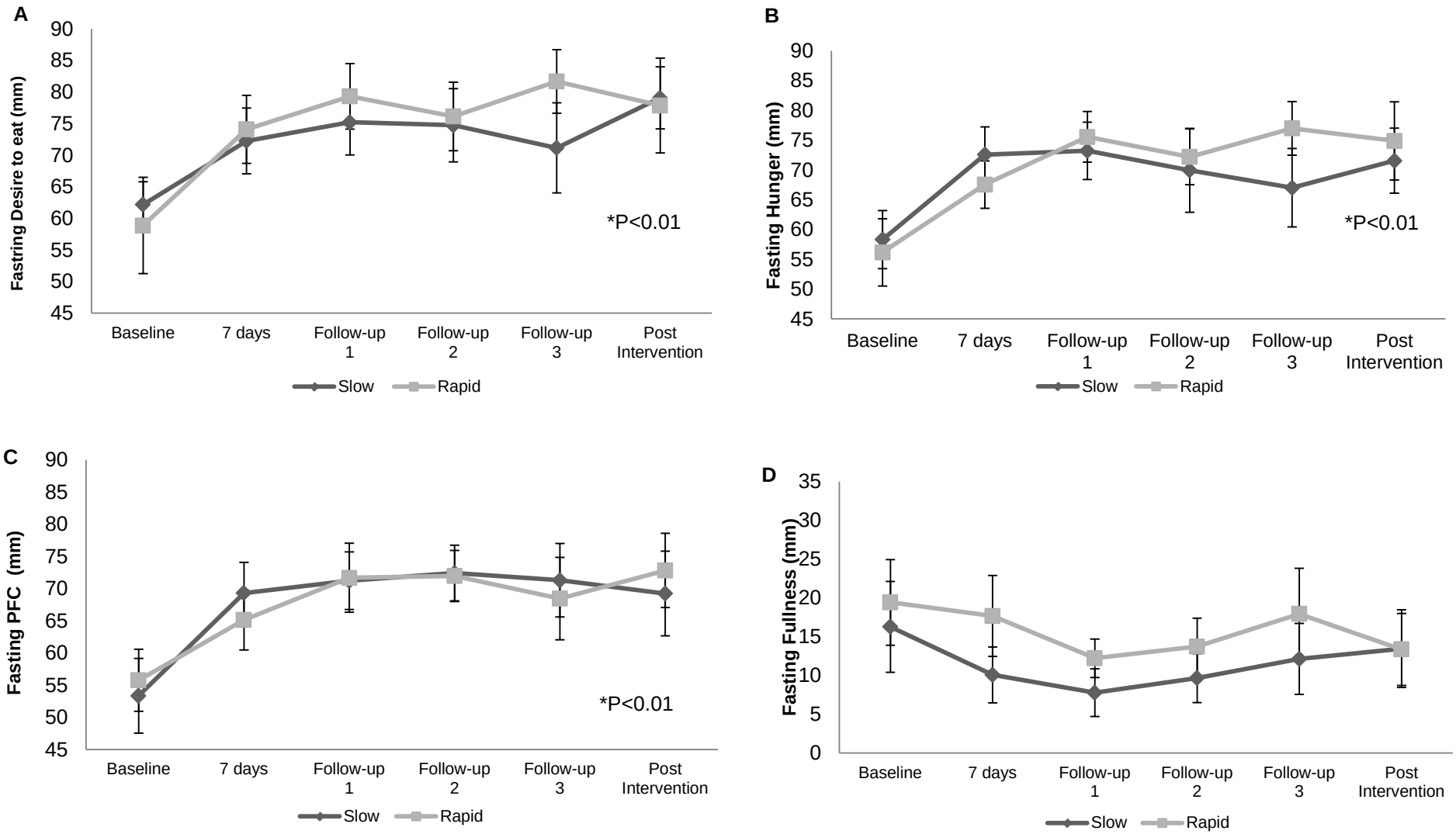
A
Fastring Desire to eat (mm)
90
85
80
75
70
65
60
55
50
45
*P<0.01
Baseline
7 days
Follow-up 1
Follow-up 2
Follow-up 3
Post Intervention
Slow
Rapid
B
Fasting Hunger (mm)
*P<0.01
C
Fasting PFC (mm)
*P<0.01
D
Fasting Fullness (mm)
35
30
25
20
15
10
5
0

Figure 2

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Chapter V: Article II

Running Head: The effects of different rates of weight loss on the relative reinforcing value of food and impulsivity in women living with obesity

Manuscript is currently in preparation to be submitted to the journal Appetite

The effects of different rates of weight loss on the relative reinforcing value of food and impulsivity in women living with obesity

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ABSTRACT

Background: Impulsivity and relative reinforcing value (RRV) of food independently and interactively predict energy intake (EI) and response to weight control programs, but little is known if the predictive utility of these variables differs by varying degrees of caloric restriction. Accordingly, the purpose of the study was to investigate the degree to which baseline values and changes in food reinforcement and impulsivity independently or interactively predict weight and fat loss in pre-menopausal women engaged in either a rapid or in a slow weight loss programs. **Methods**: The study involved 36 women with obesity. Body weight, body composition (DXA), Impulsivity (Barratt Impulsiveness Scale-BIS-11), RRV snack and fruit (Behavioural Choice Task) were measured at baseline and post-intervention. **Results**: A total of 30 participants (slow n: 14; rapid n=16) completed the study. RRV fruit significantly decreased over time and a large effect size was noted (P=0.004; η2=0.257). Non-planning scale was the only impulsivity component that significantly decreased over time (P=0.05; η2=0.128). No significant group*time effects were noted on any of the outcome variables. However, for motor scale of BIS-11 the interaction presented large effect size (P=0.081; η2=0.105). Neither baseline values for snack food reinforcement and impulsivity, nor their interaction, predicted changes in body composition. However, reductions in RRV snack food were associated with reductions in fat mass (r = 0.409; P=0.025). **Conclusion**: Our results suggest that caloric restriction affects RRV fruit in women, whereas motor impulsivity scale might be affected by different rates of weight loss. Changes in snack food reinforcement were found to predict fat loss, suggesting that dietary interventions that either mitigate increases or foster reductions in the RRV of snack food may yield greater reductions in adiposity.

Keywords: weight loss; delay discounting; reinforcement; impulsivity

INTRODUCTION

Impulsivity is a complex personality construct defined as the tendency to act without premeditation, a lower ability to control inappropriate behaviours and its consequences, as well as higher difficulty in delaying rewards (Dawe & Loxton, 2004; Patton, Stanford, & Barratt, 1995). More precisely in the body weight regulation field, this construct might provide an understanding of how different factors influence everyday choices, which can lead to positive energy balance and potential weight gain (Epstein, Leddy, Temple, & Faith, 2007; Epstein, Salvy, Carr, Dearing, & Bickel, 2010; Stojek & MacKillop, 2017). In fact, studies demonstrated that adults with a greater BMI also presented higher impulsivity (Price, Higgs, Maw, & Lee, 2016; Schag et al., 2013). Particularly in women, studies have demonstrated that women living with obesity exhibited greater discounting of future rewards compared to leaner women (Manwaring J., Green L., Myerson J, Strube M., 2011; Schiff et al., 2016; Weller, Cook, Avsar, & Cox, 2008). Impulsivity also plays a role in food choice and energy intake (EI) as women living with obesity with higher impulsivity tend to choose and consume away-from-home foods with a higher energy density (kcal/g), and in greater quantity (Appelhans et al., 2012). Measures of impulsivity in these studies included computer tasks (such as delay discounting tasks) (Leitch, Morgan, & Yeomans, 2013; Meule & Kübler, 2014) and multi-dimension self-report scales (*e.g.* Barratt Impulsiveness Scale) (Patton et al., 1995), indicating consistent findings with self-report and objective measures of impulsivity.

Another factor that has been found to be a powerful determinant of food choice and EI is the relative reinforcement value of food (RRV) (Epstein, Leddy, et al., 2007). Particularly in studies involving eating behaviours, the RRV characterizes how reinforcing energy-dense food items are to the individual in comparison to an alternative item available (Epstein, Leddy, et al., 2007). Individual differences in the RRV of food exist, whereby the RRV of palatable snack food have been reliably demonstrated to be higher in adults living with obesity compared to lean individuals (Clark, Dewey, & Temple, 2010; Epstein, Carr, Lin, & Fletcher, 2011; Giesen, Havermans, Douven, Tekelenburg, & Jansen, 2010; Goldfield, Lumb, & Colapinto, 2011; J L Temple & Epstein, 2011; Jennifer L Temple

et al., 2009), to be positively associated with laboratory-measured (Epstein et al., 2011, 2004) and free-living conditions EI (Epstein et al., 2011).

In situations where food or reinforcing items are not available, such as fasting and dieting periods, the deprivation might increase RRV, making it more difficult to resist over time (Epstein, Leddy, et al., 2007). In this case, the motivation to obtain food may gain strength over time and people may allocate more and more resources to obtain and consume these reinforcing items. Accordingly, there is evidence suggesting that after short (Epstein, Truesdale, Wojcik, Paluch, & Raynor, 2003; Polivy, Coleman, & Herman, 2005; Raynor & Epstein, 2003) and long caloric restriction periods (Best et al., 2012); individuals have an increased RRV of food. This evidence supports the idea of RRV as a potent predictive measure of short-term EI, which thus may play an important role in weight management interventions. Accordingly, a weight loss study demonstrated the decrease in RRV for food as a predictor of greater weight loss in children (Buscemi, Murphy, Berlin, & Raynor, 2014). However, less is known in about changes in RRV in adults as well as on the influence of different rates of weight loss in these variables.

RRV of food and impulsivity may independently exert effects on BMI and weight status (Carr, Lin, Fletcher, & Epstein, 2014). However, when high RRV for food and high impulsivity interact, a phenomenon recently known as reinforcement pathology, this combination of traits provides better prediction of obesity status than either construct alone (Appelhans, 2009; Epstein, Lin, Carr, & Fletcher, 2012; Meule & Kübler, 2014). However, it is still uncertain whether these variables interact to predict EI and potentially weight loss. Previous evidence demonstrated that impulsive reactions to high-calorie food-cues seem to be more pronounced when both impulsivity and food craving are high. On the other hand, in situations where levels of impulsivity are low and food cravings are high, reactions to high-calorie food-cues are less obvious (Meule & Kübler, 2014). More precisely in women, RRV of food was found to predict EI only when participants had more difficulty in delaying

gratification, which is one of the traits of impulsivity (Rollins, Dearing, & Epstein, 2010). Conversely, a recent study has shown that food reinforcement, but not impulsivity, was independently associated with EI in adults, suggesting that food reinforcement might be a more powerful independent predictor of EI (Brace & Yeomans, 2016).

This inconsistency in evidence demonstrates the need of further investigations to gain a better understanding of the independent and combined effect that impulsivity and food reinforcement have on EI and potentially on the treatment response to weight loss interventions. No previous evidence investigated the role of weight loss induced by varying degrees on RRV and impulsivity. Given that given the potential role that RRV of snack food and impulsivity may play on EI, this evaluation would be relevant. For instance, if the rapid weight loss leads to increased food reinforcement and impulsivity, and these changes are associated with poorer weight loss outcomes, it would suggest that less restricted dietary interventions designed to mitigate these changes in food reinforcement and impulsivity may produce better outcomes.

Accordingly, the purpose of the study was first to investigate the changes in RRV of food and impulsivity in pre-menopausal women engaged in either a rapid (-1000 kcal/ day, 10 weeks) or in a slow weight loss (-500 kcal/day, 20-week) programs. Second, we wanted to study whether or not baseline values or changes in RRV for food and impulsivity independently or interactively predict weight and fat mass (FM) loss. We hypothesized that: 1) only RRV for snack food would significantly increase after the intervention; 2) no differences between groups would be noted given the study was designed to promote similar weight loss; 3) that greater increases in RRV and impulsivity would be associated with poorer weight and fat loss and that 4) the interaction between impulsivity and RRV for snack food (at baseline and pre-post intervention changes) would predict final weight and fat loss better than either variable alone.

METHODS

Subjects

A total of 36 overweight and obese pre-menopausal women enrolled the program; however, only 30 completed the intervention. During the intervention period, 6 subjects (or 16.7%) quit the study. Reasons included lack of motivation (n=3), lack of time (n=2), and personal/health problems not related to the trial (n=1). As such, 30 participants completed the intervention and were included in the analyses (slow: n=14; fast: n=16). The inclusion criteria were as follows: 27≥BMI≥40 kg/m2, 18 years and older, waist circumference >88 cm, weight-stable (±2 kg last 6 months), not meeting the current physical activity guidelines for adults (i.e. less than 150 minutes per week), no history of alcohol or drugs abuse, no food allergies, non-smoker, pre-menopausal with a regular menstrual cycle, not pregnant, not taking any medication that can interfere with EI and energy expenditure (EE) (*e.g.* psychiatric medications, appetite suppressants), normal scores in Binge Eating (Gormally, Black, Daston, & Rardin, 1982) and depression symptoms (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Furthermore, participants who self-reported having any history or evidence of: 1) cardiovascular disease, peripheral vascular disease, or stroke, 2) diabetes (75g oral glucose tolerance test), 3) known renal and liver disease, 4) asthma requiring therapy, plasma cholesterol > 8 mmol/L, 5) systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, 6) previous history of inflammation disease, or cancer, 7) untreated thyroid or pituitary disease, 8) medications that could affect cardiovascular function and/or metabolism, 9) food allergies, could not be included in the study (n=12). All participants gave their written informed consent to participate in this study, which was approved by the University of Ottawa, Research Ethics Board.

Study design and procedures

Participants who met all inclusion criteria and completed all measures of the preliminary session were then randomized in two distinct groups: rapid weight loss (-1000 kcal/day) and slow weight loss (-500kcal/day). The total duration of the program was thus 10 and 20 weeks for the fast and slow

groups, respectively, since we wanted to match the total weight loss between groups. Both groups were assessed at baseline, 5 to7 days after starting the program and post-intervention for body composition, REE, fasting and postprandial appetite sensations, olfactory performance and palatability. More details of the study design in previous papers.

Nutritional intervention

The nutritional interventions consisted of caloric restrictions of -500 kcal/day and -1000 kcal/day, for the slow and fast weight loss, respectively. These restrictions were calculated from their individual daily energy requirements (Ereq). Total EE was estimated from measures of indirect calorimetry and biaxial accelerometer placed around the upper arm (mid-distance between the acromion and the olecranon). The diet macronutrient composition was personalized for each participant based on the results of 2-day EI during the preliminary session, as previously described (Hintze *et al.*, *under revision)*. To achieve and maintain their respectively degrees of energy restriction, each participant received explanation about the Food exchange system - Canadian Diabetes Association (Lawton, n.d.) , which is an easy way for subjects to monitor their EI. In this system, foods are categorized into the seven following groups: milk and dairy products; meat and substitutes; vegetables (one portion containing 7g of carbohydrates); fruits; bread and cereals; fat (including oils, margarine, butter, nuts and seeds); unlimited consumption. This method allows participants to select foods that they enjoy during the weight loss, however in smaller quantities.

Measures

Body composition

Body weight was measured to the nearest 0.1 kg on a calibrated balance (HR-100; BWB-800AS, Tanita Corporation, Arlington Heights, IL.,USA) and standing height was measured using a wall stadiometer (Tanita HR-100, Tanita Corporation of America, Inc, Arlington Heights, IL). Fat Free

Mass (FFM) and FM were measured using dual energy X-ray absorptiometry – DXA (Lunar Prodigy, General Electric, Madison, WI, USA). In our laboratory, the coefficient of variation and correlation for body fat percentage measured by DXA scanner in 12 healthy participants were 1.8% and r=0.99, respectively.

Relative Reinforcing Value of Food

RRV of food was assessed by a computer task (Epstein et al., 2012) performed at 180 min after a standard breakfast, just prior to lunch. In our trial, the reinforcement schedule remained at variable ratio (VR2), and constant for the snack food at VR5. Food points were earned by selectively working for the food item of choice, and this was accomplished by activating a slot machine-like program with a simple 2-button joystick. Button 2 allowed the user to freely switch between the snack or fruit/vegetable screen during each trial, and button 1 started the slot game. Participants were asked to intake a 10 gr of their favourite snack and fruit/vegetable, served before starting of the computer task. They were also informed that every 5 points earned in the game, 25 gr of the item chosen would be served to them during lunch time. They had a total of 2 minutes to play as much as little they wanted. Of note, participants were asked to answer during the preliminary their favorite snack and fruit/vegetable, and it was these preferred foods that were used in the food reinforcement task.

Impulsivity

Barratt Impulsiveness Scale-11 (BIS-11) (Patton et al., 1995) was used to assess impulsivity. The BIS-11 consists in a 30 item self-report instrument designed to assess the personality/behavioral construct of impulsivity in attentional (*e.g.* I do not ‘pay attention”), motor (*e.g*. I do things without thinking) and planning (*e.g*. I am more interested in the present than the future) sub-scales. Participants were instructed to rate the frequency in which items apply on a Likert-type scale (1=rarely; 2= occasionally; 3=often; 4=almost always). The scale was computed and scored according to the authors' previous instructions (Patton et al., 1995). The measure was taken at baseline and post weight loss. High scores indicate high levels of impulsivity on all domains

Statistical Analysis

All data were analyzed with Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). Normality of the data was assessed using the Shapiro-Wilk test. Results with a parametric distribution are presented as mean ± standard deviation. Two-way repeated measures ANOVA were performed for changes in body weight, FM, RRV of food and impulsivity at baseline and post-weight loss intervention within each group and between groups (*time x group* interaction). Effects were considered significant at $P < 0.05$. Moreover, in order to assess the magnitude of observed differences, the effect size was computed (eta squared, η2). The values of 0.0099, 0.0588, and 0.1379 were considered mid-range benchmarks for small, medium, and large effect sizes (Richardson, 2011).

Linear multiple regression was used to examine the independent and combined impact of baseline and delta changes in RRV and impulsivity, as predictors of body weight and FM loss. In the first step, RRV and BIS-11 total score were entered and in the second step, the interaction term of both variables was entered. All variables were centered before entering in the linear regression model. We calculated delta change scores observed in the trial by subtracting final measures from baseline measures. Given that delta changes in some of the variables did not present parametric distribution, we used Bivariate Spearman correlations to assess the strength of the relationships between changes in impulsivity scales (attentional, motor and non-planning), RRV (snack and fruit) and changes in body weight and FM loss in the end of the intervention. Significant correlations and differences were considered at the 0.05 level (2-tailed). These relationships were also examined pooling participants into one group given the interventions groups did not differ significantly in changes in weight- or fat loss.

RESULTS

At baseline, no differences were noted between groups for any of the physical and demographic characteristics of participants as reported somewhere else (Hintze *et al.*, *under revision)*. **Figure 1** presents the changes in impulsivity and RRV in completers of the slow and rapid weight loss groups. Overall, a significant time effect with a large effect size was observed for reductions in body weight ($P<0.01$; $\eta 2$: 0.73), no time*group effects were observed ($P=0.169$; $\eta 2$: 0.067), indicating changes between groups were comparable. Body weight and body composition results were reported somewhere else (Hintze *et al*., *under revision)*.

RRV fruit significantly decreased overtime and a large effect size was noted ($P=0.004$; $\eta 2=0.257$), whereas no group*time effect was observed ($P=0.50$; $\eta 2=0.016$). No changes over time ($P=0.428$; $\eta 2=0.023$) or group*time interaction ($P=0.978$) were noted in RRV of snack food.

No effects of time were noted for any component of the impulsivity data, except for the non-planning scale ($P=0.05$; $\eta 2=0.128$). A similar trend was observed for the BIS-11 total score ($P=0.079$; $\eta 2=0.106$). No group*time interactions were observed for any of the variables; however for motor scale of BIS-11, the interaction tended to be significant and a large effect size was noted ($P=0.081$; $\eta 2=0.105$). More precisely for this variable, the slow weight loss group showed increases over time whereas values decreased over time in the rapid weight loss, reflective of a time*group effect for this variable.

Table 1 displays the results of the regression models for baseline RRV, impulsivity and their interaction as independent variables. The results demonstrated that any of the baseline variables (impulsivity traits, RRV of snack and fruit) entered independently were found to predict either body weight or FM loss. The interaction between impulsivity and RRV did not predict final weight and FM loss either. Along the same lines, **Table 2** shows the results of regression models where changes in RRV, impulsivity and their interaction were entered as independent variables. Similar to results from

Table 2, neither the interaction term between delta RRV fruit and impulsivity, nor the RRV of snack food and impulsivity were significant predictors of weight or FM loss. Changes in RRV of snack food independently tended to explain FM loss; however, the results were not significant (β=0.249, P=0.191).

We also ran Spearman bivariate correlations between changes in BIS-11 scales (planning, motor, non-planning, total score) and RRV (fruit and snack) with final outcomes (changes in body weight and FM). RRV of snack food change was the only variable found to predict changes in FM (r = 0.409; P=0.025).

DISCUSSION

This study is among the first to examine the effects of different rates of weight loss on impulsivity and RRV food, as well as to examine whether the interaction between those two constructs would predict final outcomes (changes in body weight and FM) in women living with obesity. The findings of the present study do not support our initial hypothesis that RRV would increase at the end of the intervention. In fact, the results demonstrated an opposite direction to what we have previously hypothesized, given RRV fruit significantly decreased with the intervention and no changes in RRV of snack food were noted. On the other hand, the rate of weight loss seemed to play a role only in impulsivity (motor scale) and total score. Participants in the rapid weight loss group presented lower scores in motor and planning scales, as well as total score of the BIS-11; whereas participants enrolled in the slow weight loss presented a slight increase in motor scale. We did not confirm our second hypothesis either, given that baseline impulsivity and RRV did not interact to predict final body weight and FM loss. Finally, we partially confirmed our third hypothesis, that greater increases in RRV of snack food were associated with poorer FM loss.

Impulsive characteristics were previously found to be greater in subjects who were energy and water deprived (Kirk & Logue, 1997; Manasse et al., 2017), and it was found to be positively associated

with weight management (Best et al., 2012; Brockmeyer, Simon, Becker, & Friederich, 2017; Kishinevsky et al., 2012; Weygandt et al., 2015). In fact, previous evidence has shown that when participants were more energy and water deprived, they presented lower self-control and were less able to wait for food reinforcers (Kirk & Logue, 1997). Along the same lines, a recent study suggested that two constructs of impulsivity inhibitory control and delay discounting may play a role in predicting weight loss outcomes (Manasse et al., 2017). Specifically, poorer general inhibitory control was associated with reduced weight loss after 12 months. Moreover, in a clinical context, greater inhibitory control promoted better adherence to the diet and made it less difficult to resist palatable, high-calorie food items (Manasse et al., 2017). Our study did not confirm these previous findings. In fact, our results demonstrated no impact of dieting on any of the impulsivity traits and none of them were found to predict weight or FM loss. Of note, we did not measure inhibitory control, but we measured impulsivity sub-traits, which may be good indicators of better inhibitory control such as the motor facet impulsivity (acting quickly) and self-control (plans and thinks deliberatively). The difference in the tools used to assess impulsivity might explain the discrepancy in the results between studies.

Despite the fact impulsivity in our study was not a significant weight loss predictor and that it did not change over time, the total scores we obtained were relatively low. Comparing other studies that used the BIS-11, the scores obtained from our sample were similar to those previously reported for normal-weight subjects (Babbs et al., 2013; Siep et al., 2009) and below those observed in individuals persons living with overweight and obesity (Babbs et al., 2013; Schiff et al., 2016; Weller et al., 2008). According to our observations, it would seem that our participants did not present impulsive characteristics, at least when using the BIS-11 for assessment of impulsivity. This may partially explain the lack of associations between impulsivity and total weight and FM loss.

In our study, RRV fruit significantly decreased with the intervention. This finding might be associated with the habituation theory (Swithers & Hall, 1994); which states that repeated exposure to a food item causes a decrease in the response for that specific food, increasing satiation for that food (Swithers & Hall, 1994). Accordingly, a handful of previous studies conducted in both animals and humans demonstrated decreased RRV when participants were frequently exposed to only one food item (Myers Ernst & Epstein, 2002; J. Temple et al., 2008; Jennifer L Temple, Chappel, Shalik, Volcy, & Epstein, 2008). In our study women were allowed to choose a wide array of foods; and considering that in order to lose weight it is preferable to avoid high-dense energy foods items, individuals who lose weight commonly exchange their favourite snack for lower energy-dense food items such fruits and vegetables (Lawton, n.d.). Accordingly, our participants were encouraged to incorporate this exchange on regular basis, which potentially increased their fruit consumption during the weight loss program and consequently it decreased their RRV fruit.

Conversely, no group differences were noted over time for the RRV of snack food in agreement with previous evidence (Cameron, Goldfield, Cyr, & Doucet, 2008). On the other hand, other studies suggested that caloric restriction increases RRV of snack food after short (Epstein et al., 2003; Polivy et al., 2005; Raynor & Epstein, 2003) and long caloric restriction periods (Best et al., 2012); which might lead to increases in EI, an effect that could compromise weight loss and maintenance.

Indeed, our results also demonstrated that RRV of snack food changes were positively associated with changes in FM. In other words, increases in RRV were associated with higher adiposity at the end of the study. In accordance with our results, previous evidence demonstrated that RRV predicts BMI increases after 12-months of follow up in both adults (Carr et al., 2014) and children (Feda, Roemmich, Roberts, & Epstein, 2015; Hill, Saxton, Webber, Blundell, & Wardle, 2009); while decreases in RRV food were found to predict greater weight loss at 6 months of weight loss in adults living with obesity (Buscemi et al., 2014).

Along the same lines, several evidence has associated greater RRV of snack food with increased EI (Brace & Yeomans, 2016; Epstein et al., 2011, 2004; Epstein, Temple, et al., 2007). A recent study has shown that food reinforcement, but not impulsivity, was independently associated with EI in adults, suggesting that food reinforcement might be a more powerful independent predictor of EI (Brace & Yeomans, 2016). In the long-term, the change in food reinforcement could complicate the achievement and maintenance of a negative energy balance thus compromising weight loss and weight loss maintenance.

The present study has some limitations. First, our sample size is limited to 30 pre-menopausal women, and this study was composed of relatively “healthy” individuals, which delimits the finding for this specific population. Second, we measured impulsivity with a questionnaire that was not specifically developed to measure impulsivity towards food. Accordingly, the use of more specific tools such as computer tasks could have led to different results. Of note, previous evidence demonstrated positive and significant correlations between BIS-11 and time reaction to high fat pictures (Meule & Kübler, 2014). Finally, the correlations presented in the present study cannot infer causality.

On the other hand, our results are strengthened by its design (randomized clinical trial), as well by novelty of the study. Other aspects of the methods of our study such as the use of gold-standard techniques in the measure of body composition and control for the phase of the menstrual cycle are other aspects that strength our results. Finally, both groups lost a similar amount of weight, which decreases the impact of the magnitude of the weight loss on the variables included in the study.

In conclusion, our results suggest that caloric restriction affects RRV for fruit in women. Moreover, the motor scale might be affected by different rates of weight loss. On the other hand, only changes in RRV of snack food were found to predict fat loss, whereas the interaction between RRV and

impulsivity traits was not found to predict final weight and/or FM loss. The results reinforce the need to address changes in RRV during weight loss in order to optimize the outcome of weight loss interventions.

Table and Figure Legends

Table 1. Summary of hierarchical regression analysis for baseline variables predicting changes in body weight and FM

RRV: Relative Reinforcing Value; BIS: Barratt Impulsiveness Scale; BW: Body Weight; FM: Fat Mass

Table 2. Summary of hierarchical regression analysis for delta changes in variables predicting changes in body weight and FM

RRV: Relative Reinforcing Value; BIS: Barratt Impulsiveness Scale; BW: Body Weight; FM: Fat Mass

Figure 1. Changes in Impulsivity, Relative Reinforcing Value of food at baseline and post dietary intervention

Data presented as mean ± SD; BIS: Barratt Impulsiveness Scale; BCT: Behavioural Choice Task; **significant differences**

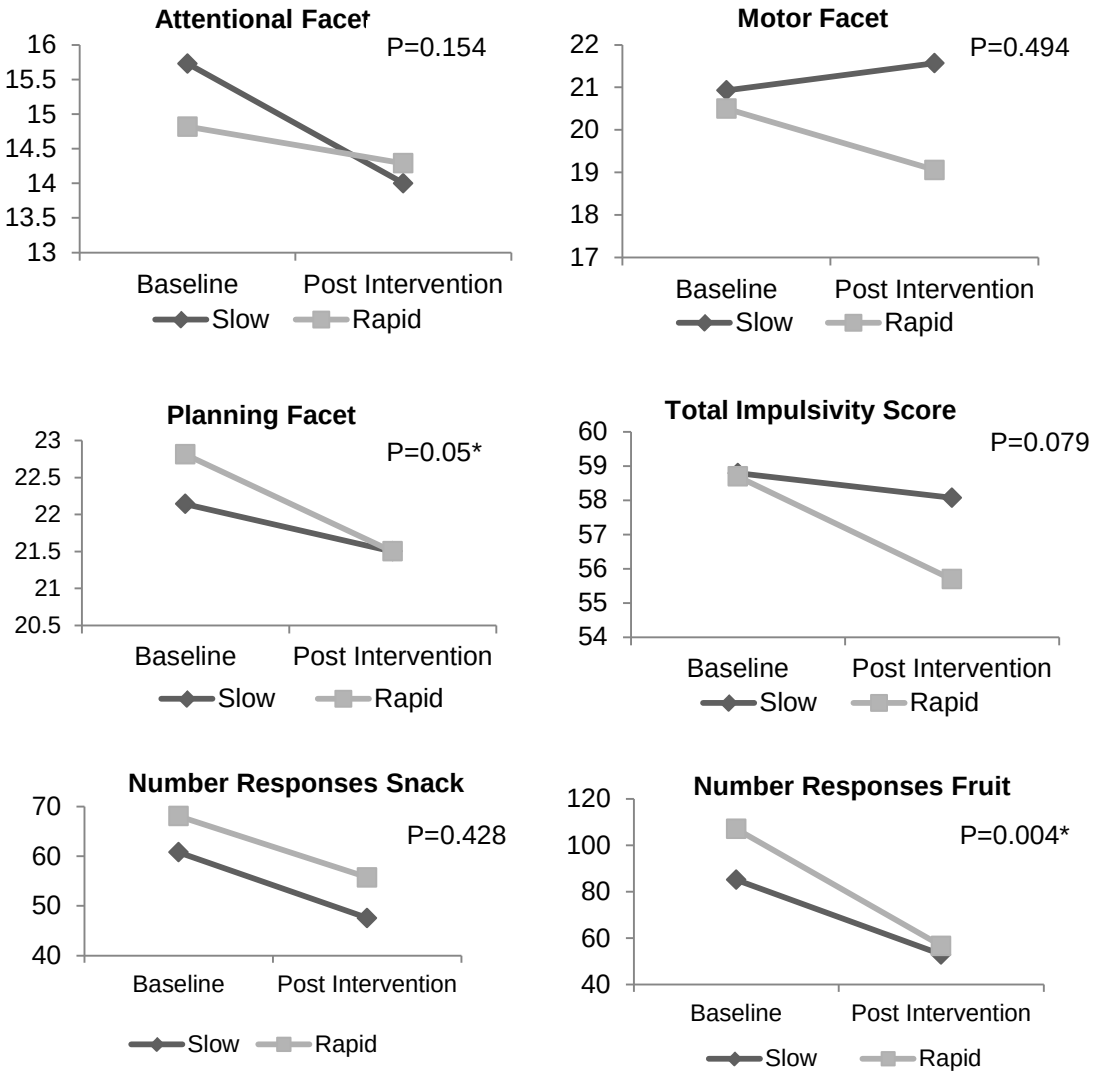
Attentional Facet
P=0.154
16
15.5
15
14.5
14
13.5
13
Baseline
Post Intervention
Slow
Rapid
Motor Facet
P=0.494
22
21
20
19
18
17
Baseline
Post Intervention
Slow
Rapid
Planning Facet
P=0.05*
23
22.5
22
21.5
21
20.5
Baseline
Post Intervention
Slow
Rapid
Total Impulsivity Score
P=0.079
60
59
58
57
56
55
54
Baseline
Post Intervention
Slow
Rapid
Number Responses Snack
P=0.428
70
60
50
40
Baseline
Post Intervention
Slow
Rapid
Number Responses Fruit
P=0.004*
120
100
80
60
40
Baseline
Post Intervention
Slow
Rapid

Figure 1

Table 1

	Δ BW				Δ FM			
Baseline Variables	r	R2	β	P	r	R2	β	P
Step 1	0.071	0.005			0.176	0.031		
RRV fruit			-0.69	0.734			-0.153	0.436
BIS-11 Total score			-0.047	0.818			0.055	0.777
Step 2	0.268	0.072			0.25	0.062		
RRV fruit			-0.069	0.732			-0.168	0.395
BIS-11 Total score			0.354	0.327			0.314	0.355
RRV fruit x BIS-11 Total Score			0.476	0.183			0.317	0.35
Step 1:	0.083	0.007			0.202	0.041		
RRV snack			0.062	0.749			-0.112	0.55
BIS-11 Total score			-0.059	0.76			-0.162	0.389
Step 2	0.084	0.007			0.274	0.075		
RRV snack			.064	.750			-0.764	0.452
BIS-11 Total score			-.062	.762			-0.664	0.512
RRV snack x BIS-11 Total Score			0.01	0.959			-0.191	0.327

Table 2

	Δ BW				Δ FM			
	r	R2	β	P	r	R2	β	P
Step 1	0.139	0.019			0.105	0.011		
Δ RRV fruit			0.139	0.473			0.092	0.634
Δ BIS-11 Total score			0.004	0.997			-0.49	0.8
Step 2	0.151	0.023			0.167	0.028		
Δ RRV fruit			0.109	0.62			0.028	0.898
Δ BIS-11 Total score			0.004	0.985			-0.043	0.827
ΔRRV fruit x Δ BIS-11 Total Score			0.068	0.757			0.145	0.509
Step 1	0.142	0.02			0.265	0.07		
Δ RRV snack			-0.033	0.866			0.249	0.191
Δ BIS-11 Total score			0.718	0.479			0.105	0.575
Step 2	0.17	0.029			0.282	0.08		
Δ RRV snack			-0.054	0.786			0.227	0.252
Δ BIS-11 Total score			0.161	0.428			0.13	0.511
Δ RRV snack x Δ BIS-11 Total Score			0.098	0.635			0.101	0.617

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Chapter VI: Article III

Running Head:

Appetite changes after 7-day of caloric restriction predict final weight and fat mass loss in pre-menopausal women living with obesity

This paper is currently in preparation to be submitted

Appetite changes after 7-day of caloric restriction predict final weight and fat mass loss in pre-menopausal women living with obesity

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ABSTRACT

Background: Long and short-term caloric restriction are known to affect appetite, olfaction, energy intake (EI) and resting energy expenditure (REE). However, it is still uncertain if acute changes in those variables might be associated with poorer treatment outcomes. Accordingly, the objective of the present study was to identify acute-response predictors of successful weight loss in women living with obesity. **Methods**: The study involved 36 women with obesity. Body weight, body composition (DXA), REE (indirect calorimetry), olfactory performance (Sniffin' Sticks), appetite and palatability (Visual Analogue Scale) were measured at baseline, after 7-day period of caloric restriction as well as post-intervention. Eating behaviours (Three Factor Eating Questionnaire) were measured at baseline and post-intervention. **Results**: Thirty women completed the study. Significant negative correlations were noted between early changes in fasting fullness and final body weight (r= -0.415; P=0.023) and fat mass (FM) (r=0.389, P=0.034) loss. Similarly, changes in fasting desire to eat were also associated with fat loss (r= -0.457; P=0.011). Moreover, changes in 7-day AUC desire to eat was negatively associated with final FM loss (r= -0.353; P=0.05). Early changes in SQ desire to eat at 60 min (r=-0.403; P=0.023) and at 180 min (r=0.404; P=0.023) were also associated with fat loss. Changes in eating behaviours, REE and oro-sensory variables were not associated with final body weight or FM loss. **Conclusion**: Our results suggest that increases in fasting subjective appetite in the first week of caloric restriction predict greater diet-induced weight and FM loss, whereas increases in postprandial subjective appetite ratings predict poorer fat loss.

KEY-WORDS: weight loss; predictors; energy expenditure; appetite; energy intake; reward

INTRODUCTION

The ever-increasing worldwide prevalence of obesity supports the urgent need for improving weight loss interventions (Sturm & Hattori, 2013). However, the large variability in response to weight loss interventions (Blundell et al., 2005; King, Hopkins, Caudwell, Stubbs, & Blundell, 2008), as well as the often high rates of weight loss relapse (Tsai & Wadden, 2005) creates a huge challenge for patients living with obesity. Some participants achieve large weight and FM loss whereas other subjects report very little reductions in body weight, or might even note increases in their body weight at the end of the intervention (Blundell et al., 2005; King et al., 2008).

As such, several studies have been conducted to investigate which factors might be related to greater weight loss outcomes and weight maintenance. Pre-intervention variables such as higher maximum lifetime body weight (Byrne, Cooper, & Fairburn, 2004; Weiss, Galuska, Kettel Khan, Gillespie, & Serdula, 2007), baseline body weight (Byrne et al., 2004; Weiss et al., 2007) and resting energy expenditure (REE) (Vogels, Diepvens, & Westerterp-Plantenga, 2005) predicted greater weight loss; whereas higher dieting frequency (number of previous periods under caloric restriction to lose weight) (Pasman, 1999; Vogels et al., 2005), fasting appetite scores (Drapeau et al., 2007) have been reported to predict the poorer weight loss. In the case of prospective predictors, it has been reported that poorer initial weight loss response (below percentile 50) predicted smaller weight loss (Astrup & Rössner, 2000), whereas more pronounced decrease in REE after 8 weeks of very low caloric restriction diet was associated with higher weight loss (Pasman, 1999).

While some studies have investigated predictors of weight loss by associating final outcomes (*e.g.* poorer weight loss) to final responses (*e.g.* decreases in REE) (Astrup & Rössner, 2000; Pasman, 1999), others have used either historical or pre-treatment variables to predict final weight loss outcomes as above described (Byrne et al., 2004; Pasman, 1999; Vogels et al., 2005; Weiss et al., 2007). To our knowledge, no study has investigated whether early responses to a weight loss

intervention is predictive of final weight loss outcomes. This is an important gap in the literature given short-term caloric restriction increases appetite, and oro-sensory variables such as palatability and olfaction, and also decreases REE (Alajmi et al., 2016; Cameron, Goldfield, & Doucet, 2012; Cameron, Goldfield, Finlayson, Blundell, & Doucet, 2014; King et al., 2011), which collectively could undermine the maintenance of sustained negative energy balance needed for weight loss. In addition, it is also known that eating behaviours measured with the Three Factor Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985) might be significant mediators of final outcomes in individuals seeking for weight loss treatments. In fact, increases in dietary cognitive restraint (Bas & Donmez, 2009; Gilhooly et al., 2007; Tremblay, Lepage, Panahi, Couture, & Drapeau, 2015), in parallel to decreases in habitual disinhibition (Bas & Donmez, 2009; Tremblay et al., 2015) and in the susceptibility to hunger (Bas & Donmez, 2009; Batra et al., 2013; Gilhooly et al., 2007), have been reported to be positively associated with the magnitude of weight loss in previous studies; which opposes the compensatory mechanisms of energy balance previously discussed.

To our knowledge, no study has been conducted to investigate whether early changes in REE, appetite, olfactory performance and palatability induced through caloric restriction could serve as predictors of final treatment outcomes. In fact, the relative importance that acute changes in appetite-related and energy metabolism factors play in influencing post-intervention weight and fat loss remains unknown. As such, the objective of the present study was to identify whether early changes in variables related to energy balance would be predictive of successful weight loss in women living with obesity. Considering the role that eating behaviours might play in EI and weight loss, we added changes (measures post-intervention-baseline measures) in cognitive restraint, habitual disinhibition and susceptibility to hunger as co-variates in the model to predict final body weight and fat loss. We hypothesized that increases in appetite, oro-sensory variables (olfaction and palatability) and decreases in REE measured in the first week of caloric restriction would be associated with poorer fat and body weight loss in women living with obesity subjected to diet-induced weight loss. More specifically the association between appetite measures and final outcomes (body fat and body weight

loss) should be mediated by eating behaviours, higher cognitive dietary restraint as well as lower habitual disinhibition and susceptibility to hunger.

MATERIALS AND METHODS

Subjects

A total of 36 overweight and obese pre-menopausal women were recruited for this weight loss program. Thirty completed the intervention. The inclusion criteria were as follows: 27≥BMI≥40 kg/m^2, 18 years and older, waist circumference >88 cm, weight-stable (±2 kg last 6 months), be sedentary (less than 150 minutes per week), no history of alcohol or drugs abuse, no food allergies, non-smoker, pre-menopausal with a regular menstrual cycle, not pregnant, not taking any medication that can interfere in EI and EE (*e.g.* psychiatric medications, appetite suppressants), normal scores in Binge Eating (Gormally, Black, Daston, & Rardin, 1982) and depression symptoms (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Furthermore, participants who self-reported having any history or evidence of: 1) cardiovascular disease, peripheral vascular disease, or stroke, 2) diabetes (75g oral glucose tolerance test), 3) known renal and liver disease, 4) asthma requiring therapy, plasma cholesterol > 8 mmol/L, 5) systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, 6) previous history of inflammation disease, or cancer, 7) untreated thyroid or pituitary disease, 8) medications that could affect cardiovascular function and/or metabolism, 9) food allergies., could not be included in the study (n=12). All participants gave their written informed consent to participate in this study, which was approved by the University of Ottawa, Research Ethics Board.

Study design and procedures

Participants who met all inclusion criteria and completed all measures of the preliminary session were then randomized in two distinct groups: fast weight loss (-1000 kcal/day) and slow weight loss (-500kcal/day). The total duration of the program was thus 10 and 20 weeks for the fast and slow

groups, respectively. The details of this study are under review elsewhere (Hintze et al., *under revision)*. Both groups were assessed at baseline, 5 to 7 days after the onset of the dietary intervention and at the post-intervention visit (10 or 20 weeks). Body composition, REE, fasting and postprandial appetite sensations, olfactory performance and palatability were assessed.

Nutritional intervention

The nutritional interventions consisted of caloric restrictions of either -500 kcal/day or -1000 kcal/day, for the slow and fast weight loss, as described previously (Hintze et al., *under revision*). These restrictions were calculated from measured individual daily EE. Total EE was calculated from a combination of indirect calorimetry and biaxial accelerometer as previously described (Cameron et al., 2016). To achieve and maintain the prescribed energy restricted diets (-500 or -1000 kcal/day), each participant received detailed explanations about the Food exchange system - Canadian Diabetes Association (Lawton, n.d.), which is an easy way for subjects to monitor their food intake (Cameron, Goldfield, Cyr, & Doucet, 2008; Doucet et al., 2000). In this system, foods are categorized into the seven following groups: milk and dairy products; meat and substitutes; vegetables (one portion containing 7g of carbohydrates); fruits; bread and cereals; fat (including oils, margarine, butter, nuts and seeds); unlimited consumption. This method allows participants to select foods that they enjoy during weight loss, however in smaller quantities.

Measures

Body composition

Body weight was measured to the nearest 0.1 kg on a calibrated balance (HR-100; BWB-800AS, Tanita Corporation,Arlington Heights, IL.,USA) and standing height was measured using a wall stadiometer (Tanita HR-100, Tanita Corporation of America, Inc, Arlington Heights, IL). Fat Free Mass (FFM) and FM were measured using dual energy X-ray absorptiometry – DXA (Lunar Prodigy,

General Electric, Madison, WI, USA). In our laboratory, the coefficient of variation and correlation for body fat percentage measured by DXA scanner in 12 healthy participants were 1.8% and r=0.99, respectively (McNeil et al., 2014).

Resting Energy Expenditure

REE was assessed by indirect calorimetry using the ventilated hood technique and the Vmax Encore 29 N metabolic cart (SensorMedics Corporation, Yorba Linda, CA, USA). Concentrations of CO_2 and O_2 were measured during 30 min (5 min of acclimatization and the average of the following 6^{th}-25^{th} min were included in the analysis) and Weir's equation (Weir, 1949) was used to determine 24-hour resting EE. Measurements were taken between 7:00 and 9:30 AM after 12-hour fasting period. The temperature of the room was maintained at 22 °C. Ethanol burning tests were performed along the intervention in order to control quality of the measurements, as previously described (Blond et al., 2011; Cooper et al., 2009). Tests demonstrated -5% and 4.76% difference in CO2 and O2 measures, respectively.

Appetite ratings

Appetite ratings were measured using a 100-mm VAS (Marsh-Richard, Hatzis, Mathias, Venditti, & Dougherty, 2009), fasting, at 0, 30, 60, 90, 120, 180 min after a standardized breakfast. Desire to eat, hunger, fullness and PFC were rated using the following questions: 1) "How strong is your desire to eat?" (Very weak- Very strong); 2) "How hungry do you feel?" (Not hungry at all- As hungry as I have ever felt); 3) "How full do you feel?" (Not full at all- Very full), and 4) "How much food do you think you could eat?" (Nothing at all- A large amount). The measures were used to calculate the satiety quotient (SQ) for each appetite sensation (Green & Delargy, 1997). The trapezoid method was used to calculate AUC for each appetite sensation, as previously described (Drapeau et al., 2007).

Nasal Chemosensory and palatability

Nasal chemosensory performance was measured with Sniffin' Sticks (Burghart Instruments, Wedel, Germany). The assessment consisted in a 3-test battery of 16 odorized markers that measure odor detection threshold, odor discrimination, and odor identification as previously described (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). The total score was calculated with the sum of these 3 indicators. The order of each task was the same for all participants (threshold, discrimination, identification) and they were administered at 90 min after a standard breakfast. Palatability was measured using a 100 mm VAS (Blundell & Hill, 1986), taken right after a standard breakfast.

Eating behaviours

TFEQ was used to assess cognitive aspects of dietary restraint, habitual disinhibition, and susceptibility to hunger. The questionnaire has 54 items and the answers are given with Likert-type scale responses (*e.g.* "not like me" to "describes me perfectly."). Dietary Restraint reflects behaviors used to control dietary intake (*e.g.* "I consciously hold back at meals in order not to gain weight"), whereas the habitual disinhibition indicates loss of control while eating (*e.g.* "Sometimes when I start eating, I just can't seem to stop"). Susceptibility to hunger measures the response to EI, such feelings and perceptions of hunger (*e.g.* "I often feel so hungry that I just have to eat something").

Statistical Analysis

Variables are presented as median and interquartile rages since not all variables presented a parametric distribution. A non-parametric Wilcoxon test was used to compare the measures obtained in both groups at baseline and after the first week of intervention. Given there were no group differences on changes in body composition (Hintze et al., *under revision*), participants from each group were pooled for analysis (N=30). We calculated the early changes observed in the first week subtracting the 7-day measures from baseline measures. Eating behaviours, Body weight and

composition changes were obtained from subtracting final post-intervention values from baseline values. Bivariate Spearman correlations were used to assess the strength of the relationship between changes in fasting and postprandial appetite, REE, smell capacity and palatability measured in the first week of caloric restriction with pre-post changes in body weight, FM and FFM. The relationship between post-pre changes in eating behaviours (dietary restraint, habitual disinhibition and susceptibility to hunger) and final outcomes (body weight and FM loss) were also tested. Significant correlations and differences were considered at the 0.05 level (2-tailed). The enter method in hierarchical linear multiple regression was used to define whether changes in eating behaviours mediate the relationship between appetite measures and final outcomes (probability to enter in the model was set at $P<0.05$). All data were analyzed with Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the intervention period, 6 subjects (or 16.7%) stopped the study. Reasons included lack of motivation (n=3), lack of time (n=2), and personal/health problems not related to the trial (n=1). As such, 30 participants completed the intervention and were included in the analyses (slow: n=14; fast: n=16).

Early changes in REE, appetite sensations and oro-sensory variables are shown in the **Table 1.** We observed significant changes in REE, fasting and SQ desire to eat, hunger and PFC in the first week of intervention. Trends were also noted for AUC desire to eat and PFC, however the results were not statistically significant ($P=0.075$ and $P=0.072$, respectively). Cognitive dietary restraint significantly increased ~32% ($P<0.01$) after intervention, whereas habitual disinhibition and susceptibility to hunger decreased ~24% ($P<0.01$) and ~39% ($P<0.01$), respectively.

Table 2 presents the bivariate Spearman correlations between final changes in body weight and composition (FM, FFM) and early changes in fasting appetite, smell performance and palatability in women who completed the program (n=30). Significant and negative correlations were noted between Δ 7-day Fasting Fullness and Δ Final Body Weight (r= -0.415; P=0.023) and FM (r=0.389, P=0.034), highlighting that early increases in fullness were predictive of greater weight and FM loss at the end of the dietary intervention. However, changes in fasting desire to eat were negatively correlated with fat loss (r= -0.457; P=0.011), suggesting that increases in fasting desire to eat measured in the first week of caloric restriction were associated with greater total weight loss at the end of the intervention.

Changes in postprandial AUC desire to eat were positively associated with final FM loss (r= 0.353; P=0.05), indicating that increases in postprandial appetite measured in the first week of intervention predicts poorer fat loss. On the other hand, increases in SQ desire to eat at 60 min and at 180 min were also negatively associated with final fat loss (r=-0.403 P=0.023 and r=0.404; P=0.023, respectively), demonstrating that increases in satiety in the first week also predicts greater outcomes (fat loss).

Changes in oro-sensory variables (palatability and olfaction) and REE were not found to be predictive of changes in body weight, FM or FFM. Along the same lines, post-pre changes in cognitive restraint, habitual disinhibition and susceptibility to hunger were not significantly associated with final outcomes (body weight and FM loss).

The hierarchical linear multiple regression results revealed that changes in eating behaviours do not mediate the association between early changes in appetite measures and final outcomes FM loss (P=0.556). Furthermore, only early changes in fasting desire to eat and fasting fullness were found to

be significant predictors of FM loss, explaining approximately 46% of the variance in FM in our sample **(Table 3)**.

DISCUSSION

Our results demonstrated that only appetite rating changes in the first week of intervention were significant predictors of final body weight and composition. Increases in fasting desire to eat during the first week were associated with greater weight and FM loss at the end of the diet-induced weight loss, which is contrary to our hypotheses. On the other hand, increases in postprandial appetite were associated with poorer FM loss in our participants. Along the same lines, increases in satiety (fasting fullness and SQ desire to eat) during the first week were found to be associated with greater FM loss. Changes in eating behaviours variables were not found to predict final outcomes or mediate the relationship between early appetite changes and final body weight and FM loss. As such, our hypotheses were partially supported. To our knowledge, this is the first study to investigate whether early changes in energy balance variables are related final treatment outcomes (fat loss).

Our results show that changes in fasting fullness and desire to eat are significant predictors of final weight loss. Accordingly, fasting appetite measures at baseline were found to be significant predictors of final weight loss in previous studies (Drapeau et al., 2007; Gilbert, Drapeau, Astrup, & Tremblay, 2009). More precisely, higher baseline ratings for desire to eat predicted a poorer response to a caloric restriction program; whereas increases in fasting hunger, desire to eat, PFC over the intervention were also associated with smaller weight loss (Drapeau et al., 2007). Conversely, our results demonstrated that changes in fasting desire to eat and fat loss are negatively correlated, suggesting that increases in fasting desire to eat measured in the first week of a caloric restriction are actually associated with greater weight loss. Considering the association presented an opposite direction to what we have initially hypothesized, it would be plausible to consider that this relationship was mediated by cognitive restraint, given the association between this variable and EI (French,

Epstein, Jeffery, Blundell, & Wardle, 2012; Graham, Gluck, Votruba, Krakoff, & Thearle, 2014; Keränen, Strengell, Savolainen, & Laitinen, 2011). In other words, although participants were feeling hungrier, increases in cognitive restraint could have opposed the increase in the drive to eat, explaining our association. Surprisingly, none of the eating behaviours variables were significant in the model to predict final FM loss. Alternatively, it is tempting to speculate that individuals who reported greater hunger and desire to eat during the first week, were also the participants who presented the greater compliance to the dietary intervention. Increased compliance to the energy restricted diet should indeed produce more apparent increases in the desire to eat, and if maintained, greater final weight loss. Along the same lines, it has been previously reported that for each kg of fat lost after a caloric restriction intervention, participants experienced a pre-post increase in fasting desire to eat of 5.8mm and a 3.6mm decrease in fasting fullness in their rating on 150mm VAS (Gilbert et al., 2009).

Although we did not observe significant changes in postprandial AUC in the first week of intervention, our values reflect a trend toward statistical significance. Previous research conducted in our laboratory (Doucet, Pomerleau, & Harper, 2004) demonstrated that after 4-days of caloric restriction (-800kcal/day), participants presented decreases in the postprandial desire to eat, hunger, and PFC and an increase in fullness in response to the standard meal. Along the same lines, SQ for hunger, desire to eat and PFC increased in the first week of caloric restriction, indicating a greater satiating effect of the standard breakfast. Those results indicate that participants may be more sensitive to food-induced satiety signalling early after the onset of a caloric restriction, and this may be maintained during intervention to produce greater final weight loss. In fact, we noted in our study that increases in SQ desire to eat measured at 60 and 180 min after 1-week of caloric restriction were both predictors of FM loss. Increases in SQ and its association with weight loss were reported in a previous study; however, the results only demonstrated increases in SQ after participants completed the whole weight loss intervention (Drapeau et al., 2007), therefore negating comparisons to our study that examined early treatment responses.

There is a handful of studies describing the effects of short-term caloric restriction on increases in palatability and olfaction (Cameron et al., 2012, 2014, 2016; Epstein, Truesdale, Wojcik, Paluch, & Raynor, 2003). Moreover, it is known that a strong association exists between palatability and EI (Johnson & Wardle, 2014; Sørensen, Møller, Flint, Martens, & Raben, 2003), whereas EI increases as palatability increases. However, our results demonstrated no changes in these variables during the first week of caloric restriction. We believe that the main reason for the discrepancy between our results and the above-cited studies is that we measured palatability of participant' personalized breakfast whereas other studies measured palatability of high-energy snacks. Differences in the methods to measure olfaction might also explain the difference in our results compared to the other studies. Firstly, we measured olfaction only in women living with obesity. The study above mentioned included normal-weight participants from both sexes. Furthermore, the breakfast total EI of our participants in average was higher than the breakfast mentioned in previous studies, which might also have affected the results.

At the end of the weight loss intervention we observed significant increases in cognitive restraint and decreases in habitual disinhibition and susceptibility to hunger, which is in line with previous evidence (Bas & Donmez, 2009; Batra et al., 2013; Gilhooly et al., 2007; Stunkard & Messick, 1985; Tremblay et al., 2015). On the other hand, these changes were not significant predictors of final body weight or FM loss in our study. Overall, the literature shows a discrepancy regarding the role of eating behaviours in final weight loss. Increase in cognitive restraint was found to be associated with both: greater weight loss (Keränen et al., 2011; Urbanek, Metzgar, Hsiao, Piehowski, & Nickols-Richardson, 2015) and has been found to not influence weight loss (Bas & Donmez, 2009; Drapeau et al., 2007) in previous studies. Along the same lines, decreases in disinhibition seem to be mainly associated with greater weight loss (Bryant, Caudwell, Hopkins, King, & Blundell, 2012), whereas other studies indicated that only decreases in susceptibility to hunger was associated with final weight loss in women under dieting (Batra et al., 2013). These discordant results could be due many factors, such

as the difference in weight loss interventions in terms of design, duration and type of treatment offered.

Investigations on appetite control demonstrated that FFM and REE are strong predictors of acute EI (Blundell et al., 2012; Caudwell et al., 2013; McNeil et al., 2017) (higher FFM, higher REE and greater EI). However, when comes to predict daily EI, a combination between appetite measures and EE might have better prediction (Caudwell et al., 2013; McNeil et al., 2017). A secondary data analysis performed in our laboratory demonstrated that appetite ratings (PFC) and RMR were significant predictors of daily EI (McNeil et al., 2017). Given that REE is associated with EI and that EI plays an important role in weight management, we tested whether early changes in REE could predict final outcomes. Our results demonstrated that despite a significant early decrease in REE, the acute variations in REE did not predict final weight or FM loss. It is important to note some differences between the present study and the studies above cited. Firstly, we did not assess the association between REE and EI, but REE and weight loss. What is more, our participants were under dieting which *per se* plays a role in REE, whereas the participants from the other studies were not. Accordingly, it seems that when individuals are under caloric restriction, early changes in other variables, but no in REE, play a more significant role in weight loss. Studies involving weight loss predictors demonstrated that lower REE at baseline predict lower weight loss (Vogels et al., 2005) and maintenance (Buscemi, Verga, Caimi, & Cerasola, 2005; Pasman, 1999; Weinsier et al., 2000). However, those studies assessed the relationship between baseline measures of REE and weight loss, whereas our study tested the association between early changes in REE and final outcomes (body weight and FM loss). This difference contributes to explain the discrepancy between our results and previous findings.

The present study has some limitations. First, our sample size is limited to 30 pre-menopausal women, and this study was composed of relatively “healthy” individuals, which delimits the

generalizability of the findings to this specific population. Secondly, the correlations presented in the present study cannot infer causality, although the 7-day changes predated pre-post intervention effects, offering some insight into temporal sequencing of the relationships observed. Finally, we did not measure participant compliance during the diet. On the other hand, our results are strengthened by the novelty of the design and the findings in the present study, as well as the use of gold-standard techniques in the measures of EE and body composition. Moreover, other aspects of our methods such as the individualized breakfast and control for the phase of the menstrual cycle, also they strengthen our findings.

In conclusion, our results suggest that increases in fasting appetite in the first week of caloric restriction predict better weight and fat-loss at the end of the intervention. Participants who present more important increases in fasting appetite may be more compliant to the diet, presenting better outcomes in terms of weight and fat loss. On the other hand, increases in postprandial appetite were associated with poorer FM loss. Along the same lines, increases satiety in the first week also predicted better FM loss in the end of the intervention in women living with obesity. Overall our results demonstrated appetite ratings play a major role in final outcomes than early changes in REE and eating behaviours do, suggesting the importance of controlling these variables in the beginning of the intervention in order to improve the chances of success in weight loss treatments. The effects of early changes in appetite on weight loss maintenance remain to be investigated.

Table and Figure Legends

Table 1. First week changes in REE, appetite sensations and oro-sensory variables all participants

Data presented as median interquartile range (IR); AUC: Area Under the Curve; SQ: Satiety Quotient; significant differences $p<0.05$

Table 2. Bivariate Spearman correlations between final changes in body composition, body weight changes and 7-day changes in appetite and oro-sensory variables (n=30)

FM: Fat Mass; FFM: Fat Free Mass; BW: Body weight; AUC: Area Under the Curve; SQ: Satiety Quotient; PFC: Prospective Food Consumption ***significant correlation at the 0.05 level (2-tailed)**

Table 3. The amount of variance (R2) and the standardized regression coefficients (b) for the significant predictors of FM loss after controlling for eating behaviors

FM: Fat Mass; ***significant in the model**

Table 1.

	Baseline	7 days	P	Δ	Δ %
Resting Energy Expenditure	1526.80 (200.35)	1483.82 (194.73)	0.033	↓40.93	↓2.34
Fasting Desire to eat (mm)	61.13 (31.88)	70.75 (37.94)	0.004	↑11.38	↑19.23
Fasting Hunger (mm)	54.87(31.94)	72.62 (28.63)	0.001	↑15.13	↑21.71
Fasting PFC (mm)	50.50 (22.81)	64.75 (30.19)	0.001	↑10.25	↑16.15
Fasting Fullness (mm)	11.13 (22.13)	5.25 (22.69)	0.665	↓0.13	↓7.14
AUC Desire to Eat (mm.min)	10106 (8461.88)	7811.25 (9324.38)	0.075	↓900	↓18.10
AUC Hunger (mm.min)	9168.75 (8371.88)	7702.50 (8426.25)	0.192	↓828.75	↓13
AUC PFC (mm.min)	11456.25 (7353.75)	10005(9425.63)	0.072	↓1710	↓16.58
AUC Fullness (mm.min)	24191.25 (7365)	24401.25 (8465.63)	0.165	↑1458.75	↑5.61
SQ at 60 min Desire to Eat	9.58 (6.29)	13.49 (9.37)	0.032	↑1.74	↑14.25
SQ at 180 min Desire to Eat	6.8 (5.64)	8.94 (9.23)	0.003	↑2.84	↑12.53
SQ at 60min Hunger	9.46 (5.89)	12.61 (7.72)	0.011	↑3.31	↑39.26
SQ at 180min Hunger	6.17 (5.11)	9.25 (5.46)	0.002	↑3.82	↑37.44
SQ at 60min Fullness	14.97 (11.51)	14.58 (7.73)	0.734	↓0.32	↓1.44
SQ at 180min Fullness	10.54 (8.51)	10.73 (7.37)	0.491	↑0.81	↑0.95
SQ at 60min PFC	7.10 (6.27)	9.88(7.49)	p<0.001	↑1.74	↑9.28
SQ at 180min PFC	4.45 (4.45)	7.34 (3.99)	p<0.001	↑1.53	↑10.77
Smell Threshold	9 (3.13)	9 (4.94)	0.574	0	0
Smell Discrimination	12 (1)	13 (3)	0.86	0	0
Smell Identification	13 (2)	13.5 (3)	0.206	↑0.40	↑3.94
Smell Total Score	34.5 (5.31)	36.37 (6.44)	0.186	↑1.75	↑5.09
Palatability	84 (20.56)	87.88 (24.88)	0.658	↑0.50	↑0.53

Table 2.

Δ 7 days	Final Δ BW	Final Δ FM	Final Δ FFM
Δ Resting Energy Expenditure	-0.092	-0.142	-0.056
Δ BW - 7 days	0.283	-0.058	**0.396*** (P=0.03)
Δ Fasting Desire to eat (mm)	-0.144	**-0.457*** (P=0.011)	0.345
Δ Fasting Hunger (mm)	0.061	-0.128	0.261
Δ Fasting PFC (mm)	0.246	0.214	0.191
Δ Fasting Fullness (mm)	-0.415* (P=0.023)	**-0.389*** (P=0.034)	-0.219
Δ AUC Desire to Eat (mm.min)	-0.032	0.217	-0.18
Δ AUC Hunger (mm.min)	0.143	0.353* (P=0.05)	-0.137
Δ AUC PFC (mm.min)	0.128	0.34	-0.137
Δ AUC Fullness (mm.min)	0.058	-0.253	0.279
Δ SQ at 60 min Desire to Eat (mm/100 kcal)	-0.211	**-0.403*** (P=0.027)	0.191
Δ SQ at 180 min Desire to Eat (mm/100 kcal)	-0.161	**-0.404*** (P=0.027)	0.238
Δ SQ at 60min Hunger (mm/100 kcal)	0.021	-0.124	0.196
Δ SQ at 180min Hunger (mm/100 kcal)	0.024	-0.119	0.231
Δ SQ at 60min Fullness (mm/100 kcal)	0.174	0.172	0.16
Δ SQ at 180min Fullness (mm/100 kcal)	0.233	0.129	0.257
Δ SQ at 60min PFC (mm/100 kcal)	0.099	-0.106	-0.034

Δ SQ at 180min PFC (mm/100 kcal)	0.07	-0.071	0.308
Δ Smell Threshold	0.056	-0.215	0.225
Δ Smell Discrimination	0.079	0.035	0.281
Δ Smell Identification	-0.122	0.028	0.016
Δ Smell Total Score	-0.013	-0.1	0.171
Δ Palatability	-0.206	-0.06	-0.321

Table 3

					95%IC for β	
		R2	β	P-value	Lower Bound	Upper Bound
FM Loss	Model 1	0.075				
	Changes in Cognitive Restraint		0.042	0.852	-0.37	0.445
	Changes in Habitual Disinhibition		0.313	0.203	-0.184	0.825
	Changes in Susceptibility to Hunger		-0.048	0.822	-0.425	0.341
	Model 2	0.46				
	Changes in Cognitive Restraint		0.167	0.388	-0.198	0.492
	Changes in Habitual Disinhibition		0.242	0.256	-0.192	0.688
	Changes in Susceptibility to Hunger		-0.082	0.669	-0.415	0.271
	Early changes in AUC desire to eat		0.207	0.197	0	0
	Early changes in Fasting Desire to eat		-0.475	**0.03**	-0.109	-0.006
	Early Changes in Fasting Fullness		-0.422	**0.021**	-0.083	-0.007

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Chapter VII: Article IV

Running Head: A one-year resistance training program following weight loss has no impact on body composition and energy expenditure in postmenopausal women living with overweight and obesity, published in Physiology Behavior, **volume 15, issue 189, pp:99-106, 2018.**

A one-year resistance training program following weight loss has no impact on body composition and energy expenditure in postmenopausal women living with overweight and obesity

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Running head: Resistance training and weight maintenance

ABSTRACT

Resistance training (RT) has been shown to decrease fat mass (FM), and increase fat-free mass (FFM), which can be a useful for weight loss maintenance. **Objective:** To examine the effects of a 1-year RT intervention on weight loss maintenance following a 6-month dietary weight loss intervention. **Design:** Following a 6-month dietary weight loss intervention (-6% ±5.8; 5.05 kg ±4.45), 70 postmenopausal women with overweight or obesity were randomized to a control group (n=34) or a RT group (n=36) (3 x/week first 6 months; 2 x/last 6 months, 70-80 % of 1-repetition maximum). Body composition (DXA), abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (CT scan), resting energy expenditure (EE) (indirect calorimetry), physical activity EE (doubly-labeled water) and total daily EE were measured. **Results:** Significant regains were observed for body weight 0.98 ±3.71kg *vs.* 1.33 ±3.94 kg and FM regain 1.32 ±2.69kg *vs.* 0.81 ±3.26 kg in control and RT groups after the 1-year weight maintenance phase. No difference between groups was noted. Resting EE and total daily EE did not change after the weight maintenance phase, and no differences were observed between groups. Both groups had significant greater than predicted decrease in resting EE after the 6-month dietary intervention and 1-year maintenance phase. **Conclusions:** Our results suggest that RT intervention over a 1-year following a 6-month dietary weight loss intervention does not improve weight loss maintenance, body composition or EE in postmenopausal women living with overweight or obesity.

Keywords: resistance training, weight loss maintenance, obesity, postmenopausal women.

INTRODUCTION

Dieting is the most common approach employed for losing weight in individuals living with obesity [1]. Restricting intake leads to weight loss in the short term however, it induces relatively poor long-term success rate for weight reduction [2,3]. In fact, data from the 1999-2006 National Health and Nutrition Examination Survey have shown that only 18% of individuals who attempted to lose weight were able to maintain the weight loss over a period of 1-year [4].

This high rate of recidivism can be partially explained by the existence of central and peripheral adaptations that promote increased appetite and suppressed energy expenditure (EE), which collectively compromise weight loss maintenance [5]. Given the high correlation between fat-free mass (FFM) and restring EE [6], a decrease in body weight and FFM, are consequently accompanied by a decreased EE [7,8]. A common observation after weight loss is that measured resting EE is also often lower than expected [9,10]. More specifically, a portion of the decrease in resting EE would seem to partly stem from adaptive changes in thermogenesis [11], which has been described as a decrease in resting EE beyond what can be predicted by loss of fat mass (FM) and FFM [12]. Sustained lower thermogenesis following weight loss can compromise weight maintenance and increase the likelihood of weight regain [5].

Despite previously discussed observations [7–9,12], some individuals are able to maintain their weight loss over extended periods of time [13,14]. Indeed, data from the National Weight Control Registry reported that increased levels of physical activity is one of the most common characteristics of successful weight losers [14–16]. In fact, exercising has been reviewed as a potentially useful strategy for weight loss maintenance since it is the only component of EE that is under voluntary control [17] and was proposed to be easier to manipulate than caloric restriction for long-term maintenance of weight loss [18].

Along these lines, a 1-year endurance training program was shown to improve weight loss maintenance compared to the control condition in men, whereas the regain in FM was also significantly lower in the training group [19]. Similarly, the inclusion of a walking program following weight loss improved weight loss maintenance in both men and women [20,21]. However, little attention has been given to the role of resistance training (RT) post-weight loss on weight maintenance and on the weight loss induced changes in EE, particularly in postmenopausal women.

RT could prove useful for improving weight loss maintenance since it can contribute to increase FFM [22], resting EE and physical activity EE [22–24]; as well as to influence substrate partitioning [24–26]. The re-analysis of the results from the classical Minnesota study revealed that FFM may well be an important driver of appetite and energy intake after weight loss [12]. Indeed, a sustained hyperphagic response was noted during the refeeding phase after weight loss; which only ceased when participants had recovered 100% of their pre-weight loss FFM. However, at that point, FM exceeded baseline values by 74% [12]. From these observations, one could hypothesize that accelerated recovery of FFM following weight loss could be associated with a reduced hyperphagic drive, and possibly to better weight loss maintenance.

The purpose of the study was to investigate the effects of a 1-year RT program on weight loss maintenance and measures of EE following a 6-month dietary weight loss intervention in postmenopausal women. We first hypothesized that RT would lead to better body weight loss and FM loss maintenance in postmenopausal women than a diet only intervention. Second, we also hypothesized that RT would be associated with higher resting EE when compared to a diet only intervention.

METHODS

MONET project

This project of the MONET study (Montreal Ottawa New Emerging Team) designed to investigate, using a randomized controlled design, the impact of 6-month dietary *vs.* dietary + RT on weight loss following by a sub-randomization of participants of the dietary arm to a 12-month weight loss maintenance phase with and without RT intervention (**Figure 1**). Metabolic, inflammatory and hormonal profiles, as well as body composition, measures of EE, psychosocial profiles were studied. The 6- month dietary intervention phase and results has been described in details elsewhere [27]. This manuscript presents results on weight, body composition and energy expenditure for the second phase, the 1-year maintenance phase.

Subjects

This prospective study included 71 overweight and obese postmenopausal women, who first completed a 6-month caloric-induced weight loss intervention. The study design is presented in the **Figure 1.** Seventy subjects who completed the weight loss phase were randomized into a control (n=34) or RT group (n=36). One woman refused randomization. The study was approved by the University of Montréal, Faculty of Medicine Ethics Committee. Data were collected from 2003 to 2008. The inclusion criteria were as follows: 1) body mass index ≥ 27 kg/m^2, 2) cessation of menstruation for more than 1 year and a follicle-stimulating hormone level ≥ 30 U/l, 3) non-smokers, 4) low to moderate alcohol consumption (< 2 drinks/day), 5) free of known inflammatory disease, 6) no use of hormone replacement therapy, and 7) physical activity levels (less than 2 h per week of structured exercise). Furthermore, upon physical examination or biological testing, no participants had history or evidence of: 1) diabetes (fasting glucose > 7.1 mmol/l or 2-h plasma glucose of > 11.1 mmol/l after a 75-g OGTT), 2) untreated thyroid or pituitary disease, 3) chronic liver or renal disease, 4) asthma requiring therapy with steroids, 5) cardiovascular disease, peripheral vascular disease or stroke, 6) dyslipidaemia or hypertension requiring immediate medical intervention (total cholesterol > 8 mmol/l,

systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg), 7) history of alcohol or drug abuse, 8) abnormal blood laboratory values (haematocrit < 32 or > 48%; creatinine > 130 µmol/l), 9) use of medications that could affect cardiovascular function and/or metabolism, 10) known history of inflammatory disease as well as cancer, and 11) orthopaedic limitations.

Pre-, post-weight loss intervention as post 1-year follow-up testing was preceded by a 1-month weight stabilization period (weight stability within ± 2 kg was verified by monitoring body weight of each subject on a weekly basis for 1 month at our laboratory), followed by a 1-month testing period to assess anthropometric, metabolic, and EE measurements.

Nutritional and RT intervention

The nutritional intervention consisted of monthly meetings with a registered dietitian. The total daily caloric intake prescribed to each participant (control and RT) was calculated based on their individual daily EE requirements measured by indirect calorimetry and by doubly labelled water (DLW) obtained from the measurements performed after the weight loss phase. The macronutrient composition of the diets was set at: 55%, 30%, and 15% of energy intake from carbohydrates, fats, and proteins, respectively.

The 1-year RT weight loss maintenance intervention was performed weekly on 3 non-consecutive days for the first 6 months and on 2 non-consecutive days for the last 6 months. The intensity of the RT was set at approximately 70-80 % of 1-repetition maximum (1RM). Each training session included a warm-up period consisting of low intensity walking on a treadmill for 10 min. Each exercise session was individually monitored for proper technique and optimal progression. The RT program consisted of the following exercises: 1) leg press; 2) chest press; 3) lateral pull downs; 4) shoulder press; 5) arm curls; and 6) triceps extensions. These exercises provided a RT for the major muscle groups of the

body. Each participant was given a target load range and attempted to keep each set (n = 3-4) within the target range by adjusting the load to allow for the prescribed number of repetitions (n = 10-12). Resting periods were 1-1.5 min between sets. The exercise program was supervised by qualified personal trainers.

Strength testing

A 1RM was performed to measure maximal dynamic voluntary strength in participants of the RT group. After warming-up on a treadmill, women were asked to position themselves in the leg press machine for the first test. A comfortable weight was set, and the participants were asked to slowly complete 10 repetitions at their full range of motion. The range of motion recorded from this first attempt was considered as a reference range of motion. A heavier weight was set after a 2-minute recovery period, complete a maximum of repetitions while maintaining the reference range of motion. If they were able to complete more than 10 repetitions, the participants were asked to stop in order to avoid any unnecessary fatigue. In case the participant was able to complete more than 10-rep, participants had a 3-minute recovery period and repeated the test with more weight added. The same procedure was repeated until only one repetition could be completed or until five attempts were achieved. After 5 attempts, in case the 1RM was not achieved, the 1RM value was predicted using the Wathen [28] equation. Tests for lower body and upper-body strength were performed in leg press and seated chest press positions, respectively. All tests were conducted over three non-consecutive days 1 week after the end of the 6-month dietary intervention and repeated 1 week after the end of the 1-year RT program.

Measures

Body composition

Body weight was measured to the nearest 0.1 kg on a calibrated balance (Balance Industrielle Montreal, Montreal, Quebec, Canada) and standing height was measured using a wall stadiometer (Perspective Enterprises, Portage, USA). FFM and FM were measured using dual energy X-ray absorptiometry (General Electric Lunar Corporation version 6.10.019, Madison, USA). In our laboratory, the intraclass coefficient correlation (ICC; 2-factor random effect) for test-retest for FM and LBM was 0.99 (n = 18). Body mass index [BMI = body weight (Kg)/Height (m^2)] was calculated.

Computed Tomography (CT)

A GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) was used to measure abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) levels. The subjects were examined in the supine position with both arms stretched above their head. The position of the scan was established at the L4-L5 vertebral disc using a scout image of the body. VAT area was quantified by delineating the intra-abdominal cavity at the internal most aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The SAT area was quantified by highlighting fat located between the skin and the external most aspect of the abdominal muscle wall [29,30].

Resting EE

Resting EE was assessed by indirect calorimetry after 12-hour fasting period (SensorMedics Delta Track II, Datex-Ohmeda, Helsinki, Finland). Measures were taken for 40 min (10 min of acclimatization and 30 min of measurements) between 6:30 and 9:00 AM. Subjects were lying down in a hospital bed in a room with minimum noise and light. They were asked to be as immobile and silent as possible. The temperature of the room was maintained at an average of 22 °C. In our laboratory, the ICC (2-factor random effect) for resting EE determined by using a test- retest condition in 19 different subjects is 0.92 ($P<0.01$).

Total daily energy expenditure (EE)

Total daily EE was measured with the DLW method using stable isotope during a 10-day period before and after the weight loss phase and after the 1-year follow-up. A more detailed description of the procedure has been previously presented [31]. Physical activity EE was calculated as follows: Physical activity EE = total daily EE x 0.9 – resting EE [32], whereas 0.9 is factored into the equation to account for the thermic effect of food.

Statistical analysis

All data were analyzed with Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). Results with a parametric distribution are presented as mean ± standard deviation, while variables with a non-parametric distribution (weight loss and % weight loss recovery) were presented in median and interquartile range (IR). Values for the 137 women from the weight loss phase (phase 1) of the trial have been reported elsewhere [27,33]. Stepwise multiple regression analyses were used to define the best predictors of resting energy expenditure (probability to enter the model was set at $P<0.05$). The independent variables entered into the model were age, height, weight, FM and FFM. However, only age, FFM and body weight met the entry criteria of $P<0.05$. The following equation was then computed: Predicted Resting EE=526.098 + (18,787×FFM) - (5.234×age) + (3.019×body weight).

Two-way repeated measures ANOVA were performed for changes in body composition and EE variables at baseline, after weight loss and after 1-year follow-up within each group and between groups (*time x group* interaction). Effects were considered significant at $P < 0.05$. Moreover, in order to assess the magnitude of potential observed differences, the effect size was computed (eta squared, η2). The values of 0.0099, 0.0588, and 0.1379 were considered benchmarks for small, medium, and large effect sizes [34]. We also performed a secondary data analyses by comparing

results for the main outcomes (body weight, FM, FFM, resting EE, physical activity EE and total EE of participant of participant in the RT group who attended 75% or more of the RT sessions (n=9) vs participant of the control group and RT group who attendance was below 75%.

RESULTS

During the 1-year follow-up, 16 subjects (or 23%) quit or stopped the study. Reasons included lack of motivation, injury related to RT, refused post-testing, and health problems not related to RT. As such, 54 subjects completed the follow-up and were included in the analyses (control: n=29; RT: n=25).

Physical characteristics of completers are reported in **Table 1**. Overall, a significant *time* effect was observed for body weight, FM, FFM, VAT and SAT. However, no interaction was observed between groups. Weight loss after the 6-month dietary intervention was 4.16 (IR 5.42) and 4.80 (IR 4.97) kg (p=0.434) in the control and in the RT group, respectively. Following the 1-year RT weight loss maintenance intervention, the control group maintained a weight loss of 2.72(IR 4.5) kg, while the RT maintained a 3.32 (IR 6.64) kg weight loss (p=0.403), representing weight relapse of approximately 37.96 (IR 77.74) % and 20.42 (IR 131.39) % (p=0.478) in the control and intervention group, respectively. Similarly, at the end of weight loss maintenance phase, FM regain was 1.32 ±2.69 kg (4.8 ±8.2 %) in the control group vs 0.81 ± 3.26 kg (2.2 ± 10.4 %) in the RT group. FFM also decreased after the dietary weight loss intervention (-1.26 ±2.45 kg ; -2.49 ±4.32%) in control vs -0.38 ±1.81 kg; 0.68 ±3.86% in RT) and after maintenance phase (-1.33 ±2.43 kg; 2.72 ±4.21% in the control vs -0.24 ±2.49kg; 0.37 ±4.97% in RT), however no interaction between time and group was observed (P=0.264) and a small effect size was noted ($\eta 2$= 0.051).

Changes in VAT and SAT were significant overtime (P<0.001, $\eta 2$=0.240 and P<0.001, $\eta 2$= 0.372 for VAT and SAT, respectively). No interaction between time and group and small effect sizes were

observed for VAT (P=0.126, η2= 0.042) and SAT (P=0.447, η2= 0.017). In the control group, participants recovered approximately 2.57% of VAT and 3.52% of SAT after the maintenance phase, while the RT group recovered 2.5 % of VAT but lost additional 0.2% of SAT.

The **Table 2** shows the measures of EE before and after follow-up. Absolute resting EE was decreased significantly over time (P<0.001), while a large effect size was observed (η2=0.266). On the other hand, no significant interaction was noted (P=0.196), while a small effect size was observed (η2=0.032). Similar results were observed for physical activity EE (P=0.981, η2=0.001) and in total EE (P= 0.241, η2= 0.035). Finally, a small effect size and no interaction was observed for physical activity EE (P=0.198, η2= 0.041) and for total EE (P= 0.104, η2= 0.055).

We also compared RT participants with “higher attendance” to RT sessions (>75%) to those with “lower attendance” (<75%) and controls. Results showed no interaction and small effect size for weight (P=0.712, η2=0.022), FM (P=0.372, η2=0.041) and FFM (P=0.523, η2=0.031). EE measures showed similar results, with small effects sizes and no interaction for physical activity EE (P=0.645, η2=0.032) and total EE (P=0.393, η2=0.051). Finally, resting EE presented a medium effect size (P=0.134, η2=0.070).

The analysis of results from women engaged in the RT and that completed 1RM tests (n=11), showed a significant increase in lower-body strength of 34.7 ± 21.07% (P<0.001) and of 26.8 ±18.49% (P<0.001) in upper-body strength.

Figure 2 presents the predicted and the measured values for resting EE in both groups during the dietary weight loss intervention and maintenance phases. Significant differences between the measured and the predicted values of resting EE were noted at the end of the dietary weight loss

intervention and, differences persisted after 1-year follow-up in both groups (P=0.002; η2= 0.122). However, a small effect size and no interaction between groups for measured vs predicted resting EE was noted (P=0.244; η2= 0.027).

DISCUSSION

The major finding of the present study is that our results do not support our first hypothesis that weight loss maintenance would be better with RT since body weight and FM regain were not different between control and RT groups following the 1-year weight maintenance phase. Previous evidence has shown that aerobic exercise can be effective in improving weight loss maintenance in women [20,21]. To our knowledge, only a handful of studies have evaluated the impact of RT on weight loss maintenance (17,32,33,34), with one study reporting positive effects on maintenance of weight loss [36] and two studies reporting a positive impact on maintenance of FM loss [36,37]. Of note, one of the above cited study (35-50 year old) was conducted in men [37] and presented a shorter intervention phase (6-month) than what we report herring (1-year). The other study was performed in premenopausal women (21-46 year old) who achieved ~12 kg weight loss, assessed following 1-year weight loss. In fact, it has been reported that for the same RT volume, men present a better body composition response to RT than do women [38,39] and younger women present a better response to weight and fat loss following RT than post-menopausal women [22]. This could likely explain the discrepant results.

Our second hypothesis that women engaged in RT would present higher EE than the control group was also rejected. Although the impact of exercise on energy metabolism following weight loss is a topic widely discussed in the literature [20,40–43], no study has to our knowledge evaluated physical activity EE and total EE after during a 1-year weight maintenance intervention including RT in post-menopausal women. The study that most resembles our study design was the one conducted by Villanova [20]. They showed that increasing the number of steps per day (+20%) increases resting EE

by 100 kcal/day, in spite of body weight loss (-1.8%). In contrast, we showed that regular RT sessions had no impact on resting EE following 6-month dietary intervention [44] and after 1-year post weight loss follow-up. Our design substantially differs from the study conducted by Villanova [20]. First, the differences between our results and theirs could be partly explained by the age and sex differences between the studies' samples. Villanova [20] included men and women aged 44 years old on average, while our study involved only postmenopausal women (58.3±4.8 years). It was previously reported that RT can improve body composition and increase resting EE in young women [22] and in men [38,39], but this was not the case in our sample of postmenopausal women. Second, the exercise intervention was also different. We conducted a RT -based intervention while Villanova physical activity intervention aimed to promote a daily increase in the number of steps among participants.

Our results show EE adaptations were present after the 6-month dietary intervention (800 caloric restriction per day) as previously reported [45] and persisted after the 1-year maintenance phase in the present study. Similarly to what we observed, previous studies also reported the existence of metabolic adaptations in resting EE after weight loss [5,46–48], which could partly be explained by decreases in heart rate, activity of the sympathetic nervous system, blood pressure, liver and kidney activities [48,49]. This depression in resting EE has been reported to persist for as long as 6-year after massive weight loss [50] and could be considered a factor that contributes to long-term weight-regain. To our knowledge, our study is the first to show that lower resting EE persist in postmenopausal women even if RT is added after weight loss. These results contribute to our understanding of the challenges associated with the maintenance of lowered body weight.

We have previously reported no changes in both physical activity EE and total EE after the 6-month dietary intervention [44,45]. Along the same lines, physical activity EE and total EE were not changed after 1-year RT intervention. Studies that looked at physical activity EE after weight loss, reported

significant decreases in both physical activity and the cost of physical activity following weight loss by caloric restriction [40,48,51–54]. However, no differences were noted after 12-month follow-up period [40,51]. In fact, evidence has shown that participants can become apathetic and less active during prolonged energy deficits periods [55,56], which could expedite weight regain among weight-reduced subjects. In postmenopausal women, an inverse association between decreases in physical activity EE and the amount of weight recovered after weight loss was reported. In other words, women who witnessed the greatest decrease in physical activity EE during energy deficit, were the ones who recovered more weight during follow-up [40]. This observation is problematic since the menopause transition *per se* was also found to be associated with declines in physical activity EE and in total EE [57].

Even though our results do not support that RT increases EE in postmenopausal women after 6-month of dietary intervention, it is important to consider that RT might promote other benefits among our participants. As recently reviewed, RT also significantly improves upper and lower body muscle strength and muscle morphology in healthy older adults [58]. In fact, our secondary analyses including a partial sample have shown a significant increase in upper and lower body strength after the 1-year RT intervention among the participants that completed the 1RM post-test evaluation. Along the same lines, a previous study from our group has shown a positive impact of RT on general strength in postmenopausal women [59]. This increase could promote other benefits beyond the weight loss *per se* such as preventing falls [60] and increasing the functional capacity in this population [61].

Previous evidence shows that adaptive thermogenesis is sustained only when body weight remains below the baseline measure. Indeed, in individuals who recovered their initial body weight, adaptive thermogenesis are no longer present [5,47]. Our participants recovered on average ~33% of their weight loss, which could partly explain the observed adaptive thermogenesis after the 1 year follow-up (**Figure 1**). Our results also demonstrate that RT was not sufficient to correct the effects of weight

loss on adaptive thermogenesis mechanisms in post-menopausal women, since no group difference was observed. Our findings are in line with previous research which reported that adaptive thermogenesis is still present in individuals who lose weight through a combination of diet and exercise [8,45,54] and in individuals who employ exercise to maintain weight loss [7]. However, our results extend these findings to RT.

The present study has some limitations. First, our sample size is limited to 54 post-menopausal women and this cohort was composed of relatively “healthy”, non-diabetic postmenopausal women living with overweight or obesity. Second, even though the RT intervention was designed according to the American College of Sport Medicine recommendations, the EE achieved might have been too low, either because of low total duration [62], intensity and/or frequency, to observe significant improvement in body composition. Moreover, adherence to the RT program during weight maintenance was only moderate (64 %). We ran secondary data analyses including only participants who completed 75 % or more of the RT sessions and compared results to controls and to the participants who performed less than 75% of the RT sessions for weight, FM, FFM and EE, no differences were noted between groups. Our results are strengthened by the inclusion of a well-characterized sample of weight-reduced postmenopausal women and by the utilization of gold-standard techniques to measure EE and body composition.

In conclusion, our results suggest that diet alone and diet + RT presented similar effects on body weight and composition maintenance as well as on EE in postmenopausal women after a 1 y post-weight loss follow-up. Furthermore, RT training did not attenuate the greater than predicted decrease in EE during the 1-year follow-up. Whether the modalities of the RT program (intensity, frequency, total workload) used in this study were sufficient elicit the hypothesized effects remains to be determined.

Table and Figure Legends

Table 1. Changes in body composition following 6-month dietary intervention and 1-year weight maintenance phase

Data presented in mean and standard deviation; BW: body weight; BMI: body mass index; FM: fat mass; FFM: fat free mass; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue ***** Significant changes overtime ($p < 0.05$), VAT & SAT: n=28 (control group) and n=22 (resistance training group).

Table 2. Changes in energy expenditure following 6-month dietary intervention and 1-year weight maintenance phase

Resting EE: resting energy expenditure (measured value); FFM: Fat Free Mass; Physical Activity EE: Physical Activity Energy Expenditure; Total EE: Total energy expenditure, ***** Significant changes overtime ($p < 0.05$), PAEE & TEE: n=20 (control group) and n=18 (resistance training group)

Figure 1. Study Design

Figure 2. Individual Body weight changes in participants enrolled in the RT group

Figure 3. Predicted vs measured values of resting energy expenditure (REE) following 6-month dietary intervention and weight maintenance phase in the control (A) and resistance (B) groups, * represents a significant change overtime; ** represents a significant different between measured vs predicted values .

Table 1

	Control Group (n=29)			Resistance Training group (n=25)						
	Baseline	**Post dietary Intervention**	**Post-maintenance phase**	**Baseline**	**Post dietary intervention**	**Post-maintenance phase**	**p**	**Effect Size**	**time* group**	**Effect size**
BW (kg)	84.21(13.47)	79.05(14.11)	80.03(14.27)	81.18 (13.98)	76.85(14.09)	78.19(15.29)	p<0.001*	0.454	0.543	0.012
BMI (kg/m2)	32.07(3.75)	30.07(3.95)	30.47(4.16)	31.61(4.16)	29.91(4.23)	30.44(4.90)	p<0.001*	0.548	0.578	0.028
FFM (kg)	45.19(6.04)	43.93(4.94)	43.86(5.31)	44.59(6.99)	44.21(6.58)	44.35(6.82)	0.007*	0.037	0.150	0.037
FM (kg)	37.66 (9.21)	33.31(10.01)	34.63(9.70)	35.31(8.18)	31.81(8.61)	32.62(9.65)	p<0.001*	0.457	0.611	0.009
Peripheral FM (kg)	18.22(4.60)	16.36(5.01)	16.75(4.56)	18.00(4.33)	16.03(4.26)	16.87(5.19)	p<0.001*	0.398	0.621	0.009
Central FM (kg)	17.76(4.45)	15.18(4.69)	16.20(5.17)	16.25(4.29)	14.78(4.91)	14.77(4.76)	p<0.001*	0.330	0.121	0.041
VAT (cm2)	187.84(51.28)	158.96(57.82)	163.04(59.41)	158.43(49.75)	144.54(43.72)	148.14(56.21)	p<0.001*	0.240	0.126	0.042
SAT (cm2)	455.50(119.81)	409.69(126.96)	424.12(123.59)	446.07(107.22)	408.74(117.28)	408.04(129.02)	p<0.001*	0.372	0.449	0.017

Table 2.

	Control Group (n=29)			Resistance Training Group (n=25)						
	Baseline	**Post dietary intervention**	**Post-maintenance phase**	**Baseline**	**Post dietary intervention**	**Post-maintenance phase**	**p**	**Effect size**	**time* group**	**Effect Size**
Resting EE (Kcal/day)	1311.45 (195.1)	1238.28 (147.29)	1216.89 (138.93)	1282.28 (174.3)	1230.4 (201.23)	1244.83 (206.62)	p<0.001*	0.266	0.077	0.032
Physical Activity EE (Kcal/day)	981.55 (256.82)	940.21 (226.79)	931.25 (203.73)	810.11 (281.39)	909.43 (356.39)	899.71 (251.10)	0.937	0.005	0.270	0.037
Total EE (Kcal/day)	2528.05 (282.808)	2410.9 (285.86)	2389.15 (267.32)	2310 (297.99)	2351.22 (413.49)	2365.17 (341.80)	0.699	0.010	0.174	0.047

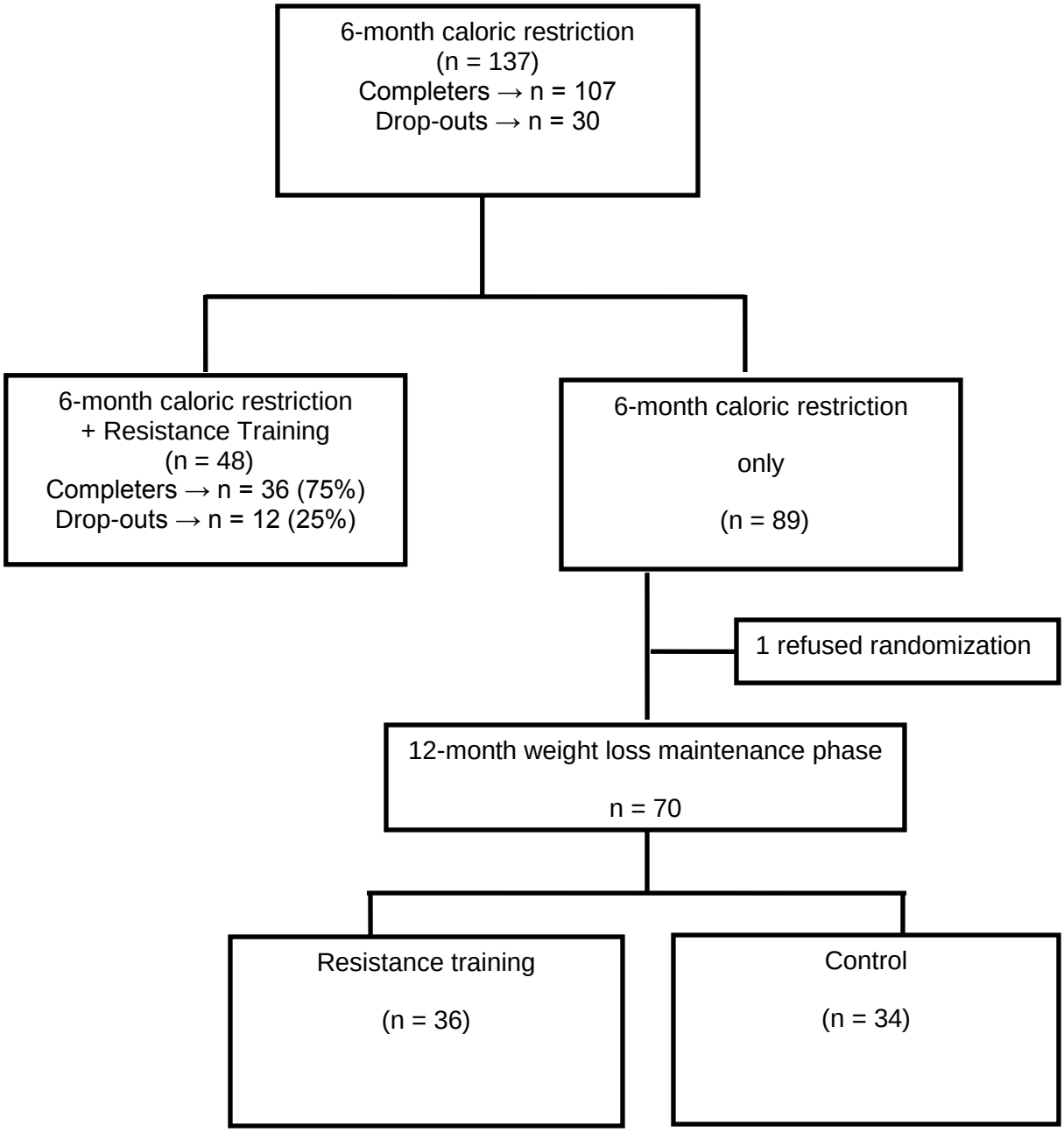
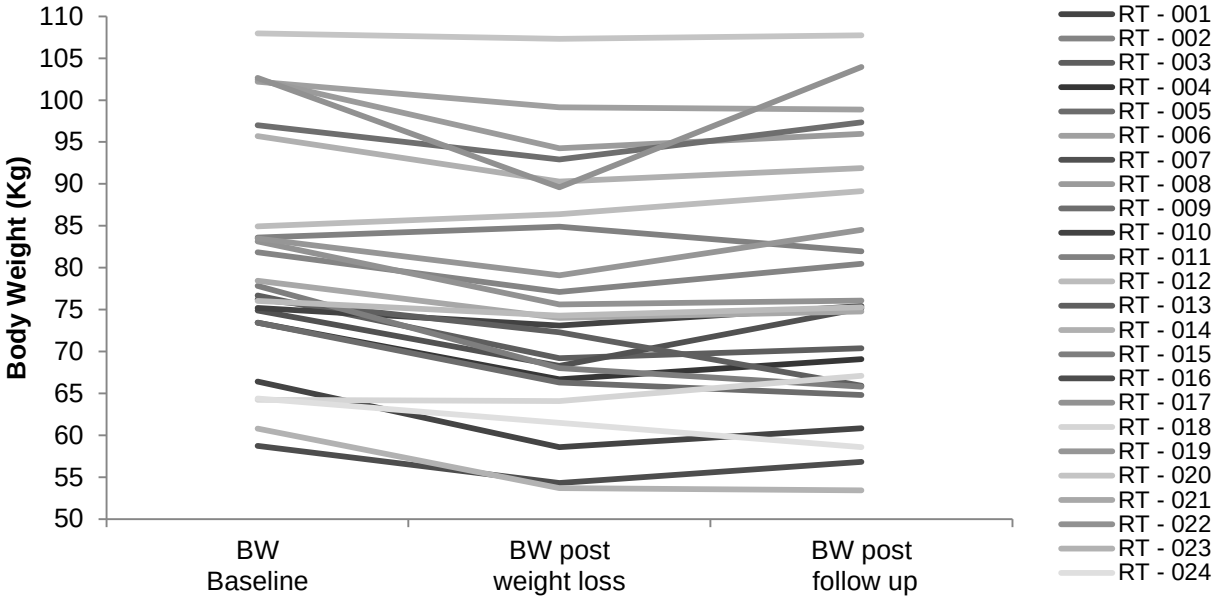

6-month caloric restriction
(n = 137)
Completers → n = 107
Drop-outs → n = 30
6-month caloric restriction
+ Resistance Training
(n = 48)
Completers → n = 36 (75%)
Drop-outs → n = 12 (25%)
6-month caloric restriction
only
(n = 89)
1 refused randomization
12-month weight loss maintenance phase
n = 70
Resistance training
(n = 36)
Control
(n = 34)

Figure 1


Body Weight (Kg)
110
105
100
95
90
85
80
75
70
65
60
55
50
BW Baseline
BW post weight loss
BW post follow up
RT - 001
RT - 002
RT - 003
RT - 004
RT - 005
RT - 006
RT - 007
RT - 008
RT - 009
RT - 010
RT - 011
RT - 012
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RT - 024

Figure 2

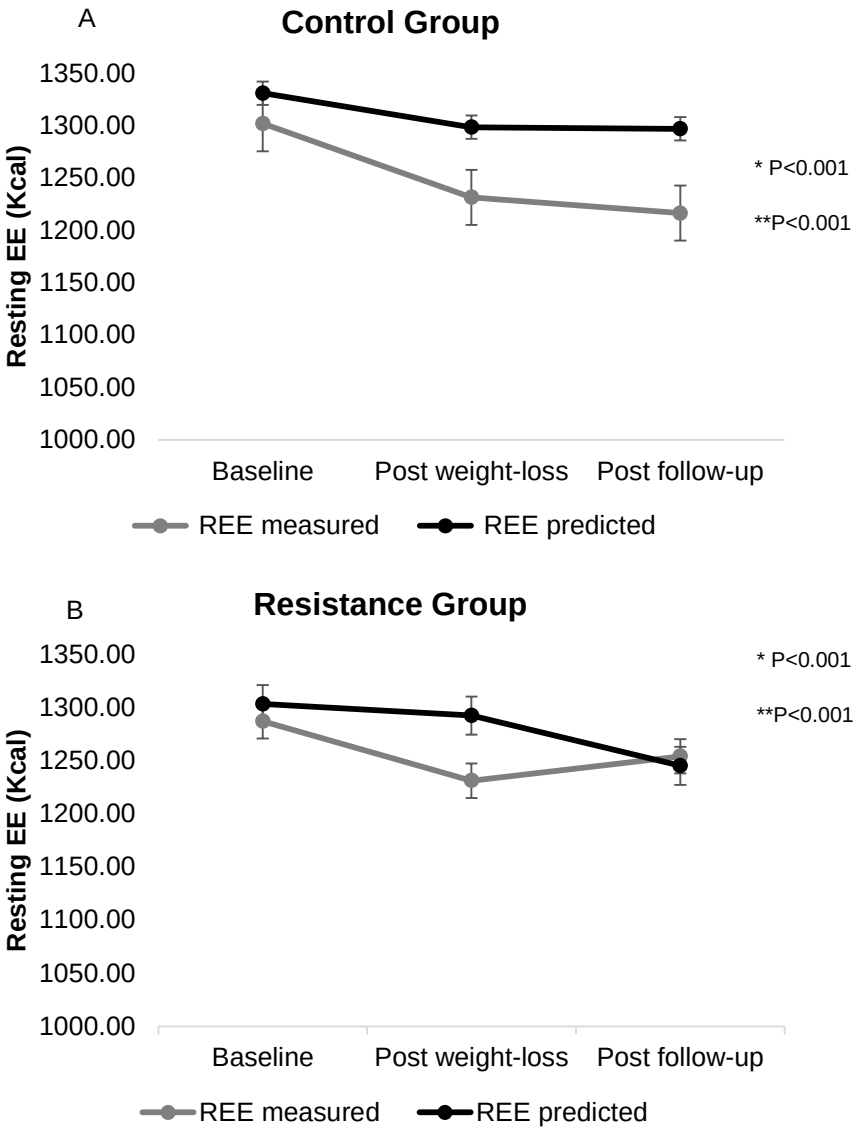
A
Control Group
Resting EE (Kcal)
1350.00
1300.00
1250.00
1200.00
1150.00
1100.00
1050.00
1000.00
Baseline
Post weight-loss
Post follow-up
* P<0.001
**P<0.001
REE measured
REE predicted
B
Resistance Group
Resting EE (Kcal)
1350.00
1300.00
1250.00
1200.00
1150.00
1100.00
1050.00
1000.00
Baseline
Post weight-loss
Post follow-up
* P<0.001
**P<0.001
REE measured
REE predicted

Figure 3

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PART THREE: CONCLUSIONS AND RECOMMENDATIONS

CHAPTER VIII: CONCLUSIONS AND RECOMMENDATIONS

The present thesis aimed to investigate whether 1) different rates of weight loss would impact variables related to energy balance differently and 2) early changes in EI and EE related variables could also predict final weight and adiposity outcomes. Accordingly, we added together all the data collected in both groups: rapid and slow weight loss, including body composition, fasting and postprandial appetite measures, satiety, olfaction, palatability, EI, REE, RRV and impulsivity.

Figure 1 illustrates the main findings of the study. Overall, our results demonstrated that the changes observed in the first week of caloric restriction remained until the end of the intervention independently of the rate of weight loss. Accordingly, different rates of weight loss were not found to affect physiological or psychological aspects related to EI and EE differently. Early responses to caloric restriction in feeding behaviour were found to predict final outcomes (body weight and FM loss) in our study, independently of changes in cognitive restraint, habitual disinhibition or susceptibility to hunger. Furthermore, we demonstrated that metabolic adaptations remain significant after 1-year follow up independently of practice of RT.

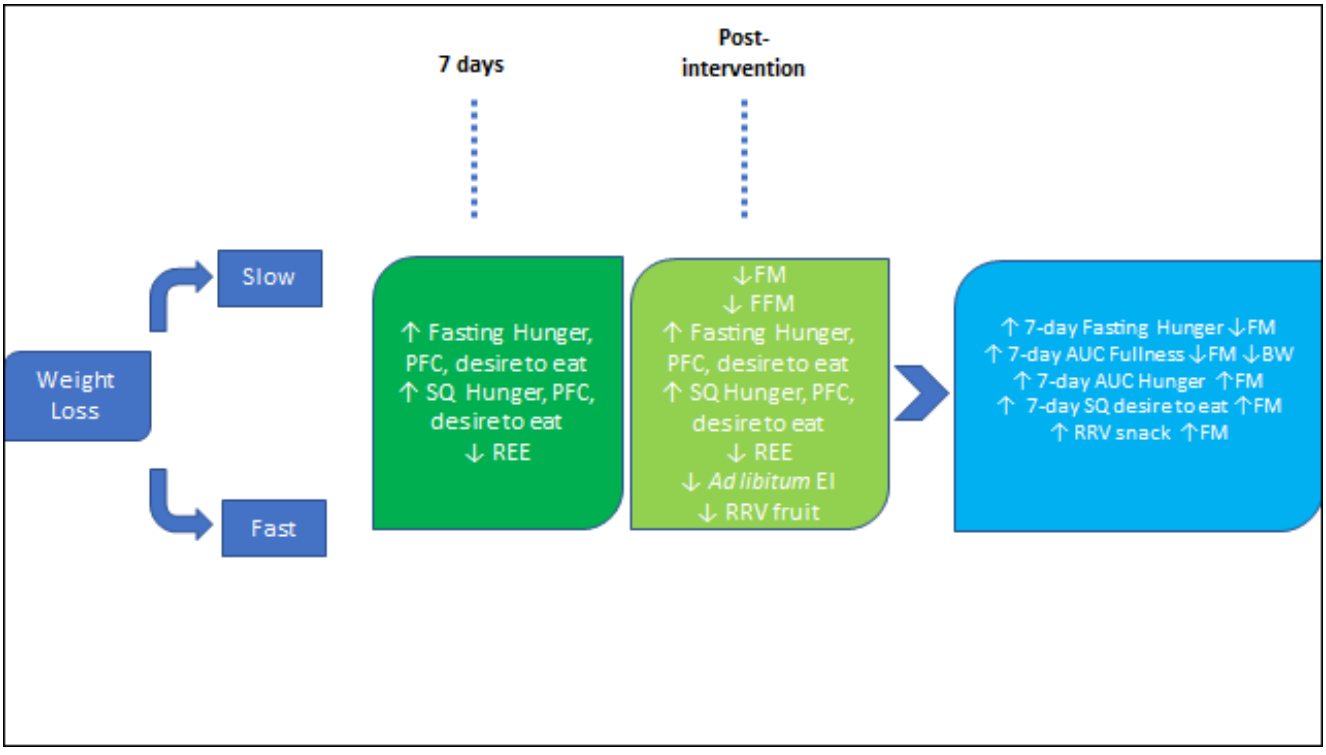

Figure 1. Summary of the Study I main findings

PFC: Prospective Food consumption, SQ: Satiety Quotient; REE: Resting Energy Expenditure; FM: Fat Mass; FFM: Fat Free Mass; EI: Energy Intake; RRV: Relative Reinforcing Value; AUC: Area under the curve

Changes in appetite ratings

Articles I and III describe the impact of weight loss on appetite measures. Our results demonstrated that caloric restriction caused increases in appetite ratings; however, different rates of weight loss did not play a role in these compensatory mechanisms. Previous studies observed that different rates of weight loss present an impact on appetite measures; however, they did not observe differences in final weight and FM loss (Coutinho et al. 2017, Purcell et al. 2014). Participants from both groups: rapid and slow weight loss presented similar weight and FM loss. Taken together, these findings suggest that total weight loss plays more important role in increases on appetite ratings than the 'speed' of this loss. In fact, previous evidence demonstrated that higher weight loss would promote higher increases in appetite ratings (Gilbert et al. 2009b). This relationship could partially be explained by the relationship between appetite-related hormones and fat loss as we previously reviewed (Hintze et al. 2017b). Indeed, decreases in leptin levels were found to be similar in women under different weight loss restriction (intermittent fasting, VLCD and LCD) only when fat loss was comparable between groups (Wisse et al. 1999). Along the same lines, serum ghrelin concentrations increases with weight loss was not associated with different rates in weight loss in previous study (Purcell et al. 2014). Similar results were observed for basal PYY and insulin (Coutinho et al. 2017).

In sum, our results show that increases in appetite were similar for both groups slow and rapid; which question the superiority of slow *vs.* rapid weight loss treatments. Indeed, a previous study suggested that participants are more likely to achieve greater weight loss if undertaken rapidly (Purcell et al. 2014). The main argument of these study is the fact that participants could become more motivated to maintain their low energy diet given they were having weight loss more quickly. On the other hand, our study has shown that rapid weight loss has similar impact on appetite rates

(compared to slow weight loss) as long as they present similar weight loss. Furthermore, these results might be extended even when non-homeostatic variables of energy balance such as palatability, olfactory functions and food reinforcement are included in the variables. Accordingly, the degree of deprivation might be prescribed considering participant's personal choices. It could potentially increase the chances of better compliance to the prescribed diet, and thus, greater weight and FM loss. Similarly, other studies on rate of weight loss reported the importance of personalize participant's diet in order to improve compliance (Coutinho et al. 2017).

Importantly, increases on appetite observed in our study were significant as early as the first week and remained significant until the end of the intervention. In line with our findings, previous studies also reported that short-term (Alajmi et al. 2016, Cameron et al. 2016, King et al. 2011) and long-term (Anton et al. 2009, Drapeau et al. 2007b, Gilbert et al. 2009a, Tremblay et al. 2015) increases in fasting appetite occur as a result of caloric restriction. As extensively discussed in the present thesis, increases in appetite might increase driving to eat, promoting positive energy balance over time given the association between appetite ratings and EI (Drapeau et al. 2007a, Green & Delargy 1997). Indeed, the results from the paper III demonstrated that increases in appetite ratings the first week of intervention significantly predicted final outcomes (weight and FM loss). Accordingly, a closer follow up in appetite measures in the first days of intervention might be an important tool to increase the chances of weight loss success.

Relative reinforcing value of food and impulsivity

It was previously reported that RRV increases with weight loss (Epstein et al. 2007a), similarly to what is observed for impulsivity (Kirk & Logue 1997, Manasse et al. 2017). Conversely, our results did not show increases in impulsivity or RRV variables over time whereas RRV of fruit significantly decreased. We believe that the fact that both groups using the Food exchange system from the Canadian Diabetes Association contributed to these findings. This system allows participants to select foods that they enjoy during the weight loss, however in smaller quantities. Accordingly, our

participants were still allowed to have their favorite snacks and/or fruit during the trial and possibly were not feeling deprived, which could explain the lack of increases in RRV in those types of palatable foods. Indeed, previous evidence suggested the role of regular snack intake to control RRV of food (Myers Ernst & Epstein 2002; Temple et al. 2008b,a). Accordingly, it is possible to speculate that the fact that participants were consuming their snacks during the weight loss phase played a role in our results. However, we could not confirm this speculation since no dietary recall was performed during the intervention.

Even though the increases in RRV were not significant in our study, our results demonstrated that greater RRV increases were associated with poorer weight and fat loss outcomes. Indeed, previous evidence suggested the importance of controlling this variable to control EI. In the long-term, the control of RRV could promoter greater weight management as previously suggested (Buscemi et al. 2014). These results highlight the importance of strategies for effective RRV control during weight loss interventions in order to improve the chances of better outcomes in terms of body weight and FM loss.

Given that RRV is higher for high-calories food items, it would plausible to speculate that the rapid weight loss group would present greater increases in RRV of snack food. Given that they are more deprived, they potentially should avoid more often their favourite snack consumption in order to attend the prescribed calories per day. However, our results observed that the rate of weight loss did not play a major role in RRV increases. As such, it seems that RRV is not related to the degree of deprivation either.

Even though previous evidence suggested that impulsivity might be greater in subjects who are in subjects who were energy and water deprived, (Kirk & Logue 1997, Manasse et al. 2017) we did not observed any increase in impulsivity traits as consequence of weight loss. Furthermore, we did not observe any impact of the rate of weight loss on those variables either. Other studies observed

impulsivity and delay discounting as significant predictors of subsequent weight gain in individuals who lost weight (Brockmeyer et al. 2017, Kishinevsky et al. 2012, Weygandt et al. 2015); however, it was not observed in our study either. We believe the use of different instruments to access impulsivity could explain the discrepant results. On the other hand, the assessment of impulsivity traits could be relevant in weight loss context to provide dietary recommendations more personalized to the participants. Studies investigating whether more personalized diets based on the participant's impulsive profile would promote better outcomes are still needed.

Taken together, these results regarding psychological variables of feeding behaviour reiterate demonstrated that there is no advantage of losing weight slowly for achieving weight loss.

Decreases in REE with weight loss

Significant decreases in REE were observed in articles I and III. Moreover, a sustained decreased REE were observed after 1-year follow up, as we demonstrated in the study IV. Decreases in REE are a well-known consequence of weight loss as extensively mentioned in the literature and in the present thesis (Camps et al. 2013a, Doucet et al. 2000e, Leibel et al. 1995, Martin et al. 2007). In fact, we noted a significant decrease in this component of EE as early as the first week and it declined steadily until the end of the intervention.

The main concern about significant changes in REE is the fact that the degree of deprivation during weight loss will change if the REE decreases. For example, at baseline a given EI is recommended for weight loss based on their Ereq. Particularly if REE decreases as early as the first week, it would indicate that participants were less deprived than expected, which could compromise the excepted weight loss. Accordingly, even if they present high compliance to the diet, this decrease would compromise final weight loss. However, our results did not observe these early decreases in REE as predictors of final outcomes. In fact, previous evidence demonstrated that appetite measures should

play a more important role in long-term energy balance than EE (Polidori et al. 2016). Our results confirm these previous findings, given that only appetite-related variables were significant predictors of final outcomes.

Given we noted significant decreases in REE over time in our study, we analysed in the articles I and IV whether those changes in REE were beyond to the values predicted based on body composition changes. No significant differences between measured and predicted values were observed in the Article I. On the other hand, the article IV observed significant differences between the measured and the predicted values of resting EE at the end of the dietary weight loss intervention and differences persisted after 1-year follow-up in women engaged in a RT and in a control group. Even though the sample of both groups they had similar weight loss after caloric restriction (~ 5%), it is important to consider the samples from both studies reported very different age ranges (32.6 ±9.1 article I) and (58.3 ±4.8 article IV). This could contribute to explain the discrepant results in our studies. Accordingly, it demonstrates a more difficult challenge for older women to overcome during weight loss.

Previous studies reported the existence of metabolic adaptations with weight loss (Bosy-Westphal & Kossel 2009, Müller et al. 2015), which was more evident at 10% weight loss (Leibel et al. 1995, Nymo et al. 2018). More pronounced metabolic adaptations in either the slow or the rapid weight loss could potentially predispose subjects to a faster weight loss recovery (Camps et al. 2013a, Rosenbaum & Leibel 2016, Tremblay et al. 2013); however, it seems that the REE decreases and the magnitude of REE adaptation are similar in women in different degrees of caloric restriction.

Studies discussing the impact of different rates of weight loss on the magnitude of metabolic adaptations observed that both groups (slow and rapid weight loss) presented significant metabolic adaptations (significant differences between predicted and measured values). What is more, no differences in the degree of adaption were detected between groups in previous studies (Martin et

al. 2007, Siervo et al. 2015). In accordance with other variables included in the present study, there is no evidence that slower weight loss would be a better strategy to reach better outcomes considering that adaptations were similar to both groups when overall weight loss is the same.

Furthermore, our results demonstrated that the addition of RT after caloric restriction does not offset or reverse the metabolic adaptations promoted by prolonged energy restriction. Our findings are in line with previous research that reported that greater than predicted decrease in EE is still present in individuals who lose weight through a combination of diet and exercise (Knuth et al. 2014, Martin et al. 2007) and in individuals who employ exercise to maintain weight loss (Johannsen et al. 2012). Taken together, our results demonstrate that strategies for better control in metabolic adaptations after weight loss are still needed, remaining as one more challenge for individuals living with obesity to achieve and maintain weight loss.

Recommendations and Future Perspectives

Overall, our results suggest that different interventions (slow *vs.* rapid caloric restriction weight loss or implementation of RT in the maintenance phase *vs*. control) have no impact in the magnitude of the changes of energy balance variables after weight loss. Accordingly, both weight loss approaches (greater caloric restriction for a shorter period of time as well as small restriction for longer periods) might be a suitable option for individuals seeking weight reduction treatment. What is more, RT did not promote any improvements in terms of weight or FM loss after a caloric restriction period. However, it is important to highlight that exercising might provide other benefits, such as increase in upper and lower body muscle strength and muscle morphology (Borde et al. 2015), and increases in the functional capacity in the older population (Strasser & Schobersberger 2011).

Changes in fasting and postprandial appetite were observed in the first week of caloric restriction, which were associated with final outcomes (body weight and FM loss). Whether early changes would predict long-term weight loss maintenance remains to be investigated.

Taken together, our results suggest a higher impact of appetite related variables in weight management. Accordingly, it is becoming clearer that there is a need of more personalized recommendations in order to manage appetite, food reinforcement, and EI during and after weight loss programs in women. As such, it is tempting to suggest that the inclusion of alternatives to control EI such as closer nutritional follow-up or the use of appetite supressing medications would provide more significant meaningful and sustainable results in terms of weight loss and its maintenance if such approaches were tailored individually. A closer assessment of feeding-related measures in the first days of caloric restriction is required to demonstrate the need of closer control of early in-treatment feeding-related variables.

Our findings contribute in understanding of the challenges associated with the maintenance of lowered body weight. Furthermore, it reinforces the importance of control of feeding-related such as appetite and RRV for more successful weight management.

PART FOUR: CONTRIBUTION OF COLLABORATORS

CHAPTER IX: STATEMENT OF CONTRIBUTION OF COLLABORATORS

The collaborators involved in the conception and writing of this thesis (L.J.H. and E.D.) contributed as follows: L.J.H. and E.D. interpreted all findings and collaborated to write each of the four articles presented herein in article format and also collaborated to write a review paper titled “Weight loss and Appetite Control in Women”, published in Current Obesity Reports, volume 6, issue 3, pp: 334-351, 2017, which was included in my Review of Literature. For this manuscript, L.J.H., S.M. and C.B.A. wrote the paper and designed all tables and figures. E.D. edited the all drafts.

For Articles I and III, titled “The rate of weight loss does not affect resting energy expenditure and appetite sensations differently in women living with obesity” and “Appetite changes after 7-day of caloric restriction predict final weight and fat mass loss in pre-menopausal women living with obesity”. L.J.H. performed all data collection, R.S.; A.D. and A.R collaborated with data collection. L.J.H. wrote the manuscript, and R.S.; A.D. and A.R all contributed in the editing of the manuscript. G.G. and E.D. were involved in the elaboration of the experimental design and collaborated in editing the manuscript.

For Article II, titled “The effects of different rates of weight loss on the relative reinforcing value of food and impulsivity in women living with obesity” L.J.H performed all data collection and wrote the manuscript, and G.G., and E.D. were involved in the elaboration of the experimental design and collaborated in editing the manuscript.

For Article IV, titled “A one-year resistance training program following weight loss has no significant impact on body composition and energy expenditure in postmenopausal women living with overweight and obesity”. L.J.H wrote the manuscript, M.B; J.M.L; D.P; R.R-L;E.D were involved in the elaboration of the experimental design and collaborated to edit the manuscript, V.M. and M.E.L were involved in data collection and collaborated to edit the manuscript.

PART FIVE: REFERENCES AND APPENDICES

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APPENDIX A

CONSENT FORM

Investigating the early markers of weight loss success

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1. INVITATION TO PARTICIPATE: You are invited to participate in the above named research study conducted by Luzia Jaeger Hintze M.Sc., Ph.D. (candidate), and her supervisors Dr. Éric Doucet (Ph.D.) and Dr. Gary Goldfield (Ph.D.). This study is part of Luzia Hintze's doctoral thesis project. This consent form will be explained to you, and you may choose to bring this consent form home so further reading and discussion with friends and/or family members is made possible.

2. PURPOSE OF THE STUDY: The objectives of this research study are to investigate the changes in resting metabolic rate and appetite in individuals who will lose the same amount of weight through a rapid-(10 weeks) or a slow-weight loss (20-week) program. We will also investigate whether the degree of energy deprivation has an effect on food wanting and liking, satiety efficiency, olfactory (smell) capacity and impulsivity towards food. Finally, we will investigate whether changes of the variables mentioned above observed after the first week of weight loss can predict the outcome of the weight loss program.

3. BACKGROUND: The underlying mechanisms and the role of central and peripheral systems in weight loss and weight recovery have been extensively investigated and discussed in the literature. In particular, the fat and fat free mass tissues combined with hunger and appetite centers in the central nervous system seem integrated in an important loop that drives energy intake upward. Moreover, changes in these compartments promote increased metabolic efficiency, attenuating energy expenditure among weight-losers. Taken together, it is evident that changes in energy expenditure in addition to the control of food intake play an important role in the regulation of body weight and body composition and their maintenance over time. However, whether or not a greater energy restriction and a greater rate of weight loss negatively affects changes in energy balance-related variables, remains to be determined. In the same way, a clear demonstration of the effects of the degree of energy deprivation, as well as the rate of weight loss on the reduction in energy expenditure is not yet available.

4. DESCRIPTION OF THE STUDY:

Preliminary session (Approximately 3 hours inside the lab and 7 day outside the lab)

During this visit, you will receive your consent form and you will be informed of the experimental procedures, which will be used during each experimental session, as well as the equipment that will be used to obtain the necessary data. Your weight (digital scale), height (standard standiometer), waist circumference and blood pressure will be measured at the start the session. You also will be asked to fill the inclusion criteria questionnaire, the 16-item Binge score symptoms and the Depression Beck inventory questionnaires that measures binge eating symptoms and depressive symptoms, respectively. If you present a score higher than 27 and higher than 19 for the 16-item Binge symptoms and the Depression Beck inventory questionnaire, you will not be eligible for the study. If you match the study inclusion criteria, you will have an equal chance of being assigned to one of two groups; one intervention will last 10 weeks and the second intervention will last 20 weeks but both groups are designed to produce the same amount of weight loss. We will inform you which intervention group you have been randomly assigned at the end of this visit. We will measure your resting metabolism (the energy you use while at rest) (indirect calorimetry). You will then be served a breakfast according to your personal choice and will be asked to

"eat as much or as little as you want" in 15 minutes. You will then be asked to complete other questionnaires the NEO-PI-3, Yale Food Addition Questionnaire that measure personality traits and food addiction symptoms, respectively. This session will be used to determine your breakfast during the experimental sessions and to determine the macronutrient composition (percentage of carbohydrates, fat and protein) will be adopted for you during your diet. You will be asked to fill a food menu and choose your meals for the rest of your day as well as for the day that will follow your visit. We will provide all your food items in lunch boxes and individual bags. You will be able to carry these items and you will be instructed to eat only the items that you will have chosen for these 2 days. Lastly, you will be asked to wear a biaxial accelerometer around your upper arm, 24 hours per day during 7 days, including when sleeping, but should remove it when in contact with water (for instance, when bathing, showering or swimming) because this device is not waterproof.

A. **Assessment of food intake at breakfast, for the remainder of the day and the following day of preliminary session (Approximately 1.5 hours inside the lab and 36 hours outside of the lab)—** The energy intake of breakfast will be measured with a test meal administered after anthropometric and resting metabolic rate are completed (approximately 1 hour upon you arrive at the laboratory). This test meal will be selected from a food menu, which contains 57 different food and beverage items. Once the selected food items are prepared and served, you will have 15 minutes to consume "as much or as little as you want" from the foods that you selected on the menu. The items and quantities that you will have in this session will be standardized as your breakfast during the experimental sessions. Afterwards, you will be asked to select the foods from the menu that you may want to consume after leaving the laboratory (at home or work for instance) for the rest of that day and the following day (until your habitual bedtime on day 2 of measurements). The selected food items will then be prepared, measured and placed into lunch box containers for you to take home. It is important that you only consume the foods and beverages in these lunch box containers for the remainder of the day and the following day. You will also be asked to bring back each lunch box container with any leftover foods and garbage (fruit peels and wrappings for instance) to the laboratory on day 3 (following the completion of all measurements). The macronutrient proportion (% carbohydrate, %protein and %fat) that you will intake in these days will be adopted for your diet, so it is important to maintain your diet patterns as normal as possible during these days.

B. **Assessment of energy expenditure (assessed during 7 days at home and work after the preliminary session)—**You will be asked to wear a biaxial accelerometer around your upper arm for the remainder of the day and the following 7 days (until your habitual bedtime on day 7 of measurements) to assess habitual energy expenditure during that time in your daily activities. You should wear the accelerometer 24 hours per day, including when sleeping, but should remove it when in contact with water (when bathing, showering or swimming) because this device is not waterproof.

Second Visit: (Approx. 1 hour)

Upon completion of the preliminary phase, you will be invited to a 2nd meeting at the lab, in order to receive the dietary instructions related to your weight loss program. This diet is the one that you will be instructed to follow for the duration of the weight loss program (10 or 20 weeks depending on your group). Your diet will be prescribed using the Canadian Food Exchange System. This method will allow you to select foods you enjoy during the weight loss, however in smaller quantities.

Exchange lists are groups of foods that contain a similar mix of carbohydrates, protein, fat, and calories. The Canadian exchange system there are seven exchange groups: Grains & Starches; Fruits; Milk & Alternatives; Vegetables; Meat & Alternatives; Fats; Unlimited consumption.

Within any group, you can exchange one food serving for another. For example, in the Meats group, some sample foods that equal one lean meat exchange might be: 1 oz. of white meat chicken or turkey with no skin or 1 oz. of lean beef.

The daily meal plan will contain foods from all seven Food Exchange lists in order to assure you a complete and a balanced nutrition. However, the number of portions from each group will be recommended based on your individual diet evaluated in the preliminary session. This session will also be used to clarify any potential questions that you have regarding the project and the intervention.

Third and Fourth experimental sessions (approximately 6 hours each)

Arrival at the laboratory (12 hours fasted, at 7:30 h)

You will have a total of 3 experimental sessions: before starting the diet (baseline measurement), 5 to 7 days after the beginning of the weight loss program and at the end of the weight loss program. Each of these visits will take approximately 5 hours. Here is a detailed description of the different methods/procedures that will be employed during each experimental session:

A. Anthropometric, body composition and resting metabolic rate assessments, consumption of a standard breakfast and appetite measurements (Approximately 4.5 hours)—Your height and body weight will be measured as soon as you will arrive in the laboratory for the experimental session. Your amount of body fat and muscle (by dual energy X-ray absorptiometry) and your resting metabolism (by indirect calorimetry) will also be measured. Afterwards, we will serve you breakfast. This meal will contain the exact amounts of each item that you consumed during the preliminary session. You will have 15 minutes to consume this entire meal. Additionally, you will be asked to answer 4 specific questions that quantify appetite sensations (desire to eat, hunger, fullness and prospective food consumption) using 100-millimeter visual analogue scales that will be administered before, immediately after (time 0), and every 30 minutes for 3 hours (30, 60, 90, 120, 150 and 180 minutes) following breakfast consumption.

B. Dual energy X-ray absorptiometry (Approximately 10 minutes): We will assess your body fat using the dual energy X-ray absorptiometry (DXA). You will be asked to wear a standard issue hospital gown, to lie on an examination table and do not make any movement during the assessment. In the meantime, a low-intensity X-ray will scan your entire body.

C. Indirect Calorimetry (Approximately 45 minutes) - You will be required to remain resting for 30-min during this measurement. A plexiglass hood (similar to a plastic bubble) will be placed over your head through

which fresh air will be drawn. The expired air will be sampled for analysis and percentages of oxygen and carbon dioxide will be determined over the 30-min collection period. With this measurement, we will be able to determine your resting rate of oxygen consumption. With this information we can calculate your resting rate of energy expenditure. There are no risks associated with this procedure.

D. Leeds Food Preference Questionnaire (Approximately 15 minutes)—This task provides measures of the wanting and liking for an array of food images presented to you on a computer screen. During the test, each food image is presented with every other food image in turn. You will be instructed to select the food you "most want to eat now" during each trial. You will also need to rate each of the visual food cues in turn on a 100-millimeter visual analogue scale (anchored by Not at all-Extremely), based on the following questions: "how much do you want some of this food now?" and "How pleasant would it be to experience a mouthful of this food now", respectively. This task will be completed at 60 minutes and 180 minutes post-breakfast consumption, immediately following lunch consumption.

E. Behavioral Choice Task (Approximately 15-30 minutes)— For this task, you will sit in front of a laptop which will present to you 2 slot machine games: one is to earn points towards your preferred snack food and the other is to earn points towards your favorite fruit/vegetable. You will then have the opportunity to earn points towards your favorite snack and/or favorite fruit/vegetable by playing these different slot machines. To earn points, you must press a button on the mouse when the cursor is placed over the slot machine of choice, which then starts that slot machine. Points are then earned when all three objects on the screen match. This task will be completed immediately following the Leeds Food Preference Questionnaire administered at 180 minutes post-breakfast consumption and the amount of snack/ fruit earned during the game will be served with your lunch.

F. Olfactory (smell) capacity measurement (Approximately 30 minutes)—You will be required to complete 3 different odor tests. First, a set of 3 capsules will be subsequently presented to you and you must identify which of the 3 capsules presents an odor (the other 2 capsules are odorless). Second, a set of 3 capsules will be subsequently presented to you and you must identify which of the 3 capsules presents a different odor (the other 2 capsules will have the same odor). Finally, you will be required to identify the correct odor released by the capsule. Examples of some of the odors include rose, marker, banana, and grass.

G. Impulsivity towards food (approximately 10-15 minutes)

For this computer task, you will be instructed to respond to food and non-food images based on your personal preferences and choices. Your responses will be timed. This task will be done before lunch

H. Assessment of food intake at lunch (Approximately 30 minutes)—The energy intake of lunch will be measured with a test meal administered in the end of your experimental sessions (approximately 4 hours upon you arrive at the laboratory). This test meal will be selected from a food menu, which contains 57 different food and beverage items. Once the selected food items are prepared and served,

you will have 30 minutes to consume "as much or as little as you want" from the foods that you selected on the menu. The selected food items will then be prepared, measured and placed for you to eat at the lab.

Four follow-up sessions (approximately 60 minutes each)

During the intervention, you will be asked to visit the laboratory for a bi-weekly or a monthly evaluation (depending on the group to which you will be randomized). During these follow-up sessions will evaluate your weight, resting metabolic rate and fasting appetite. As soon as you arrive at the laboratory (12 hours fasted), we will measure your current weight, your appetite and your resting metabolic rate. We will offer you breakfast before you leave.

Four nutritional sessions (approximately 30 minutes each)

During the first month of intervention, you will be asked to visit the laboratory during which a consultation will be done with a dietitian. This will be accomplished to answer any questions you may have with the dietary intervention and to make modifications to this diet when necessary. If you prefer, these sessions will also be made possible using phone consultation at the time which best suits your schedule.

5. POSSIBLE RISKS/DISCOMFORTS:

The risks associated with this project are low and do not pose a great risk to health. The measure of body composition presents a low risk for you. However, this apparatus will expose you to minimal radiation (the equivalent of a day in the sun – 0.02–0.05 millirem). During the diet intervention, you might feel some physical discomfort (e.g. tiredness, weakness, dizziness, irritability and lethargy). However, we will provide a weekly consult in the first month of intervention, to address concerns you may have with your diet plan and to provide motivation to optimize compliance to your dietary plan.

There are no risks associated with the use of the other equipment/tools (wearing the biaxial accelerometer, resting energy expenditure measurement with indirect calorimetry, olfactory capacity tests, completing the food menu, visual analogue scales, the Leeds Food Preference Questionnaire, the Behavioral Choice Task with progressive ratios of responding and the go no-go task).

6. BENEFITS:

Parking at the research center is free for participants, as are all scientific tests. Following your participation in the 3 experimental sessions and the intervention, you will receive feedback on your personal results (body composition analysis, resting energy expenditure, and total energy balance assessment) and you will also receive feedback on the general results of the study following its completion if it is of your interest. Moreover, if you show interest, upon completion of the intervention, individualized diet and exercise plans will be provided to you to help achieve a healthier long term lifestyle. Free access to the exercise facilities at the Behavioral and Metabolic Research Unit, will also be provided for 4 months following the completion of the weight loss program.

7. CONFIDENTIALITY AND ANONYMITY:

In order to guarantee the confidentiality and anonymity of participants, all precautions and necessary measures will be taken to ensure that results and personal information of participants is kept under the strictest of confidentiality.

-Only the following persons will have access to the material which links the participant to their personal information: Supervisors and Principal investigator. Any other individuals involved in the study will not have access to participant's personal information.

-The names of participants will not appear on any reports. A number code will be used to identify participants on all research documents.

-All material and information which can be linked to participants will not be made public and will be kept under the strictest confidentiality.

-Participants will not be identified in any way in publications or reports.

-The data collected will be kept in a locked cabinet in the Behavioral and Metabolic Research Unit with restricted access where all participant's folders will be kept. In addition, the computer files will be protected by a password.

-Data will be destroyed 5 years after publication of study results.

-Data will be destroyed upon one's decision to withdraw, unless permission to use it is granted.

8. VOLUNTARY PARTICIPATION

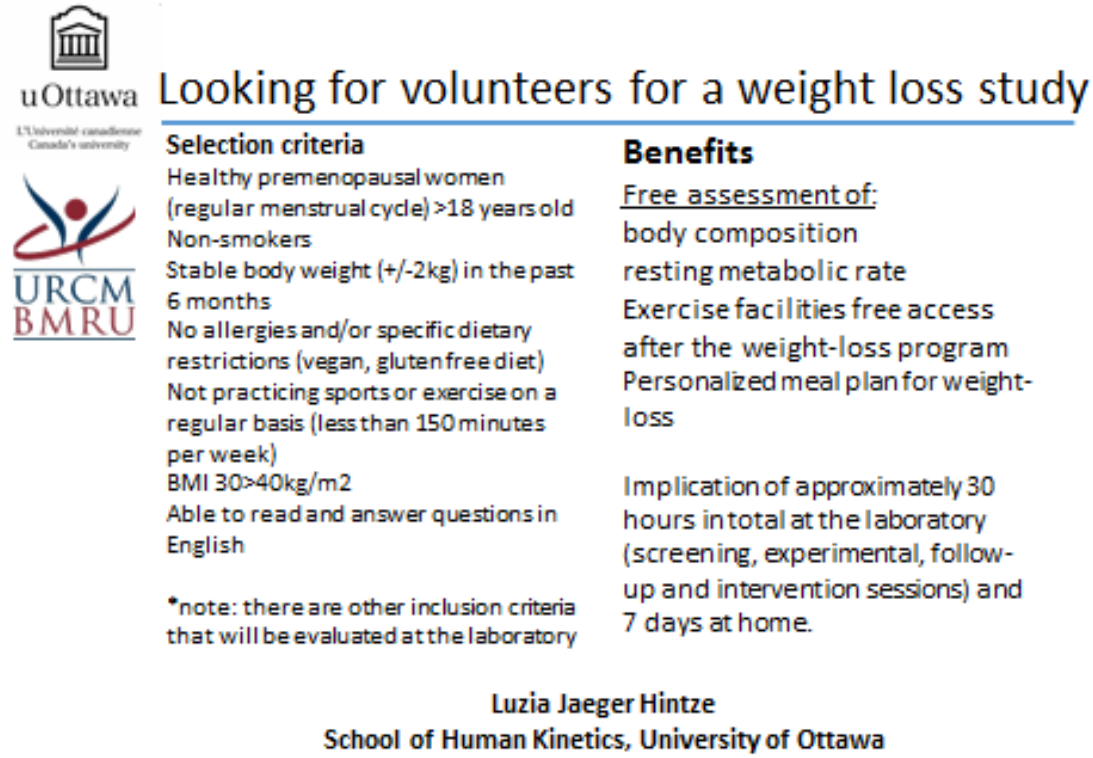
You are free to refuse to participate and if you choose to participate, you are free to withdraw from the study at any time for any reason. At any moment during this study, the best interests of participants will always prevail upon the objectives of the study. The participants will be made aware of new findings that might influence their decision to take part in the present study.

Any information about your rights as a research participant may be addressed to: Protocol officer for ethics in research, University of Ottawa, 550 Cumberland, Tabaret Hall, room 154, Ottawa, Ontario, K1N 6N5; Phone: (613) 562-5387, email: ethics@uottawa.ca.

If I have any questions about the conduct of the research project, I may contact the principal investigator **Luzia Jaeger Hintze, at 613-562-5800** or her supervisors **Dr. Éric Doucet,** at **613-562-5800** and/or **Dr. Gary Goldfield, at 613 737-7600**

There are two copies of the consent form, one of which I may keep.

APPENDIX B


uOttawa
L'Université canadienne
Canada's university
URCM
BMRU
Looking for volunteers for a weight loss study
Selection criteria
Healthy premenopausal women (regular menstrual cycle) >18 years old
Non-smokers
Stable body weight (+/-2kg) in the past 6 months
No allergies and/or specific dietary restrictions (vegan, gluten free diet)
Not practicing sports or exercise on a regular basis (less than 150 minutes per week)
BMI 30>40kg/m2
Able to read and answer questions in English
*note: there are other inclusion criteria that will be evaluated at the laboratory
Benefits
Free assessment of:
body composition
resting metabolic rate
Exercise facilities free access after the weight-loss program
Personalized meal plan for weight-loss
Implication of approximately 30 hours in total at the laboratory (screening, experimental, follow-up and intervention sessions) and 7 days at home.
Luzia Jaeger Hintze
School of Human Kinetics, University of Ottawa

APPENDIX C

File Number: H08-15-27 **Date (mm/dd/yyyy):** 10/29/2015

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Eric	Doucet	Health Sciences / Human Kinetics	Supervisor
Gary	Goldfield	Medicine / Medicine	Co-investigator
Luzia	Jaeger Hintze	Health Sciences / Others	Student Researcher

File Number: H08-15-27

Type of Project: PhD Thesis

Title: Investigating the early markers of weight loss success

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
10/29/2015	10/28/2016	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:
N/A

550, rue Cumberland, pièce 154 550 Cumberland Street, room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
(613) 562-5387 • Téléc./Fax (613) 562-5338
www.recherche.uottawa.ca/deontologie/ www.research.uottawa.ca/ethics/

File Number: H08-15-27 **Date (mm/dd/yyyy):** 10/29/2015

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement (2010) and other applicable laws and regulations in Ontario, has examined and approved the ethics application for the above named research project. Ethics approval is valid for the period indicated above and subject to the conditions listed in the section entitled "Special Conditions / Comments".

During the course of the project, the protocol may not be modified without prior written approval from the REB except when necessary to remove participants from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the project (e.g., change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, including consent and recruitment documentation, should be submitted to the Ethics Office for approval using the "Modification to research project" form available at: http://research.uottawa.ca/ethics/submissions-and-reviews.

Please submit an annual report to the Ethics Office four weeks before the above-referenced expiry date to request a renewal of this ethics approval. To close the file, a final report must be submitted. These documents can be found at: http://research.uottawa.ca/ethics/submissions-and-reviews.

If you have any questions, please do not hesitate to contact the Ethics Office at extension by e-mail at: ethics@uOttawa.ca.

Signature:

Kim Thompson
Protocol Officer for Ethics in Research
For Daniel Lagarec, Chair of the Health Sciences and Sciences REB

APPENDIX D

BARRAT IMPULSIVENESS SCALE

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	①	②	③	④
2	I do things without thinking.	①	②	③	④
3	I make-up my mind quickly.	①	②	③	④
4	I am happy-go-lucky.	①	②	③	④
5	I don't "pay attention."	①	②	③	④
6	I have "racing" thoughts.	①	②	③	④
7	I plan trips well ahead of time.	①	②	③	④
8	I am self controlled.	①	②	③	④
9	I concentrate easily.	①	②	③	④
10	I save regularly.	①	②	③	④
11	I "squirm" at plays or lectures.	①	②	③	④
12	I am a careful thinker.	①	②	③	④
13	I plan for job security.	①	②	③	④
14	I say things without thinking.	①	②	③	④
15	I like to think about complex problems.	①	②	③	④
16	I change jobs.	①	②	③	④
17	I act "on impulse."	①	②	③	④
18	I get easily bored when solving thought problems.	①	②	③	④
19	I act on the spur of the moment.	①	②	③	④
20	I am a steady thinker.	①	②	③	④
21	I change residences.	①	②	③	④
22	I buy things on impulse.	①	②	③	④
23	I can only think about one thing at a time.	①	②	③	④
24	I change hobbies.	①	②	③	④
25	I spend or charge more than I earn.	①	②	③	④
26	I often have extraneous thoughts when thinking.	①	②	③	④
27	I am more interested in the present than the future.	①	②	③	④
28	I am restless at the theater or lectures.	①	②	③	④
29	I like puzzles.	①	②	③	④
30	I am future oriented.	①	②	③	④

APPENDIX E

FOOD HABITS QUESTIONNAIRE
(Stunkard et Messick, 1984)

This questionnaire contains a certain number of propositions.

If you agree with the statement or if you feel like it can be applied to you, check the case TRUE who correspond to the statement.

If you disagree with the statement or if you feel like it does not applied to you, check the FALSE case who correspond to the statement.

You have the choice to answer (or not) certain questions.

		TRUE	FALSE
1.	**When I smell a sizzling steak or see a juicy piece of meat, I find it difficult to keep from eating, even if I have just finished a meal.**	o	o
2.	**I usually eat too much at social occasions, like parties and picnics.**	o	o
3.	**I am actually so hungry that I eat more than 3 times per day.**	o	o
4.	**When I have eaten my quota of calories, I am usually good about not eating any more.**	o	o
5.	**Dieting is so hard for me because I just get too hungry.**	o	o
6.	**I deliberately take small helpings as a means of controlling my weight.**	o	o
7.	**Sometimes things just taste so good that I keep on eating even when I am no longer hungry.**	o	o
8.	**Since I am often hungry, I sometimes wish that while I am eating, an expert would tell me that I had enough or that I can have something more to eat.**	o	o
9.	**When I feel anxious, I find myself eating.**	o	o
10.	**Life is too short to worry about dieting.**	o	o
11.	**Since my weight goes up and down, I have gone on reducing diets more than once.**	o	o
12.	**I often feel so hungry that I just have to eat something.**	o	o

	TRUE	FALSE
13. When I am with someone who is overeating, I usually overeat too.	o	o
14. I have a pretty good idea of the number of calories in common food.	o	o
15. Sometimes when I start eating, I just can't seem to stop.	o	o
16. It is not difficult for me to leave something on my plate.	o	o
17. At certain times of the day, I get hungry because I have gotten used to eating them.	o	o
18. While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	o	o
19. Being with someone who is eating often makes me hungry enough to eat also.	o	o
20. When I feel "blue", I often overeat.	o	o
21. I enjoy eating too much to spoil it by counting calories or watching my weight.	o	o
22. When I see a real delicacy, I often get so hungry that I have to eat right away.	o	o
23. I often stop eating when I am not really full as a conscious means of limiting the amount that I eat.	o	o
24. I get so hungry that my stomach often seems like a bottomless pit.	o	o
25. My weight has hardly changed at all in the last 10 years.	o	o
26. I am always hungry so it is hard for me to stop eating before I finish the food on my plate.	o	o
27. When I feel lonely, I console myself by eating.	o	o
28. I consciously hold back at meals in order not to gain weight.	o	o
29. I sometimes get very hungry late in the evening or at night.	o	o

	TRUE	FALSE
30. I eat anything I want, anytime I want.	o	o

31.	**Without even thinking about it, I take a long time to eat.**	o	o
32.	**I count calories as a conscious means of controlling weight.**	o	o
33.	**I do not eat some foods because they make me fat.**	o	o
34.	**I am always hungry enough to eat at any time.**	o	o
35.	**I pay a great deal of attention to changes in my figure.**	o	o
36.	**While on a diet, if I eat a food that is not allowed, I often them splurge and eat other high calorie foods.**	o	o

PART 2

Please answer the following questions by circling the number that best corresponds to you.

37. How often are you dieting in a conscious effort to control your weight ?

Rarely	Sometimes	Usually	Always
1	2	3	4

38. Would a weight fluctuation of 5lbs (2 kgs) affect the way you live your life ?

Not at all	Slightly	Moderately	Very much
1	2	3	4

39. How often do you feel hungry ?

Only At mealtimes	Sometimes between meals	Often between meals	Almost always
1	2	3	4

40. Do your feelings of guilt about overeating help you control your food intake ?

Never	Rarely	Often	Always
1	2	3	4

41. How difficult would it be for you to stop eating halfway through dinner and not eat for the next 4 hours ?

Easy	Slightly Difficult	Moderately Difficult	Very Difficult
1	2	3	4

42. How conscious are you of what you are eating ?

Not at all	Slightly	Moderately	Extremely
1	2	3	4

43. How frequently do you avoid « stocking up » on tempting foods ?

Almost Never	Seldom	Usually	Almost always
1	2	3	4

44. How likely are you to shop for low calorie foods ?

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

45. Do you eat sensibly in front of others and splurge alone ?

Never	Rarely	Often	Always
1	2	3	4

46. How likely are you to consciously eat slowly in order to cut down on how much you eat ?

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

47. How frequently do you skip dessert because you are no longer hungry ?

Almost Never	Seldom	At least once per week	Almost every day
1	2	3	4

48. How likely are you to consciously eat less than you want ?

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

49. Do you go on eating binges though you are not hungry ?

Never	Rarely	Sometimes	At least Once per week
1	2	3	4

50. On a scale of 1 to 5, where :

- 0 (zero) means no restraint in eating (eating whatever you want, whenever you want it) and,

- 5 means total restraint (constantly limiting food intake and never "giving in"),

What number would you give yourself?

- **Eat whatever you want, whenever you want it**
  0

- **Usually eat whatever you want, whenever you want it**
  1

- **Often eat whatever you want, whenever you want it**
  2

- **Often limit food intake, but often "give in"**
  3

- **Usually limit food intake, rarely "give in"**
  4

- **Constantly limiting food intake, never "giving in"**
  5

51. To what extent does this statement describe your eating behaviour?

"I start dieting in the morning, but because of many different things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow"

Not like Me	Little like me	Pretty good description of me	Describes me perfectly
1	2	3	4

APPENDIX F

The food menu used to assess energy and macronutrient intakes (English Version)

☐ Plain bagel

☐ Whole wheat bagel

☐ White bread

☐ Whole wheat bread

☐ Orange

☐ Apple

☐ Banana

☐ Apple sauce

☐ Raisin Bran

☐ Corn Flakes

☐ Harvest Crunch Cereal

☐ Cheerios

☐ Nature Valley Sweet and Salty Granola Bar

☐ Chocolate covered granola bar with marshmallows “Chewy Quaker”

☐ Nutri-Grain Strawberry Bar

☐ Tropicana apple juice

☐ Tropicana orange juice

☐ 7up

☐ Kit Kat

☐ Caramilk

☐ Hershey chocolate with almonds

☐ 70% dark chocolate

☐ Chocolate chip cookies

☐ Lays nature chips

☐ Lays BBQ chips

☐ Water

☐ 1% milk

☐ 2% milk

☐ Chocolate milk

☐ Butter

☐ Silhouette 0% yogurt

☐ Danone yogurt (1.5%)

☐ Red pepper

☐ Baby carrots

☐ Cucumber

☐ Ranch dip

☐ Cheddar cheese

☐ Breton original crackers

☐ Rice crackers

☐ 3 cheese pizza

☐ Meat lasagna

☐ Vegetable lasagna

☐ Marinara grilled chicken

☐ Vegetable soup

☐ Chicken noodle soup

☐ Beef and vegetable soup

☐ Creamy peanut butter

☐ Cream cheese

☐ Strawberry jam

☐ Mustard

☐ Mayonnaise

☐ Ketchup

APPENDIX G

List of Published Papers and Papers Accepted for publication that are not included in the thesis (2013-2018)

Dada, R.P., Branco, B.H.M., Terra, C.M.O., Larazin, S.P.B., **Hintze, L.J.**, Nardo Junior, N. Nutritional Status and Cardiometabolic Risk in Women: relationship with usual and unusual components of body composition [Estado Nutricional e Risco Cardiometabólico em Mulheres: relação com componentes usuais e não usuais da composição corporal] 2018 J. Phys. Educ. *In press*. [Article in Portuguese]

Mcneil, J , Forest, G. , **Hintze, L. J.** , Brunet, J-F. ; Doucet, É. 2017 The effects of partial sleep restriction and altered sleep timing on olfactory performance. Eur J Clin Nutr. 71, 1471-1472.

McNeil, J., Forest, G., **Hintze, L.J**, Brunet, J-F., Finlayson, G., Blundell, J.E., Doucet, É. 2017 The effects of sleep restriction and altered sleep timing on appetite and food reward. Appetite. 109, 48-56.

McNeil, J., Doucet, É., Brunet, J-F., **Hintze, L.J.**, Chaumont, I., Langlois, É., Maitland, R., Riopel, A., Forest, G. 2016 The effects of sleep restriction and altered sleep timing on energy intake and energy expenditure. Physiol Behav. 164, 157-163.

Hintze, L.J., da Silva, D.F., Bianchini, J.A.A., Dada, R.P., McNeil, J., Nardo Junior, N. 2016 Longer time after bariatric surgery and sedentary leisure modify anthropometric parameters, body composition and sarcopenic obesity markers in women. Rev Bras Ativ Fís Saúde. 6, 561-570.

Matsuo, A.R., da Silva, D.F., Bianchini, J.A.A., **Hintze, L.J.**, Antonini, V.D.S., Lopera, C.A., Hernandes, F., McNeil, J., Nardo Junior N. 2016 Differences between Obese and Severely Obese Adolescents in Relation to the Effects of a Multidisciplinary Intervention on Hypertriglyceridemic Waist Phenotype. J Exerc Physiol Online Online . v.19, 68-75

Silva, D.F., Bianchini, J.A.A., Barrero, C.A.L., Capelato, D.A., **Hintze, L.J.,** Nardo, C.C.S., Ferraro, Z.M., Nardo Junior, N. 2015 Impact of readiness to change behavior on the effects of a multidisciplinary intervention in obese Brazilian children and adolescents. Appetite, 87, 229-235.

Bianchini, J.A.A., Barrero, C.A.L., Silva, D.F., Seron, V.D., **Hintze, L.J.,** Nardo Junior, N. 2014 Obese adolescents who gained/maintained or lost weight have similar results in body composition and cardiometabolic risk factors following a multidisciplinary intervention. J EXERC SCI FIT, 12, 38-45.

Guilherme, F.R., Molena-Fernandes, C.A., **Hintze, L.J.**; Fávero, M.T.M., Cuman, R.K.N., Rinaldi, W. 2014 Hypertriglyceridemic Waist and Metabolic Abnormalities in Brazilian Schoolchildren. Plos One, 9 e111724.

APPENDIX H

Curr Obes Rep (2017) 6:334–351
DOI 10.1007/s13679-017-0273-8

PSYCHOLOGICAL ISSUES (M HETHERINGTON AND V DRAPEAU, SECTION EDITORS)

Weight Loss and Appetite Control in Women

Luzia Jaeger Hintze[1] · **Salma Mahmoodianfard**[1] · **Coralie Bonaparte Auguste**[1] · **Éric Doucet**[1]

Published online: 31 July 2017

Abstract
Purpose of Review The aim of this review is to describe and discuss weight loss-induced variations in appetite in women and factors responsible for these changes.
Recent Findings Studies have shown postweight loss increases in fasting and postprandial appetite in individuals engaged in weight loss trials, especially in women. Similarly, appetite-related peptides associated to the homeostatic control of feeding, such as leptin, ghrelin and peptide YY, were also found to be altered in way that promotes increased appetite after weight loss interventions. Sustained caloric deficits also drive increases in the frequency and strength of food cravings, food reward and seem to enhance oro-sensory sensations in women who lost weight. The menstrual cycle has also been to shown to influence caloric intake in women, more specifically food cravings. On the other hand, caloric restriction seems to increase cognitive restraint, decrease habitual disinhibition and susceptibility to hunger among women engaged in weight loss trials. Neural analysis corroborates these results, showing increased activation in brain areas involved in food reward and self-control processing.
Summary In conclusion, evidence supports that weight loss increases appetite sensations, and promotes changes in homeostatic and non-homeostatic control of feeding, which collectively seem to upregulate appetite in women.

Keywords Weight loss · Caloric restriction · Appetite · Energy intake

This article is part of the Topical Collection on *Psychological Issues*

✉ Éric Doucet

[1] School of Human Kinetics, University of Ottawa, Ottawa, Canada

Introduction

Worldwide BMI increased by 0.5 kg/m^2 per decade in women in recent history [1]. Non-surgical weight loss strategies are only effective over short period of times (3–6 months) [2]. Indeed, Kraschnewski et al. [3] reported that less than 20% of individuals attempting to lose a 10% weight loss were able to maintain this loss over a year. Moreover, systematic reviews have described extremely high weight recidivism with numbers ranging from 75 to 95% [3, 4]. Evidence supports that the homeostatic regulation of body weight exerts protective effects against weight loss more vigorously than against weight gain [5, 6]. These defensive predispositions involve central and peripheral systems that promote decreases in energy expenditure and increases in energy intake. The changes in energy expenditure partly stem from adaptive changes in thermogenesis [7, 8] while hunger and appetite centres simultaneously drive energy intake upward. In fact, many studies have reported increased appetite sensations following caloric restrictions, providing evidence of changes in the feedback control of energy intake, which results in a drive to eat exceeding that of prerestriction levels [9••]. Additionally, the small rates of success in conventional treatments (e.g. restricted caloric intake and increased energy expenditure) are likely not only due to increased hunger but can also be related to increased motivation to eat and to changes in rewarding components of food [10•].

The resilience of obesity might present an even greater challenge to women as they are approximately twofold more vulnerable to present severe and morbid obesity [11]. Women also often make up most of the participants in clinical trials related to weight management and other obesity treatments [12, 13]. This greater proportion of women in weight loss treatment intervention is due not only to physiological and physiological sex-related differences in eating but also to

interactions between cultural, social and biological factors as previously reviewed [14]. The present manuscript proposes a description of the changes in appetite sensations (hunger, motivation to eat, prospective food consumption and fullness) that arise from weight loss/weight maintenance strategies but more specifically in women. The aspects presented and discussed include variations in appetite sensations during the weight loss: possible factors for altered appetite during the weight loss, including appetite-related peptides and changes in food reward and eating behaviour traits.

Variations in Appetite During Weight Loss

It has been suggested that appetite is one of the predictors of energy intake and of the efficacy of a weight loss intervention [15, 16•], as well as weight loss maintenance [15, 17]. Furthermore, recent evidence has shown that changes in appetite offer a greater challenge to weight loss success than do metabolic adaptations [18•]. The objective of the following section is to present and discuss results related to changes of subjective appetite ratings after various weight loss interventions in women.

Effect of Caloric Restriction on Subjective Fasting Appetite Ratings

Caloric restrictions are commonly accompanied by changes in fasting appetite sensations. Several studies support this observation, showing increases in fasting hunger of 5 to 38%, as well as in fasting motivation to eat of 10 to 51%, and decreases in fasting fullness in 14 to 60% after caloric restriction [15, 19–21] (Table 1). Appetite markers have also been shown to remain unaltered after caloric restriction in women [15, 22]. Specifically, Moran et al. [22] reported no significant changes in fasting appetite in women with and without Polycystic Ovary Syndrome (PCOS), and increased fasting desire to eat, hunger and prospective food consumption (PFC) was reported only in men [15]. In contrast, some studies noted decreases in fasting hunger [23–25] and desire to eat [23, 24], together with an increase of fullness [24] after caloric restriction. However, it is important to note that one of the latter studies employed multivitamin and mineral supplementation [19, 24] in an attempt to downplay the effects of caloric restriction on appetite sensations. In another study, the manipulation of macronutrient distribution has been shown to attenuate the increases in fasting appetite sensations among women [25]. In sum, from the studies discussed in this section, it seems that caloric restriction per se increases fasting appetite. However, it seems that the use of calcium and vitamin D supplementation and a high-protein/low-carbohydrate diet might attenuate those increases in fasting appetite sensations after intervention.

One of the difficulties when comparing studies is the varying magnitudes of weight loss (see Table 1 for details). In fact, there are many studies showing that participants who presented higher weight losses (4 to 9%) also reported increases in fasting hunger [15, 19, 21], whereas those reporting lower decrease in percentage weight loss (3 to 6%) reported decreases in fasting hunger. On the other hand, when participants were categorized according to their weight losses (first, second and third tertiles), the ones who presented greater weight loss were the ones who had a lesser increased fasting appetite [20]. In this case, the smaller increases in appetite were related to higher weight losses in women, a factor which was considered to be a significant predictor of weight loss. Correspondingly, Gilbert et al. [21] reported a negative correlation between fasting desire to eat and changes in fat mass and a positive correlation between changes in fasting fullness and changes in fat mass. As such, it remains uncertain whether women who lose more weight also have greater increases in subjective appetite, or if women lost more weight because they presented smaller increases in subjective appetite rates. Indeed, it remains to be confirmed if higher weight loss is attributed to less important appetite changes, since it possibly facilitates tighter alignment with the dietary energy restriction.

Some studies have shown that the upregulation of fasting appetite seems to remain during the weight maintenance phase following caloric restriction. Doucet et al. [17] reported a sustained increase in fasting desire to eat, hunger and PFC during an 18-week postintervention follow-up. In parallel, after a 6-month follow-up period, Jakubowicz et al. [26] reported a 16% increase in body weight in women, which was accompanied by a 15% increase in postprandial hunger. Similarly, Sumithran et al. [34•] reported sustained increases in hunger after a 1-year follow-up during which a slight rebound in body weight was also noted. These observations suggest that individuals living with obesity, and who have lost weight, are very likely to be hosts to multiple compensatory responses related to appetite, which in concert could likely favour weight regain.

Effect of Caloric Restriction on Subjective Postprandial Appetite Ratings

Postprandial appetite is also altered by prolonged caloric restriction. For instance, increases in area under the curve (AUC) for hunger and desire to eat and a decreases in AUC for fullness and satiety were observed in several studies [17, 19, 20, 24, 27, 28]. Similarly, two studies report sustained elevations in postprandial hunger after a 6-month [26] or even a 1-year follow-up [34•]. In contrast, a 49% decrease of postprandial hunger was noted following a low-carbohydrate/high-protein dietary intervention [25]. As such, in addition to total weight losses as mentioned above, the macronutrient composition of diets employed to induce weight loss may also

Table 1 Variations on subjective appetite along weight loss

Study	Intervention	Sample size	Weight change	Results
Drapeau et al. [15]	Study 1: Drug (Topiramate) 12 months Study 2: Drug (Rimonabant) 4 weeks Study 3: Diet + fenfluramine/placebo N/A duration Study 4: Diet + PA approximately 30 weeks Study 5: Diet + Ca^{2+} + vitamin D/placebo 15 weeks Study 5: Diet + supplement/placebo N/A duration	315 obese participants (139 women)	All studies: Men: ↓4.8 kg Women: ↓4.5 kg - No initial body weight reported	↑Fasting desire to eat, ↑fasting hunger, ↑fasting PFC: in men, not in women, ↓lower satiety quotient in men
Doucet et al. [17]	Phase 1: 15-week caloric restriction (−700 kcal/day): Group 1: placebo + caloric restriction Group 2: 60 mg/day fenfluramine + caloric restriction Phase 2: 18 weeks: low-fat diet + aerobic exercise (65–70% VO_2 max 3–5×/week, 45-60 min/session)	17 overweight and obese (7 women)	Phase 1: Men: ↓11.4% Women: ↓8.4% Phase 2: Men: ↓13.7% Women: ↓10.5%	Phase 1 (baseline vs postintervention): ↑4%AUC desire to eat, ↓3.5%AUC hunger, ↑9%AUC fullness, ↓27%AUC PFC Phase 2 vs phase 1: ↑3% AUC desire to eat, ↓1% AUC hunger, ↑8% AUC fullness, ↓15% AUC PFC (in women)
Gilbert et al. [19]	6 months: caloric restriction (−600 kcal/day) Intervention: caloric restriction +calcium supplementation Control: caloric restriction + placebo	Intervention: 20 obese women Placebo: 21 obese women	Intervention: ↓9.1% Placebo: ↓6.7%	Intervention: ↑10.5% desire to eat, ↑5% hunger, ↑12.5% fullness, ↑14% PFC Placebo: ↑51% desire to eat, ↑21% hunger, ↓59% fullness, ↑12% PFC
Tremblay et al. [20]	12 to 16 weeks: caloric restriction: (−500 to 700 kcal/day)	75 women	Body weight: ↓3.7%	↑9% Fasting hunger, ↓14% fasting fullness
Gilbert et al. [21]	4 to 6 months: caloric restriction (−700 kcal/day)	54 overweight women	Body weight: ↓4.7% Body fat: ↓4.6%	VAS fasting: ↑13% desire to eat, ↑6% hunger, ↓15% fullness, ↑2.5% PFC SQ: ↑20% desire to eat, ↑11.5% hunger, ↑8.5% fullness, ↑11% PFC AUC: ↓7.5% desire to eat, ↓8.5% hunger, ↑4% fullness, ↓17% PFC
Moran et al. [22]	8 weeks: caloric restriction: (−30% total energy expenditure) EI: approx. 1200 kcal	PCOS: 14 women Control: 14 women	Intervention: ↓2.8% Control: ↓5.9%	↑Fasting fullness in PCOS and control ↓Postprandial fullness in PCOS and control No numerical baseline data provided
Hoddy et al. [23]	8 weeks: caloric restriction (−25% baseline energy expenditure) + ad libitum intake on each alternating feed day	59 obese participants (50 women)	Body weight: ↓4.2% Fat mass: ↓5.3%	↓Fasting hunger, ↑postprandial fullness, ↑AUC fullness No numerical baseline data provided
Major et al. [24]	15 weeks: caloric restriction (−700 kcal/day) (non-macronutrient-specific) Intervention: caloric restriction + calcium supplement Control: caloric restriction + placebo	Intervention: 19 (11 women) Placebo: 21 (11 women)	Intervention: ↓2.8% Control: ↓5.8%	Intervention: Fasting: ↓35% desire to eat, ↓7% hunger, ↑83% fullness, ↓19.3% PFC AUC: ↓42% desire to eat, ↓35.5% hunger, ↑24% fullness, ↓49% PFC
Nickols-Richardson et al. [25]	6 weeks: caloric restriction (EI: 1500–1700 kcal/day): low-CHO/high-PROT (LCHP) and high-CHO/low FAT (HCLF)	LCHP: 13 women HCLF: 15 women	LCHP: ↓5.7% HCLF: ↓3.3%	LCHP: ↓49% Self-rated hunger HCLF: ↓17% Self-rated hunger
Jakubowicz et al. [26]	16 weeks: EI: 1400 kcal to 1700 kcal/day Low CHO diet (LC) High CHO + breakfast dessert (HCP) 32-week follow-up	HCP: 97 overweight and obese participants (44 women) LCb: 96 overweight and obese participants (42 women)	Intervention: HCP: ↓14.9% LC: ↓16.8% Follow-up: HCP: ↓9% LC: ↑15.6%	Intervention: HCP: ↓0.2% AUC hunger, ↓1% AUC satiety LC↑14.5% AUC hunger AUC ↑5% AUC satiety Follow-up: HCP ↑3% AUC hunger AUC, ↑2% AUC satiety LCb ↓0.03% AUC hunger, ↓3.5% AUC satiety

Table 1 (continued)

Study	Intervention	Sample size	Weight change	Results
Jakubowicz et al. [27]	12 weeks: caloric restriction EI: 1400 kcal/day High-calorie breakfast (HCB): 50% daily calorie intake in their breakfast High-calorie dinner (HCD): 50% daily calorie intake in their dinner	HCB: 38 overweight and obese women HCD: 36 overweight and obese women	HCB: ↓11% HCD: ↓4%	Fasting: Hunger HCB < hunger HCD Satiety HCB > satiety HDC Post prandial: Hunger HCB < hunger HCD Satiety HCD < satiety HCB
Parra et al. [28]	8-week caloric restriction −30% of total energy expenditure (50–55% CHO, 16–20% PROT, 30–25% FAT) 1. Control: no seafood (6 placebo capsules/day) 2. Lean fish (150 g COD 3 times/week) 3. Fatty fish (150 g salmon 3 times/week) 4. Fish oil capsules (6 caps/day)	Low n-3 FA intake 112 (68 women) high n-3 FA intake 121 (67 women)	↓5.9% No specified info per group provided	Analysis: diets 1 and 2: Low FA intake diets 3 and 4: high FA intake 0 h postprandial: Fullness high FA > fullness low FA Hunger high LC FA < hunger low FA 2 h postprandial: Fullness high LC FA > fullness low FA Hunger high FA < hunger low FA
Martins et al. [29]	12 weeks: exercise program (500 kcal energy expenditure at 75% max heart rate, 5 days/week)	15 (7 women)	Weight-loss: ↓3.7%	Fasting: ↑58.5% hunger, ↑33.5% desire to eat, ↑18.5% PFC, ↓46 fullness Postprandial: ↑36% AUC hunger, ↑32% AUC desire to eat
King et al. [30]	12-week exercise program (500 kcal energy expenditure at 70% max HR, 5 days/week)	58 overweight and obese participants (39 women)	Responders: ↓5.7% Non-responders: ↓1%	Responders: ↑24% fasting hunger, ↑10%AUC hunger, ↓8.5% AUC desire to eat, ↑1%AUC fullness Non-Responders: ↑38% fasting hunger, ↑43%AUC hunger, ↑6.5% AUC desire to eat, ↓10%AUC fullness
King et al. [31]	12-week exercise program (500 kcal energy expenditure at 70% max HR, 5 days/week)	35 overweight and obese participants (25 women)	Non-compensators: ↓6.9% Compensators: ↓1.6%	AUC Compensators: ↑26% hunger Non-compensators: ↑1.4% hunger
Anton et al. [32]	6 months: Control: weight maintenance diet; Caloric restriction (CR): −25% baseline energy requirements Caloric restriction + exercise program (CR + EX; ↓12.5% baseline energy requirements + ↑12.5% total energy expenditure) Low-calorie diet (LCD): EI: 890 kcal/day	Control: 11 (6 women) CR: 12 (6 women) CR + EX: 12 (7 women) LCD: 11 (5 women)	Control: ↓1% CR: ↓10.4% CR+ EX: ↓10% LCD: ↓14%	Fasting appetite Control: ↑8% hunger, ↓26% fullness, ↑14% desire to eat, ↓22% satisfaction of appetite, ↑13% PFC CR: ↑13% hunger, ↓14% fullness, ↑23% desire to eat, ↓37% satisfaction of appetite, ↑13% PFC CR + EX: ↑11% hunger, ↓12% fullness, ↑12% desire to eat, ↓30% satisfaction of appetite, ↑21% PFC LCD: ↑13% hunger, ↓15% fullness, ↑14% desire to eat, ↓12% satisfaction of appetite, ↑15% PFC
Keim et al. [33•]	12-week caloric restriction and exercise program Nutrition: 23 to 28 kcal/body weight kg/day (60%CHO, 18% PROT, 22% FAT) + exercise: 5 days/week at 65% VO_2 max + 3 days/week resistance training	12 women	Body weight: ↓9% Fat mass: ↓21%	AUC: ↑31.5% hunger, ↓7.5% fullness, ↑39.5% desire to eat, ↑20.5% PFC

EI energy intake, *PCOS* polycystic ovary syndrome, *VAS* Visual Analogue Scale, *SQ* satiety quotient, *AUC* area under the curve, *PFC* prospective food consumption, *CHO* carbohydrates, *PROT* protein, *FAT* fat

need to be considered when comparing appetite changes during and after weight loss.

To our knowledge, there are only a handful of dietary interventions that have demonstrated decreases while others demonstrated insignificant changes in postprandial appetite markers following weight loss. Specifically, a decrease of postprandial AUC for desire to eat, AUC for hunger and AUC for PFC [24], as well as an increase postprandial AUC for fullness, were seen after caloric restriction [23, 24]. Hoddy et al. [23] have recently shown that after an 8-week alternating caloric restriction days, participants ($n = 59$, 50 women) had a non-significant change in postprandial hunger and an increase in postprandial fullness. In contrast, Moran et al. [22] reported a non-significant difference in subjective postprandial appetite markers following weight loss produced by an 8-week dietary intervention. Although a few papers have reported no increase or even a decrease in postprandial appetite in women after weight loss, it would seem that in sum, there are more studies supporting increased postprandial appetite sensations postweight loss. Such increases could potentially lead to increased energy intake, thus compromising long-term weight maintenance among women [17, 19–22, 27] and men and women together [28].

Effect of Exercise on Subjective Appetite Ratings

Exercise-induced weight loss is generally less than that obtained through dietary interventions [35]. Whether this is caused by a greater challenge to appetite control under those conditions remains to be determined. Martins et al. [29]recorded greater postprandial AUC hunger and desire to eat, as well as fasting hunger, desire to eat and PFC after a 12-week intervention. Fasting fullness and satisfaction of appetite decreased even if these changes were not reflected by actual changes in energy intake. Similarly, other studies have shown modifications in fasting appetite, which were reflected through increased energy intake only in the non-responders to the exercise intervention [30, 31]. On the other hand, results from this set of studies also demonstrated that exercise intervention can improve meal-induced satiety in both responders and non-responders. The above-mentioned studies included both men and women in their sample, and no sex effects were reported. In sum, a trend toward an increase in fasting appetite seems to emerge after exercise-induced weight loss, an observation mostly apparent in participants who presented some form of resistance to slimming. The role of exercise in satiety remains to be fully elucidated.

Effect of Caloric Restriction and Exercise on Subjective Appetite Ratings

Interventions combining caloric restriction and exercise exhibit similar influence on subjective appetite ratings, whereby appetite is stimulated. Anton et al. [32] led a 6-month weight loss study in four groups including men and women: control, caloric restriction, caloric restriction + exercise and very low-calorie diet also involving men and women. All groups had varying percentage weight losses (see Table 1 for details). Although the low-calorie diet produced the greatest percentage weight loss, the caloric restriction group reported increases in hunger (13%) and desire to eat (23%) and decreases in fullness (26%) and satisfaction of appetite (37%). The exercise plus caloric restriction group presented the highest increase in PFC (+21%). Along the same lines, Keim et al. [33•] reported increased AUC hunger, desire to eat and PFC, while decreased in fullness after 12-week of diet and exercise intervention in normal weight women. Overall, the studies combining caloric restriction and exercise that were reviewed also showed increased subjective appetite ratings. However, whether this increase translates to increased free-living energy intake remains to be clearly established. In addition, it would seem that an energy deficit imposed through caloric restriction poses a greater strain to appetite regulation in men, at least in the short-term [36]. It is unknown at this point whether this would also be the case in women.

Sex-Related Effects

Even though some of the studies reviewed in this section included men and women, for the better part, these studies included a greater number of women in their samples. Correspondingly, a total of 883 women vs 456 men out 1339 individuals participated in the studies reviewed. Given that these weight loss studies included a majority of women, it is reasonable to conclude that sex does not play a major role in appetite variations upon energy deficits leading to weight loss.

Collectively, changes in appetite during weight loss interventions are highly variable and dependent on various factors such as the type of intervention, individual characteristics and percentage of weight and fat loss. Those changes in appetite, or the absence thereof, are very likely influenced by the interplay between central and peripheral signalling, which also fluctuate in response to perturbations of energy intake. The following section explores some of the appetite-related peptides and reward driven behaviours, and how they could explain the modulations in the drive to eat that arise from weight loss interventions.

Possible Mechanisms for Altered Appetite Along the Weight Loss

Appetite-Related Peptides

Compensatory responses to energy deficits likely compromise weight loss and its maintenance. In this section, weight loss-

induced changes in appetite-related peptides will be discussed. Appetite-related peptides include, but are not limited to, leptin (long-term signal mainly released from adipose tissue) and gut-released ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) involved in short-term control of food intake and appetite regulation [37]. Briefly, short-term signals are modulated, at least in part, by meal size and composition, as well as by daily caloric intake, while long-term signals mostly fluctuate in response to fluctuations in energy storage [38]. The central nervous system (mainly the hypothalamus and hindbrain) integrates short- and long-term signals in an attempt to regulate energy stores, food intake and energy expenditure. Collectively, these peptides exert a coordinated action to direct feeding. Most of these have been shown to fluctuate with changes in adiposity. In fact, there have been numerous reviews extensively covering the role of these peptides during and after weight loss [37, 38]. The objective of the next section is not to present another similar review, but to rather highlight how these signals change during weight loss in women, and to discuss their role in influencing appetite responses. The studies reviewed in this section are presented in the Table 2.

Directors of Appetite and Food Intake

Several studies have investigated the relation between gut peptides and energy intake and appetite regulation in healthy subjects. Intravenous administration of ghrelin has been associated with immediate increases in appetite and food intake [56]. In contrast to ghrelin, fasting reduces leptin concentrations. Higher levels of adiposity are commonly accompanied by hyperleptinemia [57]; however, it seems that appetite suppression is not effectively occurring in individuals living with obesity despite the anorexigenic effects of leptin [39], probably due to a potential leptin resistance in individuals chronically exposed to higher adiposity [57]. Intravenous administration of PYY causes reductions in appetite and energy intake together with a subsequent decrease in ghrelin levels [56]. Like PYY, both central and peripheral administrations of GLP-1 have been reported to reduced food intake [58] and appetite [56], and it would seem that these effects are enhanced when both PYY and GLP-1 are administered conjointly [56]. CCK also exerts suppressive effects on food intake [59]. Indeed, intravenous administration of CCK1 receptor antagonists is associated with decreased satiety and increased hunger and meal size [60]. Collectively, these peptides are associated to fluctuations of acute and chronic energy status.

Appetite-Related Peptides After Weight Loss

Changes in the circulating levels of appetite-related peptides have been proposed to facilitate weight regain following weight loss in women living with obesity and overweight [61]. Energy restrictions trigger a more profound decrease in leptin concentrations during dynamic weight loss than during weight maintenance period [38]. In the first study of leptin after weight loss, Considine et al. in 1996 [40] reported that a 10% body weight reduction was associated with a 53% reduction in serum leptin. A few years later, Wisse et al. [41] subjected three groups of women living with obesity to different degrees of caloric restriction, fasting, very low-calorie diet (VLCD) and balanced-deficit diet (BBD). They reported that more severe restriction induced a greater decline in leptin during the first week. However, the difference was less dramatic when all subjects showed comparable fat losses at the end of the fasting, VLCD and BBD interventions (76, 61 and 52% reduction in leptin levels, respectively). Similarly, other studies reported a reduction in leptin concentration of 26% by diet alone [42] and by 40 and 67%, respectively [33, 43], from a moderate energy deficit in combined physical exercise. Moreover, administrating weight loss diets with different macronutrient compositions [44, 45] reduced serum leptin concentrations in similar ways regardless of dietary pattern. Overall, most studies have shown that weight loss induces reductions in leptin concentrations.

Similar to leptin, ghrelin is influenced by short and long-term energy imbalance. In the first documented report of the effects of weight loss on ghrelin, Cummings et al. [46] demonstrated that fasting leads to a sharp increase, while feeding contributes to its downfall. A 17% diet-induced weight loss in 13 obese individuals (8 women and 5 men) was associated with a 24% increase in AUC-ghrelin concentrations. Similarly, studies have reported lower circulating levels of ghrelin in people living with obesity compared to matched lean controls individuals, which may reflect a compensatory adaptation that contributes to a reduction hunger [62]. Weight loss following hypocaloric diets [47] or in combination with exercise [48] causes a significant elevation in ghrelin concentrations in overweight or women living with obesity by 18 and 72%, respectively. Weight loss induced by diet, exercise and drug therapy (Orlistat) in women with overweight was accompanied by a significant increase in ghrelin concentrations of 19% during 6 months of gradual weight loss but returned to baseline levels at subsequent 6 months of weight maintenance period [49]. In the same study, baseline ghrelin levels were also inversely correlated to the degree of weight reduction. In contrast, ghrelin concentrations remained unaltered following short-term energy-restricted diets for participants living with overweight or obesity (n = 132, 77 women) [22, 39]. The difference in results compared to other studies may be due experimental variations [39] or to the modest weight loss [22]. Collectively, available evidence supports a role for ghrelin in the regulation of long-term energy homeostasis.

Weight loss is also accompanied by reduced CCK response, which is associated with decreased leptin levels, an effect that could result in reduced satiety after meal consumption [60]. Weight loss induced by energy-restricted diet was significantly

Table 2 Peptide-hormonal changes after weight loss

Study	Intervention	Sample size	Weight changes	Results
Moran et al. [22]	8 weeks: caloric restriction EI: 1240 kcal/day	PCOS: 14 Control: 14 (only women)	Weight loss: PCOS: ↓4.1% Control: ↓5%	No change in ghrelin No change on fasting and postprandial CCK or PYY
Sumithran et al. [34•]	8 weeks: VLED EI: 500-550 kcal/day 62-week follow-up	34 overweight or obese participants (23 women)	Week 10 Weight loss: ↓14% Fat loss: ↓9.8% Week 62 (vs baseline) ↓Weight loss: 8.2%: ↓Fat loss: 5.3%	Week 10 ↓65% leptin, ↓25% PYY, ↓29% CCK ↓15% GLP-1, ↑45% ghrelin Week 62 (vs baseline): ↓36.5% leptin, ↓24% PYY, ↓6% CCK, ↓8% GLP-1, ↑20% ghrelin
Keim et al. [33•]	12 months: caloric restriction (−478 kcal/day + ↑energy expenditure 191 kcal/day)	12 women BMI: 23-37 kg/m^2	Weight loss: ↓9%	↓67% leptin
Crujeiras et al. [39]	8 weeks: caloric restriction (−30% total energy expenditure) 32-week follow-up	104 participants (49 women)	Week 8: weight loss ↓4.5% (women) ↓5.9% (men) Week 32: (25 women and 30 men) maintained the weight loss 49 subjects (24 men and 25 female) regained at least 10% of the lost weight	Weight loss >5% ↓51% leptin ↑Ghrelin 5.3% Weight loss <5% ↓28% leptin ↓5% ghrelin
Considine et al. [40]	8 to 12 weeks: caloric restriction EI: 800 kcal/ day (liquid diet)	7 obese participants (6 women)	Weight loss of 10% of the initial weight	↓53% leptin
Wisse et al. [41]	4 weeks: caloric restriction Total fasting: VLED: EI approx. 454 kcal/day LED: EI approx. 1.300 kcal/day (53% CHO, 30% PROT, 17% FAT) + 2-week refeeding	Total fasting: 8 VLED: 6 LED: 7 Only women (BMI > 30 kg/m^2)	At week 1: Fat loss: Fasting: ↓3.2% VLED: ↓2.8% LED: 1.9% fat loss The rates of loss remained constant in each subsequent week up to week 4	Fasting: ↓76.5% leptin at week 2 VLED: ↓61% leptin at week 2 LED: ↓52.5% leptin at week 4
Doucet, et al. [42]	15 weeks: caloric restriction Group 1: placebo + caloric restriction (−700 kcal/day) Group 2: 60 mg/day fenfluramine + caloric restriction	17 overweight and obese (7 women)	Men: ↓11.4% Women: ↓8.4%	Phase 1: ↓Leptin 26% (women) ↓Leptin 34% (men)
Mason et al. [43]	12 months: Caloric restriction: EI 1200–2000 kcal/day (30% FAT) Exercise: (45 min/day, 5×/week) Caloric restriction + exercise	Caloric restriction: 118 Exercise: 117 Caloric restriction + exercise: 117 Control: 87	Body weight: Caloric restriction: ↓8.5% Exercise: ↓2.4%	Only among women who lost ≥10% of body weight: Caloric restriction:

Table 2 (continued)

Study	Intervention	Sample size	Weight changes	Results
	Control	Only postmenopausal women (BMI > 27 kg/m^2)	Caloric restriction + exercise: ↓10.8%	↑11% ghrelin, ↓27% leptin Caloric restriction + exercise: ↑9% ghrelin, ↓40% leptin
Miller et al. [44]	12 weeks: Low-carbohydrate high-protein (LCHP): EI approx. 1400 kcal/day (20–60 g/day CHO + PROT + FAT) High-carbohydrate-low-fat diet (HCLF) EI: 1500–1700 kcal/day (60% CHO 15% PROT, 25% FAT)	LCHP: 13 HCLF: 12 Only women (BMI > 27 kg/m^2)	Weight loss: LCHP: ↓8.5% HCLF: ↓7.8% Fat loss: LCHP: ↓14.4% HCLF: ↓16.6%	LCHP: ↓42% leptin HCLF: ↓44.3% leptin
Thompson et al. [45]	6 months: caloric restriction (−500 kcal/day) Low CHO—(32% CHO) Low FAT—(17% FAT) Control	192 overweight/obese women Low CHO: 66 Low FAT: 73 Control: 53	Weight loss: Low CHO: ↓13% Low FAT: ↓12% Fat loss: Low CHO: ↓27.4% Low FAT: ↓27%	Low CHO: ↓59% leptin Low FAT: ↓62% leptin
Cummings et al. [46]	3 months: EI 1000 kcal/day (low-fat, high-protein) + multivitamin minerals 3 months: solid diet (55% CHO, 15% PROT, 30% FAT)	13 obese subjects (8 women)	Weight loss: ↓17%	↓38% leptin ↑24% area under the curve—ghrelin
Becker et al. [47]	12 weeks: Control Low glycemic index diet (LGI) GI < 55 (50% CHO, 20% PROT, 30% FAT)—20 kcal/kg BW	LGI: 14 Control: 12 Only infertile women (BMI >27 kg/m^2)	Control: ↑1% weight gain LGI: Weight loss: ↓5.8% Fat loss: ↓3.7%	LGI: ↓26% leptin ↑18% ghrelin
Leidy et al. [48]	3 months: Control Isocaloric diet: (55% CHO, 15% PROT, 30% FAT) + exercise (5 days/week at 70–80% max heart rate)	Exercise weight stable: 5 Exercise weight loss: 10 Control: 7 Normal weight women (BMI 18.5–24.9 kg/m^2)	Weight loss: Control ↓0.3% Exercise weight-stable: ↓0.8% Exercise weight-loss: ↓5.3%	Exercise weight loss: ↑72% ghrelin
Garcia et al. [49]	12 months: caloric restriction (−500 kcal/day) + exercise (30–150 min, 5×/week) + Orlistat (120 mg) Control (no intervention)	Treatment: 25 Control: 23 Only women	Treatment: Weight loss: ↓8.5% Control: no reported	Intervention compare to baseline ↑19% ghrelin at 6 months ↓8% ghrelin at 12 months ↑35% leptin at 12 months
Due Luis [50]	3 months: caloric restriction EI: 1520 kcal (52% CHO, 23% PROT, 25% FAT) + exercise program (3×/week for 60 min).	Weight gain: 14 (12 women) Weight loss: 75 (67women)	Weight gain: ↑3.2% Weight loss: ↓5%	Weight-loss: ↓8.5% GLP-1
Svendsen et al. [51]	8 weeks: caloric restriction EI:500–600 kcal/day	17 obese women	Weight loss: ↓11%	No changes in GLP-1
Olszanecka-Glinianowicz et al. [52]	8 weeks: caloric restriction EI: 1200–1400 kcal) + exercise (5×/week/30-40 min) + G1:120 mg of Orlistat G2: placebo	40 obese women G1: 20 G2: 20	Weight loss: G1: ↓9% G2: ↓6% Fat loss: G1: ↓22% G2: ↓7.4%	G1: ↑94.11% PYY ↑92.4% GLP-1 G2: ↑68% PYY ↑51.1% GLP-1
McNeil et al. [53]	6 months: Group 1 (G1): caloric restriction (−800 kcal/day)	G1: 65 G2: 28	Weight loss: G1: ↓5.7%	G1: ↓19% leptin ↑5% PYY

Table 2 (continued)

Study	Intervention	Sample size	Weight changes	Results
	Group 2 (G2): caloric restriction + resistance training	Only postmenopausal women BMI > 30 kg/m^2	G2: ↓8.2% Fat loss: G1: ↓10.3% G2: ↓16.1%	G2: ↓29% leptin ↑4% PYY
Hill et al. [54]	12 months: caloric restriction: ↓fat intake and ↑water-rich food intake	71 obese women	Weight loss: ↓7.8% Fat loss: ↓13.5%	Month 6: ↑14% ghrelin Month 12: ↑11.5% PYY ↑9% Ghrelin
Sloth et al. [55]	Phase 1: 8 weeks: 1000 kcal/day Randomization phase 2 Phase 2: Isocaloric isoenergetic diet Moderate fat (35–45% FAT) Low fat (20–30% FAT) Control (35%)	Phase 1: 131 overweight/obese participants Phase 2: 42 overweight/obese participants Moderate fat: 15 (8 women) Low fat: 18 (10 women) Control: 9 (4 women)	Phase 1: at least ↓8% Phase 2: Moderate fat: ↑4.2% Low fat: ↑3% Control: ↑4.7%	Phase 1: ↓GLP-1; PYY↓ Numbers not specified Phase 2: Moderate fat: ↑47% GLP-1; ↑26% PYY Low fat: ↑14.5% GLP-1; ↑9.5% PYY Control: ↑51% GLP-1; ↑20% PYY

EI energy intake, *PCOS* polycystic ovary syndrome, *LED* low-energy density, *VLED* very low-energy diet, *CHO* carbohydrates, *FAT* fat, *PROT* protein, *CCK* cholecystokinin, *PYY* peptide YY

and negatively correlated with changes in AUC-CCK. However, weight loss caused no differences in fasting or postprandial CCK levels of women with and without PCOS. It is hypothesized that the low amount of protein or fat consumed by the participants may have not sufficient to stimulate postprandial CCK release [22]. The studies investigating the effects of weight loss exclusively in women are few, but weight loss following a VLCD for 10 weeks was accompanied with a 29% reduction in CCK (fasting and postprandial) levels in a group of women living with overweight or obesity, which was not different from men in the study [34].

GLP-1 regulates the homeostatic control of feeding. It reduces the rate of gastric emptying, which in turn slows nutrient absorption, leading to the decrease in postprandial glycaemia and enhanced satiety [63]. There are discrepancies as far as the effects of weight loss on GLP-1 are concerned. GLP-1 levels were reduced by 15% in men and 8.4% in women following diet-induced weight loss [34•, 50]. In contrast, a VLCD induced 11% of body weight reduction in young women with obesity did not alter GLP-1 levels [51]. On the other hand, 8 weeks of low calorie, physical activity or Orlistat (or placebo) intervention increased pre- and postprandial GLP-1 by 45% in the Orlistat group [52]. That latter result should be interpreted in light of the fact that the greater increase of plasma GLP-1 levels in women receiving Orlistat could have resulted from the inhibition of the intestinal lipase activity causing increased intestinal fat content, thus likely contributing to greater stimulation of GLP-1 release.

Some studies have reported that individuals living with obesity have lower fasting and postprandial anorexic gut peptide concentrations due to reduction in PYY synthesis or releases. It has consequently been proposed that PYY deficiency could be involved in the pathogenesis of obesity [64]. Similar to GLP-1, there are inconsistencies regarding the weight loss-induced PYY response. In the first study of acute energy deprivation in adults, a reduction ranging from 11 to 50% of fasting and postprandial PYY levels was been reported during the two to four first days of calorie intake reduction [65]. Energy restriction reduced PYY levels by 25% in a group of men and women with overweight or obesity [34•]. However, a modest increase (non-significant) in PYY levels was found after weight loss in overweight/obese postmenopausal women [53] or women with PCOS [22]. The absence of significant changes in fasting or postprandial PYY following weight loss may be due to insufficient intervention duration, to the degree of weight loss, to increased central nervous system sensitivity to the effects of PYY or to other compensatory responses set in motion to restore energy balance [22]. In contrast, a low-calorie diet and regular physical activity with or without Orlistat therapy was followed by significant increases in PYY concentrations but this elevation was about twofold higher in the group receiving Orlistat compared to placebo (105 vs 46%). The increases in PYY levels were independent

of body mass changes [52]. In line with these results, PYY levels have also been shown to increase by 11.6% after both a weight loss through low-energy density diet for 12 months and a weight maintenance period [54].

There are also several studies that have investigated appetite-related peptide profiles during a postweight loss weight maintenance phase. In the first of these, persistent reductions in leptin, insulin, PYY and CCK concentrations and significant elevation in levels of ghrelin were shown after a 12-month weight maintenance phase [34•]. These observations suggested compensatory persistent alterations in circulating mediators of appetite that could favour weight regain [66]. In a group of obese/overweight volunteers (men and women), a weight regain ≥10% after 32 weeks of initial weight loss was associated with higher baseline fasting leptin and lower ghrelin levels [39]. In this study, ghrelin concentrations were significantly higher in women than men at all points of the study. Higher levels of leptin contributed to body weight regain, more so in women. In contrast, higher levels of ghrelin were associated with less weight regain, especially in men. Findings from these suggest that weight regain following weight loss may be partly predicted from hormone levels at baseline.

As mentioned above, there are some discrepancies regarding the hormonal alterations following weight loss interventions in women. Those differences are likely due to the variety of interventions, the degree of weight loss, the duration, participant characteristics including pre- or postmenopause status and different responses in hormone regulations. Overall, it would seem that alterations in appetite-related peptides signalling are in a direction, which would favour weight regain. However, most of weight loss studies have not compared the effects of diet induced weight loss between men and women, so whether or not there are sex-related differences in the peptide signalling remains uncertain. Moreover, weight loss studies investigating alterations in levels of specific peptides following weight loss, including CCK, PYY and GLP-1 exclusively in women, are still necessary in order to clarify the effects of body weight fluctuations on appetite-related peptides only in women. Considering the small number of studies that have reported changes in gastric inhibitory polypeptide, pancreatic polypeptide and amylin in women and the lack of evidence pointing to changes in these peptides following caloric restriction, we have not included them in the present review. There is also insufficient data to conclude that for similar weight losses, exercise interventions would promote changes in appetite-related peptides that would be different from that observed from caloric restriction.

Appetite Regulation Following Gut Peptide Alterations

To our knowledge, a handful of studies have investigated the effects of appetite-related-hormones alterations induced by weight loss on changes in subjective appetite measures simultaneously and more particularly, in women (Table 2). In the study by Keim et al. [33•], the decrease in leptin levels was accompanied by increases in hunger and desire to eat and it was associated with increased AUC hunger and PFC. While weight loss increased the sensation of fasting fullness in a group of overweight age- and weight-matched women with and without PCOS, postprandial appetite hormones were not associated with weight loss or with appetite scores [22]. However, a ≥8% weight loss in subjects with obesity (men and women), followed by a 2- to 3-week weight stabilization period, was accompanied by lower levels of fasting GLP-1 and PYY along with increased appetite scores and hunger sensation [55]. Moreover, weight loss by VLED in 50 overweight or men and women with obesity resulted in reductions of leptin, PYY and CCK and to an increase in ghrelin levels. These appetite-related peptide modifications were accompanied by higher mean ratings of postprandial hunger, desire and urge to eat and of preoccupation with thoughts of food and PFC [34•].

In general, most of the studies investigating appetite-related peptide alterations following weight loss have shown that prolonged energy deficits contribute to alterations in hormonal regulators of appetite in a manner that tends to increase appetite and decrease satiety, a condition that likely produces an overall promotion of food consumption and possibly overconsumption, which likely facilitates weight regain.

Reward Driven and Eating Behaviour Traits After Weight Loss

According to Berridge et al. [67], food reward is a composite process that involves "liking", "wanting" and learning as major components. The liking component of food reward is a subjective component that refers to the psychological process that produces pleasure, also called the hedonic impact. The main brain regions involved are the amygdala, the primary and the higher-order sensory cortical areas, including the insular and orbitofrontal cortex, which are responsible to form sensory representations of food [10, 68]. The wanting component of food reward refers to a conscious or subjective desire, involving a psychological process that encourages the behaviour and the consumption, stimulating goals and expectations. It is largely mediated by cortical circuits, including mesolimbic dopamine projections [69, 70] and commonly associated with food cravings and/or the motivation to obtain food. Finally, the learning component is composed of the associations with and predictions about reward, which are mediated by different regions of the brain such as cortical and orbitofrontal areas, insular and other regions of cortex [71–73]. More specifically, liking and wanting can affect energy balance whereby they can promote overconsumption of specific food items and potentially weight gain. These effects are described in the following section.

Table 3 Reward and eating behaviour traits after weight loss

Study	Intervention	Sample Size	Weight changes	Variables	Methods to measure	Results
Cameron et al. [75]	8 weeks: caloric restriction (−700 kcal/day)	15 obese adults (9 women)	Weight loss: ↓5.2% Fat loss: ↓8.2%	Food liking Food reinforcement	Visual Analogue Scale Progressive ratio computer task	No difference in the food reinforcement; ↑10% liking favourite snack
Massey and Hill [76]	Prospective quasi-experimental	52 dieters 40 weight–maintainers 37 non-dieters (only women)	Data not shown	Food craving frequency Food craving strength	7-day food record questionnaires Visual Analogue Scale	Dieters presented stronger cravings and more difficult to resist (compared with non-dieters and maintainers)
Gilhooly et al. [77]	6 months: caloric restriction High glycemic diet (60% CHO, 20% PROT, 20% FAT) Low glycemic diet (40% CHO, 30% PROT, 30% FAT)	32 overweight women	Weight loss: ↓8.8% Fat loss: ↓14.44%	Food cravings: Dietary restraint Disinhibition Susceptibility to hunger	Food Craving Questionnaire TFEQ	↑18.5% dietary restraint ↓Food craving giving in
Y Batra et al. [78]	20 weeks: caloric restriction EI: 500 to 1000 kcal/day (48% CHO 26% PROT, 26% FAT)	Intervention: 74 (54 women) Control: 21 (18 women)	Weight loss: Intervention: ↓9.2% Control: ↑1%	Food craving (frequency and intensity) Dietary restraint, disinhibition, susceptibility to hunger	Food Craving Questionnaire Food Craving Inventory TFEQ	↓Cravings frequency and intensity intervention group
Jakubowiz et al. [26]	16 weeks: caloric restriction EI: 1400 kcal to 1700 kcal/day, low CHO diet (LC), high CHO + breakfast dessert (HCP)	HCP: 97 (44 women) LC: 96 (42 women)	Weight loss: HCP: ↓15% LC: ↓17% Follow-up: HCP: ↓9% LC: ↑15.5%	Craving frequency for sweet, carbohydrates, fast foods, high-fat food items	Craving Score Questionnaire	Intervention: all craving scores (sweets, high fats, CHO/starches and fast foods) LC > HCP
Tremblay et al. [20]	12–16 weeks Caloric restriction: (−500 to 700 kcal/day)	75 women	Weight loss: ↓3.7%	Dietary restraint Disinhibition Susceptibility to hunger	TFEQ	↑42% Dietary restraint ↓23% Disinhibition ↓39% Susceptibility to hunger
Bas and Donmez [79]	20-week caloric restriction: EI: 1400 to 1800 kcal/day	96 overweight and obese individuals (76 women)	Weight loss: Men: ↓11% Women:↓ 11.5%	Dietary restraint Disinhibition Susceptibility to hunger	TFEQ	Men ↑30% dietary restraint ↓24% disinhibition ↓34% susceptibility to hunger Women: ↑30% dietary restraint ↓33% disinhibition ↓39% susceptibility to hunger
Ely et al. [80]	Cross-sectional study	10 historical dieters 10 non dieters 10 dieters (only women)	Data not shown	Dietary restraint Disinhibition Susceptibility to hunger Activity in brain areas related to food reward processing during visual food cues	TFEQ fMRI (high palatable food images/neutral food images/neutral images)	↑Dietary restraint in dieters and historical dieters Historical dieters vs non-dieters: ↑right anterior cingulate, ↑left middle frontal gyrus Historical dieters vs current dieters: ↑right middle frontal gyrus, ↑insula, ↑caudate, ↑pallidum

Table 3 (continued)

Study	Intervention	Sample Size	Weight changes	Variables	Methods to measure	Results
DelParigi et al. [81]	Cross-sectional study	9 obese reduced individuals 20 obese individuals	Data not shown	Brain activity response after consuming liquid meal	fMRI	Obese reduced vs obese ↑Dorsal prefrontal cortex ↑Anterior cerebellar lobe
Sweet et al. [82]	Cross-sectional study	44 participants 17 successful weight loss maintainers 15 obese 12 never obese	Data not shown	Brain activity during 1-min orosensory presentation	fMRI	↑Bilateral occipital regions ↑Left posterior, left middle and right insula ↑Left inferior frontal and left post central gyrus ↑Left putamen
Jakobsdottir et al. [83•]	4-week caloric restriction (−1000 kcal/day)	18 healthy postmenopausal women	Weight loss: ↓4.8%	Brain activity during visual food cues	fMRI and food images/ landscape images	↑Left anterior insula↑Left hippocampus↑ Amygdala ↑Right cingulate gyrus
Murdaugh et al. [84]	12 weeks: psychosocial weight loss program 9-month follow-up	21 obese participants (19 women)	Weight loss: ↓3.46% (total *n*) ↓3.64% (women) Follow-up period: ↑0.75%	Brain activity during visual food cues	fMRI and food images/landscape images	Weight loss: ↑insula, amygdala, ACC insula, ACC, middle occipital cortex, postcentral gyrus, inferior temporal gyrus
McCaffery et al. [85]	Cross-sectional study	17 weight maintainers 16 obese 18 never obese	Data not shown	Brain activity during visual food cues	fMRI and high-fat food, low-fat food and neutral pictures	Weight maintainers: ↑Central gyrus Obese ↑Left anterior cingulate

EI energy intake, *SQ* satiety quotient, *CHO* carbohydrates, *PROT* protein, *TFEQ* Three-Factor Eating Questionnaire, *fMRI* functional magnetic resonance imaging

For instance, food reward is normally highest for foods with high palatability, most often a characteristic of sweet and savoury foods. Increased motivation to eat, in conjunction with the types of food that are more frequently consumed under such circumstances, can favour positive energy balance and over time lead to increased levels of adiposity [74]. Similarly, perturbations of energy balance (e.g. calorie restriction and/or increased energy expenditure) have also been shown to influence the rewarding effect of food, potentially compromising weight loss and weight maintenance. A collection of studies that have measured food reward during weight loss is presented in the Table 3.

Impact of Caloric Restriction on Food Liking

The liking component of food forward is commonly measured by ratings of the pleasantness of the taste of a mouthful and of eating these foods or by the brain activity in areas related to pleasure. Liking has been shown to increase in response to acute hunger state [86–88] and by chronic perturbations in energy balance leading to a reduction in body energy storage [75]. Indeed, a greater explicit liking for sweet beverages was observed after 4 h of caloric restriction [86], whereas an increase liking for different food categories (savoury, sweet, high fat and low fat) was noted in participants 24-h fasting [87, 88]. Those changes were also related to olfactory performance in women [88], potentially encouraging an acute compensatory feeding response among participants. Along the same lines, longitudinal studies have reported a 10% increase in liking for the participants' favourite snack after 8 weeks of caloric restriction (−700 kcal/day), while this increase was not observed after a standard meal [75]. The changes in hedonic ratings were not related to changes in body composition, and no sex-related differences were reported.

It seems that acute and chronic caloric restrictions impact on food liking, especially that of high-energy-palatable food items. This increase can lead to subsequent increases in energy intake, which can compromise weight loss and make weight loss maintenance more fragile. The studies discussed above included both men (n = 50) and women (n = 75). However, considering that women composed the greater part of this overall sample and that no sex-related differences were reported, it is possible to speculate that liking in women and in men responds similarly to caloric restriction.

Impact of Caloric Restriction on Food Wanting

Results pertaining to the wanting component of food forward have been reported in several different ways, such as from food craving questionnaires, from food craving frequency, from desire to eat a portion of a palatable item and from functional imaging studies on brain areas related to craving and/or the motivation to obtain food. In the same way as the liking component, the wanting component of food reward can also be affected by acute and long-term caloric restriction, an effect that can lead to increased energy intake. In fact, randomized crossover design studies (fed state vs fasting state) have shown increased motivation to respond to foods after 4, 13 and 24 h fasting [86, 87, 89]. Individuals under fasting condition (vs fed state) also presented increased reinforcing value of foods [86, 87], causing them to work harder for food points during a computer task with the goal of earning a palatable food items. Greater explicit wanting for different food categories has also been reported in participants who were fasted for a 24-h period [87]. This condition was associated with a 70% increase of energy intake measured in the laboratory. These studies again included both men and women, and no sex differences were reported.

Similar to acute energy deficits, cross-sectional [76] and longitudinal studies have reported increased wanting, promoting an increase in food craving frequency after longer periods of energy restriction in women [26, 27, 77, 78]. Considering that most weight loss programs restrict not only the energy intake but also the consumption of high-energy density palatable food items, these interventions may compound the increase reinforcement value of the restricted food, which may be expressed as increased cravings for the restricted foods [77, 86]. In fact, food craving frequency was found to be a predictor of weight loss in women, whereas women who reported higher scores on Frequency Craving Questionnaire at baseline also had lesser weight losses [90]. Similarly, the reported percentage of time an individual gave in to food cravings was found to be a significant predictor of percent weight loss and weight maintenance. Conversely, women who presented a higher percentage of weight loss were also the ones who indicated a lower frequency of "giving in" to their food cravings [77].

Collectively, these findings highlight that increases in food wanting measured by computer tasks or measured through increased cravings may be part of the integrated appetite responses to caloric restriction in women. Furthermore, the strength and frequency of food cravings may mitigate the response to weight loss interventions and potentially weight loss maintenance.

Menstrual Cycle, Caloric Restriction and Food Wanting

The menstrual cycle seems to modulate total energy intake, craving frequency and energy expenditure as previously reported and reviewed [91]. In fact, during the follicular phase, it appears that women experience more frequent food cravings [92], particularly for chocolate [93] and increased explicit wanting for high fatty food [92], which could impact energy balance. More related to the context of this review, it was recently reported that permitting the ingestion of dark chocolate during the luteal phase, thereby increasing energy intake by 200 kcal, enhanced the compliance to a weight loss diet

[94]. Although it is likely that appetite control was improved as a result of the latter intervention because women lost more weight, appetite-related peptides measurements were not actually performed in this study.

Effects of Weight Loss on Eating Behaviour Traits

The following section will describe the effects of weight loss on eating behaviour traits, as measured with the TFEQ developed by Stunkard and Messink [95]. Results from weight loss studies commonly report significant increases in restraint [20, 77, 79, 96] and decreases in disinhibition [20, 79] and in the susceptibility to hunger [77–79]. Those results are also supported by functional neuroimaging analysis conducted in individuals who have lost weight and were able to maintain reduced body weight [80, 81].

More specifically, the decrease in the susceptibility to hunger in women seems to be more apparent in those who have lost more weight [20]. Indeed, Gilhooly et al. [77] reported a positive association between susceptibility to hunger and food craving frequency observed at baseline and after 6 months of caloric restriction in women. It was also recently reported that after controlling for sex and age in a model that included craving-trait and eating behaviours (restraint, disinhibition and susceptibility to hunger), only susceptibility to hunger was a predictor of weight changes after 20 weeks of caloric restriction [78].

Eating behaviours would thus seem to be influential mediators of diet-induced weight loss. In fact, increases in dietary restraint, in parallel to decreases in disinhibition and in the susceptibility to hunger, have been reported to be positively associated with the magnitude of weight loss in women. Interestingly, these associations may be reflective of the fact that eating behaviour trait modifications may be necessary to oppose other adaptive appetite responses that are discussed in this paper.

Neural Studies in Food Reward

In order to locate brain areas involved in the perception of food-related stimuli, functional neuroimaging modalities are commonly used. fMRI is the method most commonly employed to evaluate the brain activity while participants are exposed to external stimuli (visual or sensory). For instance, analysis comparing brain activity in lean and individuals living with obesity revealed activation of different areas involved in food reward processing [82, 97]. Along the same lines, longitudinal studies, including subjects during and after weight loss, have noted increased activation in food reward brain circuit (insula, amygdala, ACC, middle occipital cortex areas) among weight losers [83•, 84].

Investigations of post weight loss neural activity have revealed increased activity in parts of food reward brain circuit (insula, amygdala, ACC, middle occipital cortex areas) when exposed to high caloric food vs neutral images [84]. Results from 21 women with obesity exposed to high-caloric food vs control pictures revealed associations between weight loss and neural activation of brain regions mediating motivational and attentional salience of food cues implicated in reward-system processes, such as the nucleus accumbens, anterior cingulate and insula [83•]. The study also reported that at the onset of the caloric restriction, higher levels of glucose were associated with lower levels of activity in brain regions related to food reward processing (hippocampus and insula). However, these effects were no longer observed after the caloric restriction period, which could be an indicative of changes in satiety signalling [83•].

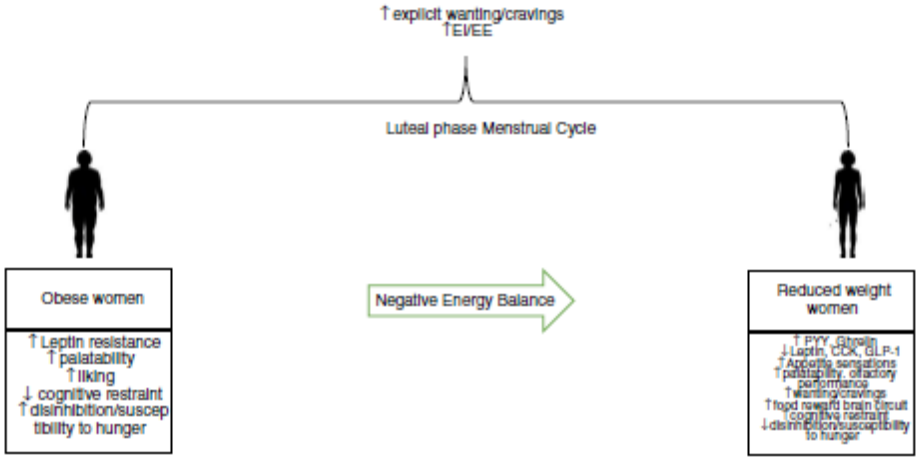


Fig. 1 Changes in subjective appetite, food reward, behavioural traits, peptides, and hormones in obese and weight reduced women after weight loss

Activity patterns in brain areas such as the insula, hippocampus and amygdala are altered not only during and after weight loss but also seem to persist after the weight loss. Cross-sectional analyses have shown increased activation in anterior cingulate and left middle frontal gyrus in historical dieter women compared to non-dieters [80]. Historical dieters also exhibited elevated response of the bilateral occipital regions, right middle insula, left middle, posterior insula, IFG, postcentral gyrus and putamen when exposed to a highly palatable food item [82, 85]. Using evidence of the implication of leptin in the control of feeding, Rosenbaum et al. [98] reported that subcutaneous injections of leptin in a small sample of weight maintainers (four women and two men) were sufficient to reverse the effects of weight loss on brain areas responsible for emotional and cognitive control of food intake.

There is evidence to support that successful weight losers present greater activation in reward circuitry. There is also data showing that those individuals present greater visual attention and great inhibitory control in response to food cues [85]. Greater activation in the dorsal prefrontal cortex, dorsal striatum and anterior cerebellar lobe in response to meal consumption has been noted in successful dieters when compared to non-dieters. Considering that the dorsal prefrontal cortex is responsible for the control of inappropriate behaviour, it may explain the high level of cognitive restraint normally observed in successful dieters. In fact, the stepwise regression models dietary restraint was the only variable associated with changes in neural activity after a standard meal (compared to 36-h fasting) in the dorsal prefrontal cortex and in the anterior cerebellar lobe [81]. Again, evidence presented in this section reflects the elevated reward circuitry activation in response to highly palatable food in weight-reduced women. Furthermore, these adaptations seem to persist after weight loss, and could seemingly be compensated by a greater engagement of inhibitory control of certain brain regions, a modification that could partly explain how some individuals afford to maintain weight loss.

Taken together, studies presented herein point out to a neurophysiological response in individuals who are exposed to acute or chronic caloric restrictions. Such responses could in turn increase their susceptibility to overeat when exposed foods of higher hedonic value. Individuals exposed to calorie restriction present increased reward driven behaviours, reflected by increased liking and wanting, observations that are supported by functional neuroimaging studies. Considering none of these studies reported the results separately for men and women, it is not possible at this time to ascertain whether or not these increases are more pronounced in women. Individuals who are more successful at maintaining weight loss also seem to display increased cognitive restraint and decreased susceptibility to hunger. Again, these observations are supported by increased activation in brain areas responsible for self-control among women who have maintained their weight loss. This could be interpreted as an attempt to counteract weight loss-induced increases in food reward among other appetite changes that occur with weight loss.

Conclusion

Most of the evidence presented and discussed points out to increased fasting and post prandial appetite after weight loss in women. Those changes are supported by alterations in hormonal regulators of appetite in a manner that tends to increase appetite and decrease satiety after caloric-restriction periods. Similarly, weight loss seems to increase food reward-driven behaviours such that it results in increased liking and wanting, observations that are supported by functional neuroimaging studies. Associations between magnitude of weight loss and increase in dietary restraint in parallel to decreases in disinhibition and in the susceptibility to hunger may be reflective of the fact that eating behaviour trait modifications are necessary to oppose other adaptive appetite responses to weight loss. Sex does not seem to play a major role in appetite variations after weight loss since no sex-related differences were reported in the studies included in this review. Studies comparing neuroimaging responses to caloric deprivation in men vs women are necessary in order to clarify if sex plays any role in the neurobiology of energy regulation. Furthermore, most of the changes presented throughout this review seem to persist after the weight loss. As illustrated in Fig. 1, collectively these demonstrations illustrate the inherent challenge that prolonged negative energy balance impose on appetite control, which very likely impedes both desired weight loss and long-term maintenance of lower body adiposity.

Compliance with Ethical Standards

Conflict of Interest Luzia Jaeger Hintze, Salma Mahmoodianfard, Coralie Bonaparte Auguste, and Éric Doucet declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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APPENDIX I

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A one-year resistance training program following weight loss has no significant impact on body composition and energy expenditure in postmenopausal women living with overweight and obesity

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ABSTRACT

Resistance training (RT) has been shown to decrease fat mass (FM), and increase fat-free mass (FFM), which can be a useful for weight loss maintenance.

Objective: To examine the effects of a 1-year RT intervention on weight loss maintenance following a 6-month dietary weight loss intervention.

Design: Following a 6-month dietary weight loss intervention (−6% ± 5.8; 5.05 kg ± 4.45), 70 post-menopausal women living with overweight or obesity were randomized to a control group (n = 34) or a RT group (n = 36) (3×/week first 6 months, 2×/week last 6 months, 70–80% of 1-repetition maximum). Body composition (DXA), abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (CT scan), resting energy expenditure (EE) (indirect calorimetry), physical activity EE and total daily EE were measured (doubly-labelled water).

Results: A total of 54 participants completed the study (control group n = 29; RT group n = 25) and compliance to the RT program was on average 64%. Significant regains were noted for body weight 0.98 (3.71) kg *vs.* 1.33 (3.94) kg and FM regain 1.32 (2.69) kg *vs.* 0.81 (3.26) kg in control and RT groups after the 1-year weight maintenance phase. No group differences were noted. Resting EE and total daily EE did not change after the weight maintenance phase, and no differences were observed between groups. Both groups had significantly greater than predicted decrease in resting EE after the 6-month dietary intervention and at the end of the 1-year weight-loss maintenance phase.

Conclusions: Our results suggest that a 1-year RT intervention following a 6-month dietary weight loss intervention does not improve weight loss maintenance, body composition or EE in post-menopausal women living with overweight or obesity.

1. Introduction

Dieting is the most common approach employed for losing weight in individuals living with obesity [1]. Restricting intake leads to weight loss in the short term however, it induces relatively poor long-term success rate for weight reduction [2,3]. In fact, data from the 1999–2006 National Health and Nutrition Examination Survey have shown that only 18% of individuals who attempted to lose weight were able to maintain the weight loss over a period of 1-year [4].

The high rate of recidivism can be partially explained by the existence of central and peripheral adaptations that promote increased appetite and suppressed energy expenditure (EE), which collectively

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compromise weight loss maintenance [5]. Given the high correlation between fat-free mass (FFM) and resting EE [6], a decrease in body weight and FFM, are consequently accompanied by a decreased EE [7,8]. A common observation after weight loss is that measured resting EE is also often lower than expected [9,10]. More specifically, a portion of the decrease in resting EE would seem to partly stem from adaptive changes in thermogenesis [11], which has been described as a decrease in resting EE beyond what can be predicted by loss of fat mass (FM) and FFM [12]. Sustained lower thermogenesis following weight loss can compromise weight maintenance and increase the likelihood of weight regain [5].

Despite previously discussed observations [7–9,12], some individuals are able to maintain their weight loss over extended periods of time [13,14]. Data from the National Weight Control Registry reported that increased levels of physical activity is one of the most common characteristics of successful weight losers [14–16]. In fact, exercising has been reviewed as a potentially useful strategy for weight loss maintenance since it is one of the components of EE that is under voluntary control [17] and it has been proposed to likely be easier to manipulate than caloric restriction for long-term maintenance of weight loss [18].

Along these lines, a 1-year endurance training program was shown to improve weight loss maintenance compared to the control condition in men, whereas the regain in FM was also significantly lower in the training group [19]. Similarly, the inclusion of a walking program following weight loss improved weight loss maintenance in both men and women [20,21]. However, little attention has been given to the role of resistance training (RT) on post-weight loss weight maintenance and on the weight loss induced changes in EE, particularly in postmenopausal women.

RT could prove useful for improving weight loss maintenance since it can contribute to increase FFM [22], resting EE and physical activity EE [22–24]; as well as to influence substrate partitioning [24–26]. The re-analysis of the results from the classical Minnesota study revealed that FFM may well be an important driver of appetite and energy intake after weight loss [12]. Indeed, a sustained hyperphagic response was noted during the refeeding phase after weight loss; which only ceased when participants had recovered 100% of their pre-weight loss FFM. However, at that point, FM exceeded baseline values by 74% [12]. From these observations, one could hypothesize that accelerated recovery of FFM following weight loss could be associated to a reduced hyperphagic drive, and possibly to better weight loss maintenance.

The purpose of the study was to determine the effects of a 1-year RT program on weight loss maintenance and measures of EE following a 6-month dietary weight loss intervention in postmenopausal women. We first hypothesized that RT would lead to better body weight loss and FM loss maintenance in postmenopausal women than a diet only intervention. Second, we also hypothesized that RT would be associated with higher resting EE when compared to a diet only intervention.

2. Methods

2.1. MONET project

The first phase of the MONET study (Montreal Ottawa New Emerging Team) included a randomized controlled design to investigate the impact of a 6-month dietary *vs.* dietary + RT on weight loss in postmenopausal women. The second phase involved the sub-randomization of women of the dietary arm only to a 12-month weight loss maintenance phase that either included dietary recommendations with and without a RT intervention (Fig. 1). Metabolic, inflammatory and hormonal profiles, as well as body composition, measures of EE, psychosocial profiles were studied. The 6- month dietary intervention phase and results have been described in details elsewhere [27]. This manuscript presents results of women from the dietary arm only who completed both the weight loss and the weight maintenance phases of the study. Measures presented include body weight and composition as well as energy expenditure.

2.2. Subjects

This prospective study included 71 overweight and obese postmenopausal women, who first completed a 6-month caloric-induced weight loss intervention. The study design is presented in the Fig. 1. Seventy subjects who completed the weight loss phase were randomized into a control ($n = 34$) or RT group ($n = 36$). One woman refused randomization. The study was approved by the University of Montréal, Faculty of Medicine Ethics Committee. Data were collected from 2003 to 2008. The inclusion criteria were as follows: 1) body mass index ≥ 27 kg/m^2, 2) cessation of menstruation for > 1 year and a follicle-stimulating hormone level ≥ 30 U/l, 3) non-smokers, 4) low to moderate alcohol consumption (< 2 drinks/day), 5) free of known inflammatory disease, 6) no use of hormone replacement therapy, and 7) physical activity levels (< 2 h/week of structured exercise). Furthermore, upon physical examination or biological testing, no participants had history or evidence of: 1) diabetes (fasting glucose > 7.1 mmol/l or 2-h plasma glucose of > 11.1 mmol/l after a 75-g OGTT), 2) untreated thyroid or pituitary disease, 3) chronic liver or renal disease, 4) asthma requiring therapy with steroids, 5) cardiovascular disease, peripheral vascular disease or stroke, 6) dyslipidaemia or hypertension requiring immediate medical intervention (total cholesterol > 8 mmol/l, systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg), 7) history of alcohol or drug abuse, 8) abnormal blood laboratory values (haematocrit < 32 or > 48%; creatinine > 130 μmol/l), 9) use of medications that could affect cardiovascular function and/or metabolism, 10) known history of inflammatory disease as well as cancer, and 11) orthopaedic limitations.

Pre-, post-weight loss intervention and post 1-year follow-up testing was preceded by a 1-month weight stabilization period. Body weight was measured over the course of 4 consecutive weeks in order to verify weight stability (± 2 kg). Assessment of anthropometric, and EE variables were performed after this period and were completed over approximately a month.

2.3. Nutritional intervention

The nutritional intervention for both groups consisted of monthly meetings with a registered dietitian. The total daily caloric intake was recommended to each participant (control and RT) and it was calculated based on their individual daily EE requirements measured by indirect calorimetry and by doubly labelled water (DLW) obtained from the measurements performed after the weight loss phase. All participants were encouraged to maintain their caloric intake based on their daily energy needs, with a macronutrient composition corresponding to 55%, 30%, and 15% of energy intake from carbohydrates, fats, and proteins, respectively. However, no individual meal plans were provided.

2.4. RT intervention

The 1-year RT weight loss maintenance intervention was performed weekly on 3 non-consecutive days for the first 6 months and on 2 non-consecutive days for the last 6 months. There is evidence in the literature demonstrating that RT practiced twice a week should be sufficient to promote healthy improvements in post menopausal women [28,29]. Accordingly, we opted to decrease the training frequency from 3 to 2 times a week in order to increase exercise compliance in our sample. The intensity of the RT was set approximately at 70–80% of 1-repetition maximum (1RM). Each training session included a warm-up period which consisted of low intensity walking on a treadmill for 10 min. Each exercise session was individually monitored for proper technique

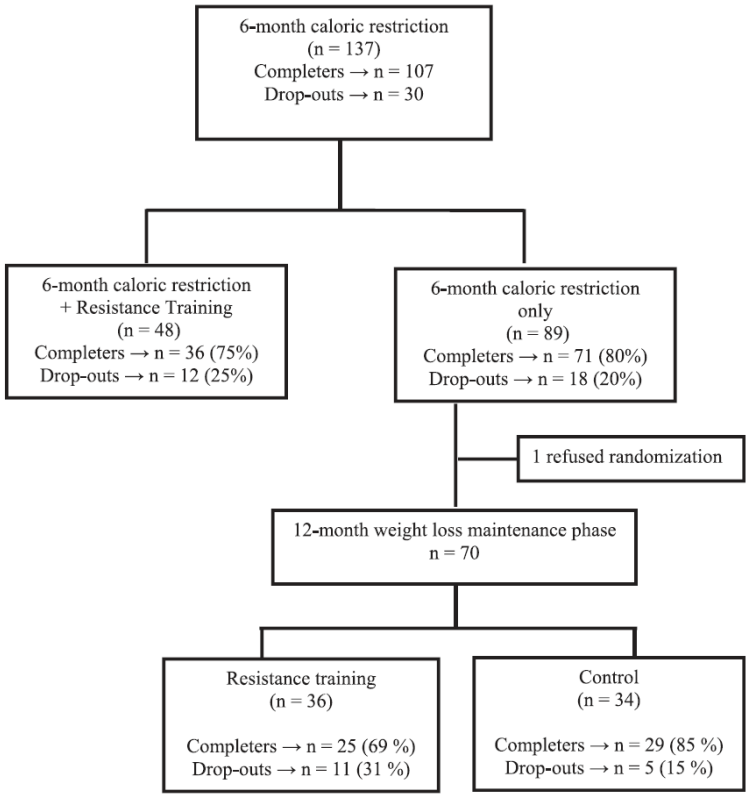

Fig. 1. Study design.

and optimal progression. The RT program consisted of the following exercises: 1) leg press; 2) chest press; 3) lateral pull downs; 4) shoulder press; 5) arm curls; and 6) triceps extensions. These exercises provided a RT for the major muscle groups of the body. Each participant was given a target load range and attempted to keep each set (n = 3–4) within the target range by adjusting the load to allow for the prescribed number of repetitions (n = 10–12). Resting periods were 1–1.5 min between sets. The exercise program was developed based on the ACMS guidance for RT [30] and it was supervised by qualified personal trainers.

2.5. Strength testing

A 1RM was performed to measure maximal dynamic voluntary strength in participants of the RT group. After warming-up on a treadmill, women were asked to position themselves in the leg press machine for the first test. A comfortable weight was set, and the participants were asked to slowly complete 10 repetitions at their full range of motion. The range of motion recorded from this first attempt was considered as a reference range of motion. A heavier weight was set after a 2-min recovery period, complete a maximum of repetitions while maintaining the reference range of motion. If they were able to complete > 10 repetitions, the participants were asked to stop in order to avoid any unnecessary fatigue. In case the participant was able to complete > 10-rep, participants had a 3-min recovery period and repeated the test with more weight added. The same procedure was repeated until only one repetition could be completed or until five attempts to determine 1RM were achieved. After 5 attempts, in case the 1RM was not achieved, the 1RM value was predicted using the Wathen [31] equation. Tests for lower body and upper-body strength were performed in leg press, lateral pull down and seated chest press positions, respectively. All tests were conducted over three non-consecutive days 1 week after the end of the 6-month dietary intervention and repeated 1 week after the end of the 1-year RT program.

2.6. Body composition

Body weight was measured to the nearest 0.1 kg on a calibrated balance (Balance Industrielle Montreal, Montreal, Quebec, Canada) and standing height was measured using a wall stadiometer (Perspective Enterprises, Portage, USA). FFM and FM were measured using dual energy X-ray absorptiometry (General Electric Lunar Corporation version 6.10.019, Madison, USA). In our laboratory, the intraclass coefficient correlation (ICC; 2-factor random effect) for test-retest for FM and FFM was 0.99 (n = 18). Body mass index [BMI = body weight (Kg)/height (m^2)] was calculated.

2.7. Computed tomography (CT)

A GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) was used to measure abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) levels. The subjects were examined in the supine position with both arms stretched above their head. The position of the scan was established at the L4-L5 vertebral disc using a scout image of the body. VAT area was quantified by delineating the intra-abdominal cavity at the internal most aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The SAT area was quantified by highlighting fat located between the skin and the external most aspect of the abdominal muscle wall [32,33].

Table 1
Changes in body composition following 6-month dietary intervention and 1-year weight maintenance phase.

	Control group (n = 29)			Resistance training group (n = 25)			p	Effect size	Time* group	Effect size
	Baseline	Post dietary Intervention	Post-maintenance phase	Baseline	Post dietary intervention	Post-maintenance phase				
BW (kg)	84.2 (13.5)	79.1 (14.1)	80.0 (14.3)	81.2 (14.0)	76.9 (14.1)	78.2 (15.3)	p < 0.001*	0.454	0.543	0.012
BMI (kg/m2)	32.1 (3.8)	30.1 (4.0)	30.5 (4.2)	31.6 (4.2)	29.9 (4.2)	30.4 (4.9)	p < 0.001*	0.548	0.578	0.028
FFM (kg)	45.2 (6.0)	43.9 (4.9)	43.9 (5.3)	44.6 (7.0)	44.2 (6.6)	44.4 (6.8)	0.007*	0.037	0.150	0.037
FM (kg)	37.7 (9.2)	33.3 (10.0)	34.6 (9.7)	35.3 (8.2)	31.8 (8.6)	32.6 (9.7)	p < 0.001*	0.457	0.611	0.009
Peripheral FM (kg)	18.2 (4.6)	16.4 (5.0)	16.8 (4.6)	18.0 (4.3)	16.0 (4.3)	16.9 (5.2)	p < 0.001*	0.398	0.621	0.009
Central FM (kg)	17.8 (4.5)	15.2 (4.7)	16.2 (5.2)	16.3 (4.3)	14.8 (4.9)	14.8 (4.8)	p < 0.001*	0.330	0.121	0.041
VAT (cm2)	187.8 (51.3)	159.0 (57.8)	163.0 (59.4)	158.4 (49.8)	144.5 (43.7)	148.1 (56.2)	p < 0.001*	0.240	0.126	0.042
SAT (cm2)	455.5 (119.8)	409.7 (127.0)	424.1 (123.6)	446.1 (107.2)	408.7 (117.3)	408.0 (129.0)	p < 0.001*	0.372	0.449	0.017

Data presented in mean and standard deviation; BW: body weight; BMI: body mass index; FM: fat mass; FFM: fat free mass; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue. VAT & SAT: n = 28 (control group) and n = 22 (resistance training group).

* Significant changes overtime ($p < 0.05$).

2.8. Resting EE

Resting EE was assessed by indirect calorimetry using the ventilated hood technique (SensorMedics Delta Track II, Datex-Ohmeda, Helsinki, Finland). Concentrations of CO_2 and O_2 were measured during 40 min (10 min of acclimatization and the average of the following 30 min were included in the analysis) and Weir's equation [34] was used to determine 24-h resting EE. Measurements were taken between 6:30 and 9:00 AM after 12-h fasting period. Subjects were lying down in a hospital bed in a room with minimum noise and light. They were asked to be as immobile and silent as possible. The temperature of the room was maintained at an average of 22 °C. In our laboratory, the ICC (2-factor random effect) for resting EE determined by using a test- retest condition in 19 different subjects was 0.92 ($P < 0.01$).

2.9. Total daily energy expenditure (EE)

Total daily EE was measured with the DLW method using stable isotope during a 10-day period before and after the weight loss phase and after the 1-year follow-up. Measurements were performed approximately 2 weeks before the beginning of the intervention and at least 48 h after the last resistance training session, after 4 weeks of weight stabilization period. A more detailed description of the procedure has been previously presented [35]. Physical activity EE was calculated as follows: Physical activity EE = total daily EE × 0.9 − resting EE [36], whereas 0.9 is factored into the equation to account for the thermic effect of food.

2.10. Statistical analyses

All data were analyzed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Results with a parametric distribution are presented as mean ± standard deviation, while variables with a non-parametric distribution (weight loss and % weight loss recovery) were presented in median and interquartile range (IR). Values for the 137 women from the weight loss phase (phase 1) of the trial have been reported elsewhere [27,37]. The enter method in linear multiple regression analyses was used to define the best predictors of resting EE (probability to enter the model was set at $P < 0.05$). The independent variables entered into the model were age, height, FM and FFM. However, only age, FFM and FM met the entry criteria of $P < 0.05$. We analyzed the model including FFM, age and FM ($R = 0.838$, $R^2 = 0.702$, standard error of estimate ± 102.3 kcal/day) and the model including only age and FFM ($R = 0.829$, $R^2 = 0.687$, standard error of estimate ± 104.6 kcal/day), and we opted to use the second model as a predictor.

The following equation was then computed: Predicted Resting EE = 564.049 + (24.084 × FFM) − (5.619 × age). Outliers were determined using exploratory data analysis. Accordingly, 4 outliers (greater than two standard deviations from the mean) for total EE and PAEE were removed from all subsequent EE analysis. Two-way repeated measures ANOVA were performed for changes in body composition and EE variables at baseline, after weight loss and after 1-year follow-up within each group and between groups (*time* × *group* interaction). Effects were considered significant at $P < 0.05$. Moreover, in order to assess the magnitude of potential observed differences, the effect size was computed (eta squared, η2). The values of 0.0099, 0.0588, and 0.1379 were considered benchmarks for small, medium, and large effect sizes [38]. We also performed additional analyses in order to compare results for the main outcomes (body weight, FM, FFM, resting EE, physical activity EE and total EE of participant of participant in the RT group who attended 75% or more of the RT sessions (n = 9) *vs* participant of the control group and RT group whose attendance was below 75%.

3. Results

During the 1-year follow-up, 16 subjects (or 23%) quit or stopped the study. Reasons included lack of motivation, injury related to RT, refused post-testing, and health problems not related to RT. As such, 54 subjects completed the follow-up and were included in the analyses (control: n = 29; RT: n = 25). The average compliance among completers of the RT intervention was 64% (minimum 12%–maximum 99%), where 9 attended at least 75% and 10 participants attended between 50% and 75% of the sessions throughout the year.

Physical characteristics of completers are reported in Table 1. Overall, a significant *time* effect was observed for body weight, FM, FFM, VAT and SAT. However, no interaction was observed between groups. Weight loss after the 6-month dietary intervention was 4.16 (IR 5.42) and 4.80 (IR 4.97) kg (p = 0.434) for participants who were then randomized to the control and in the RT group for the 1-y follow-up, respectively. Following the 1-year RT weight loss maintenance intervention, the control group maintained a weight loss of 2.72 (IR 4.5) kg, while the RT maintained a 3.32 (IR 6.64) kg weight loss (p = 0.403), reflecting a weight relapse of approximately 37.96 (IR 77.74) % and 20.42 (IR 131.39)% (p = 0.478) in the control and RT groups, respectively. Fig. 2 shows the individual changes in body weight in participants from the RT intervention.

Similarly, at the end of weight loss maintenance phase, FM regain was 1.3 ± 2.7 kg in the control group *vs* 0.8 ± 3.3 kg in the RT group. FFM also decreased after the dietary weight loss intervention

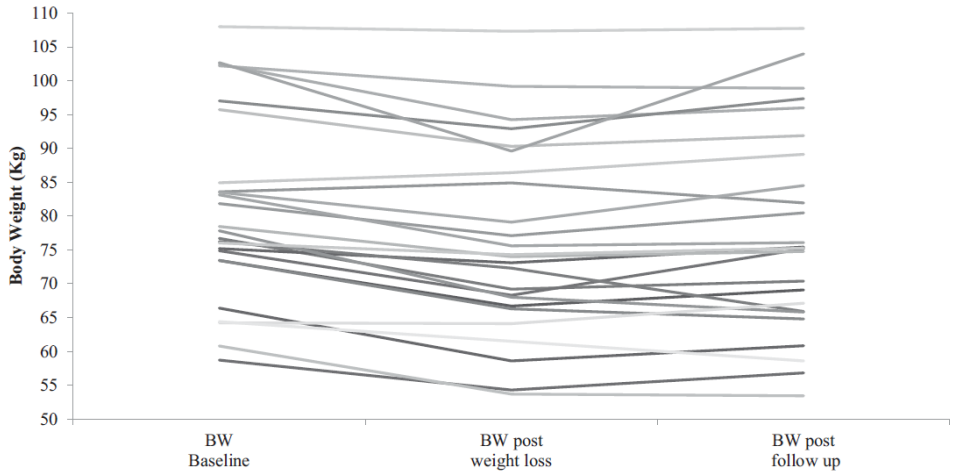

Fig. 2. Individual body weight changes in participants enrolled in the RT group.

(−1.3 ± 2.5 kg; −2.5 ± 4.3%) in control *vs* in RT (−0.4 ± 1.8 kg) and after 1-year of the weight loss maintenance phase it was −1.3 ± 2.4 kg in the control *vs* −0.2 ± 2.5 kg in RT). However, no interaction between time and group was observed ($P = 0.264$) and a small effect size was noted ($\eta2 = 0.051$).

Changes in VAT and SAT were significant overtime ($P < 0.001$, $\eta2 = 0.240$ and $P < 0.001$, $\eta2 = 0.372$ for VAT and SAT, respectively). No interaction between time and group and small effect sizes were observed for VAT ($P = 0.126$, $\eta2 = 0.042$) and SAT ($P = 0.447$, $\eta2 = 0.017$). In the control group, participants recovered approximately 2.57% of VAT and 3.52% of SAT after the maintenance phase, while the RT group recovered 2.5% of VAT but lost additional 0.2% of SAT.

Table 2 shows the measures of EE before and after follow-up. Resting EE was decreased significantly over time ($P < 0.001$), while a large effect size was observed ($\eta2 = 0.266$). On the other hand, no significant interaction of time*group was noted ($P = 0.077$) for resting EE, while a small effect size was observed ($\eta2 = 0.032$). Similar results were observed for physical activity EE ($P = 0.937$, $\eta2 = 0.005$) and in total EE ($P = 0.699$, $\eta2 = 0.037$) after 4 outliers (3 control and 1 RT) were removed from the analysis. Finally, a small effect size and no interaction was observed for physical activity EE ($P = 0.270$, $\eta2 = 0.041$) and for total EE ($P = 0.174$, $\eta2 = 0.047$).

We also compared RT participants with "higher attendance" to RT sessions (> 75%) to those with "lower attendance" (< 75%) and controls. Results showed no interaction and small effect sizes for weight ($P = 0.712$, $\eta2 = 0.022$), FM ($P = 0.372$, $\eta2 = 0.041$) and FFM ($P = 0.523$, $\eta2 = 0.031$). EE measures showed similar results, with small effects sizes and no interaction for physical activity EE ($P = 0.645$, $\eta2 = 0.032$) and total EE ($P = 0.393$, $\eta2 = 0.051$). Finally, resting EE presented a medium effect size ($P = 0.134$, $\eta2 = 0.070$). In addition, we performed correlations between changes in outcome variables and frequency of attendance (results not shown). No significant correlations were noted between frequency of attendance and changes in body weight and composition or changes in EE variables.

The analysis of results from women engaged in the RT who completed 1RM tests ($n = 11$), showed a significant increase in lower-body strength of 34.7 ± 21.1% ($P < 0.001$) and in upper-body strength of 26.8 ± 18.5% ($P < 0.001$).

Fig. 3 presents the predicted and the measured values for resting EE in both groups during the dietary weight loss intervention and maintenance phases. Significant differences between the measured and the predicted values of resting EE were noted at the end of the dietary weight loss intervention and differences persisted after 1-year follow-up in both groups ($P < 0.001$; $\eta2 = 0.262$). However, a small effect size and no interaction between groups for measured *vs* predicted resting EE was noted ($P = 0.435$; $\eta2 = 0.012$).

4. Discussion

Our results do not support our first hypothesis that weight loss maintenance would be better with RT since body weight and FM regain

Table 2
Changes in energy expenditure following 6-month dietary intervention and 1-year weight maintenance phase.

	Control group (n = 29)			Resistance training group (n = 25)			p	Effect size	Time* group	Effect size
	Baseline	Post dietary intervention	Post-maintenance phase	Baseline	Post dietary intervention	Post-maintenance phase				
Resting EE (kcal/day)	1311.5 (195.1)	1238.3 (147.3)	1216.9 (138.9)	1282.3 (174.3)	1230.4 (201.2)	1244.83 (206.62)	p < 0.001*	0.266	0.077	0.032
PAEE (kcal/day)	981.6 (256.8)	940.2 (226.8)	931.3 (203.7)	810.1 (281.4)	909.4 (356.4)	899.71 (251.10)	0.937	0.005	0.270	0.037
Total EE (kcal/day)	2528.1 (282.1)	2410.9 (285.9)	2310.0 (298.0)	2294.0 (298.9)	2351.2 (413.4)	2365.17 (341.80)	0.699	0.010	0.174	0.047

Resting EE: resting energy expenditure (measured value); PAEE: Physical Activity Energy Expenditure; FFM: Fat Free Mass; Physical Activity EE: Physical Activity Energy Expenditure; Total EE: Total energy expenditure. PAEE & TEE: $n = 20$ (control group) and $n = 18$ (resistance training group).

* Significant changes overtime ($p < 0.05$).

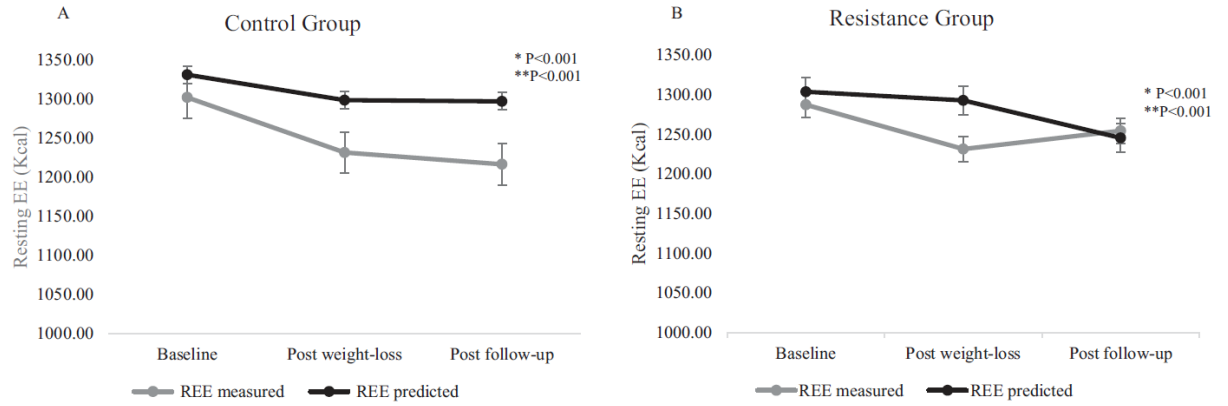

Fig. 3. Predicted *vs* measured values of resting energy expenditure (REE) following 6-month dietary intervention and weight maintenance phase in the control (A) and resistance (B) groups, * represents a significant change overtime; ** represents a significant different between measured *vs* predicted values.

were not different between control and RT groups following the 1-year weight-maintenance phase. Previous evidence has shown that aerobic exercise can be effective in improving weight loss maintenance in women [20,21]. To our knowledge, only a handful of studies have evaluated the impact of RT on weight loss maintenance [19,39,40], with one study reporting positive effects on maintenance of weight loss [40] and two studies reporting a positive impact on maintenance of FM losses [40,41]. Of note, one of the above cited study (35–50 year old) was conducted in men [41] and presented a shorter intervention phase (6-month) than what we report herein (1-year). The other study was performed in premenopausal women (21–46 year old) who achieved ~12 kg weight loss, assessed following 1-year weight loss. In fact, it has been reported that for the same RT volume, men present a better body composition response to RT than do women [29,42] and younger women present a better weight and fat loss responses following RT than postmenopausal women [22]. This could likely explain the discrepant results.

Along the same lines, our data did not show the anticipated effect of RT on body composition, even though RT has been shown to be as an effective approach to prevent FFM loss during caloric restriction and to promote an increase in FFM in elderly subjects [43,44]. It is well described in the literature that a single session of RT can stimulate acute increases in circulating testosterone, growth hormone and insulin-like growth factor-1 in different populations [45,46], an effect that may not be as pronounced in postmenopausal women [29]. Moreover, a lower anabolic response in postmenopausal women has been reported previously, an effect mainly accounted for by lower levels of testosterone [29]. All those factors could have together contributed to explain the lack of differences in body composition between RT and control groups in our study.

Our second hypothesis that women engaged in RT would present higher EE than the control group was also rejected. Although the impact of exercise on energy metabolism following weight loss is a topic widely discussed in the literature [20,47–50], no study has to our knowledge evaluated physical activity EE and total EE after during a 1-year weight maintenance intervention including RT in postmenopausal women. The study that most resembles our study design was the one conducted by Villanova [20]. They showed that increasing the number of steps/day (+20%) increases resting EE by 100 kcal/day, in spite of body weight loss (−1.8%). In contrast, we showed that regular RT sessions had no impact on resting EE following 6-month dietary intervention [51] and after 1-year post weight loss follow-up. Our design substantially differs from the study conducted by Villanova [20]. First, the differences between our results and theirs could be partly explained by the age and sex differences between the studies' samples. Villanova [20] included men and women aged 44 years old on average, while our study involved only postmenopausal women (58.3 ± 4.8 years). It was previously reported that RT can improve body composition and increase resting EE in young women [22] and in men [42,52], but this was not the case in our sample of postmenopausal women. Second, the exercise intervention was also different. We conducted a RT-based intervention while Villanova physical activity intervention aimed at promoting a daily increase in the number of steps among participants.

Our results also show that EE adaptations were present after the 6-month dietary intervention (800 caloric restriction/day) as previously reported [53] and persisted after the 1-year maintenance phase in the present study. Similarly to what we observed, previous studies also reported the existence of metabolic adaptations in resting EE after weight loss [5,54–56], which could partly be explained by decreases in heart rate, activity of the sympathetic nervous system, blood pressure, liver and kidney activities [56,57]. This depression in resting EE has been reported to persist for as long as 6-year after massive weight losses [58] and could be considered as a factor that contributes to long-term weight-regain. To our knowledge, our study is the first to show that lower resting EE persist in postmenopausal women even if RT is added after weight loss. These results contribute to our understanding of the challenges associated to the maintenance of lowered body weight.

We have previously reported no changes in both physical activity EE and total EE after the 6-month dietary intervention [51,53]. Along the same lines, physical activity EE and total EE were not changed after 1-year RT intervention. Studies that looked at physical activity EE after weight loss, reported significant decreases in both physical activity and the cost of physical activity following weight loss by caloric restriction [47,56,59–62], although no differences were noted after 12-month follow-up period [47,59]. In fact, evidence has shown that participants can become apathetic and less active during prolonged energy deficit periods [63,64], which could expedite weight regain among weight-reduced subjects. In postmenopausal women, an inverse association between decreases in physical activity EE and the amount of weight recovered after weight loss was reported. In other words, women who witnessed the greatest decrease in physical activity EE during energy deficit, were the ones who recovered more weight during follow-up [47]. This observation conflicting with some evidence indicating that menopause transition *per se* was also found to be associated with declines in physical activity EE and in total EE [65].

Even though our results do not support an increase in EE by RT in postmenopausal women after 6-month of dietary intervention, it is important to consider that RT might promote other benefits among our participants. As recently reviewed, RT also significantly improves upper and lower body muscle strength and muscle morphology in healthy

older adults [66]. In fact, our secondary analyses including a partial sample have shown a significant increase in upper and lower body strength after the 1-year RT intervention among the participants that completed the 1RM post-test evaluation. Along the same lines, we previously reported increases in strength in postmenopausal women were subjected to diet and RT during weight loss [67]. This increase could promote other benefits beyond the weight loss *per se* such as preventing falls [68] and increasing the functional capacity in this population [69].

Previous evidence has shown that adaptive thermogenesis is sustained only when body weight remains below the baseline values. Indeed, in individuals who recover their initial body weight, lower than predicted EE is no longer apparent [5,55]. Our participants recovered on average ~33% of their weight loss, which could partly explain the lower than predicted EE after the 1 year follow-up (Fig. 3). Our results also demonstrate that RT was not sufficient to correct the effects of weight loss on the greater than predicted decrease in EE in post-menopausal women, since no group differences were observed. Our findings are in line with previous research that reported that a greater than predicted decrease in EE is still present in individuals who lose weight through a combination of diet and exercise [8,53,62] and in individuals who employ exercise to maintain weight loss [7]. However, our results extend these findings to RT.

The present study has some limitations. First, the major limitation of the study is the adherence to the RT program during weight maintenance which was only moderate (64%). Despite this limitation, we ran additional analyses including only participants who completed 75% or more of the RT sessions and we compared results to controls and to the participants who performed < 75% of the RT sessions for weight, FM, FFM and EE, no differences were noted between groups. We also ran additional linear regression considering body weight and body composition changes in weight-maintenance phase (FFM, FM) as dependent variables and including RT attendance frequency as a potential predictor. Similarly, none of the changes in body composition correlated with RT attendance frequency (data not shown). Second, even though the RT intervention was designed according to the American College of Sport Medicine recommendations for elderly people, the EE achieved might have been too low, either because of low total duration [70], intensity and/or frequency, to observe significant improvement in body composition. We recognize that the volume of training could be a limitation of this study. However, considering our sample was composed of postmenopausal women living with overweight or obesity, the intervention prescribed and performed was realistic for the population studied. Thirdly, our sample size was limited to 54 postmenopausal women, and this cohort was composed of relatively "healthy", non-diabetic postmenopausal women living with overweight or obesity. Our results are strengthened by the inclusion of a well-characterized sample of weight-reduced postmenopausal women and by the utilization of gold-standard techniques to measure EE and body composition.

In conclusion, our results suggest that diet alone and diet combined with RT (2-3 ×/week – 45 min/session) have similar effects on body weight and composition maintenance as well as on EE in post-menopausal women after a 1 y post-weight loss follow-up. Furthermore, RT training did not attenuate the greater than predicted decrease in EE during the 1-year follow-up. Whether increases in the intensity, frequency and compliance to the RT program would have elicited the hypothesized effects remains to be determined.

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