The Effects of Caloric Restriction on Physical Activity, Energy Expenditure, and Weight Loss in Obese Adults

Hollie Kicinski

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Abstract

The prevalence of obesity continues to rise, and with it, an increased risk of associated cardiometabolic diseases. Obesity is a result of many factors leading to an energy imbalance between dietary energy intake and energy expenditure. Caloric restriction has shown its effectiveness in weight reduction intervention programs; however, the extent to which the components of energy expenditure are related to caloric restriction, weight loss, and weight loss maintenance is not well understood. The purpose of this study was to evaluate the relationship between non-exercise activity thermogenesis (NEAT), resting energy expenditure (REE), and the ability of obese adults to lose weight and maintain this weight loss. Obese adults (BMI>30 kg/m^2) were recruited from the Investigational Weight Management Clinic (IWMC) at the University of Michigan. Participants consumed a very low calorie diet (~800 kcal/day) using meal replacement shakes to promote 15% weight loss and then transitioned to a moderate calorie diet employing conventional foodstuffs. Habitual free-living physical activity was objectively assessed at baseline and at various prescribed intervals throughout the 2-year clinical program. REE was assessed at baseline, after 15% weight loss and again at the end of the two-year program.

The impact of initial caloric restriction on NEAT differed between women and men (women -28±17 minutes, men +22±14 minutes, mean±SEM, $p<0.05$). While REE decreased with weight loss in the majority of participants, REE increased in some individuals. Initial changes in NEAT did not predict the variance in REE with weight loss. Changes in NEAT and REE did not predict initial weight loss success. Future research will further investigate the interaction of energy expenditure through NEAT and REE throughout weight loss, in order to determine the response to caloric restriction and predict weight loss success. This will allow us to select the 'ideal' weight loss program for a given individual.

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Introduction

The prevalence of obesity has doubled in the past fifty years alone (Ogden CL, Carroll MD, 2010). While more than one in three American adults is obese today (Flegal KM, Carroll MD, Kit BK, Ogden CL, 2012), this has not always been the case. Much of the growth in obesity can be attributed to environmental factors encouraging the overconsumption of energy-dense, nutrient-poor foods and increasingly sedentary lifestyles – both of which come as consequences of the industrialization of labor and food systems (Ulijaszek and Lofink, 2006). A resulting "obesogenic" environment has worked in concert with conservative metabolic adaptations to restrict expenditure and maintain excess energy as fat (Swinburn et al., 1999; Ulijaszek and Lofink, 2006). Given the association of excess weight with the leading causes of preventable death, including heart disease, stroke, and type II diabetes, the prevalence of obesity poses a significant risk to public health (National Institutes of Health, 1998).

Obesity treatment focuses on altering the positive imbalance of energy intake over expenditure by changing diet and/or physical activity in order to promote weight loss. While caloric intake encompasses consumed energy (i.e. food calories), energy expenditure includes the various ways in which energy is used to move and maintain the body. The majority of this expenditure is attributed to resting energy expenditure (REE) and to a more variable degree, low-intensity involuntary physical activity categorized as non-exercise activity thermogenesis (NEAT) (Levine and Kotz, 2005).

Resting energy expenditure (REE) accounts for the energy expended to maintain an individual's metabolism while awake and alert but at rest. In most people, REE makes up the greatest portion of an individual's total energy expenditure, as the majority of energy consumed is used to support the body's metabolic processes and maintain its tissues (Redman et al., 2009).

In sedentary individuals, non-exercise activity thermogenesis (NEAT) makes up the majority of active energy expenditure (Redman et al., 2009). NEAT is the expended energy associated with non-volitional physical activity, including low intensity activities such as fidgeting and subtle movements of the body that occur during day-to-day life. Energy expenditure attributable to NEAT can vary up to 1500 $kcal \cdot day^{-1}$ between individuals of similar size, and up to 2000 $kcal \cdot day^{-1}$ within an individual, making it a key determinant of an individual's energetic state (Levine and Kotz, 2005). The significant contributions of NEAT and REE to energy expenditure make these critical variables of interest in studying weight loss and maintenance of weight loss.

As alterations to both energetic intake and expenditure are critical to achieve weight loss and maintenance, the interaction of the two sides of the energetic equation is important to understand. Studies in animals have explored this interplay by imposing caloric restriction and observing the effects on physical activity. Non-mammalian vertebrates such as zebrafish, as well as mammals including rats and rhesus macaques among others, have shown increased body movement with caloric restriction (Hebebrand et al., 2003; Novak et al., 2005; Tou and Wade, 2002; Weed et al., 1997). Humans with Anorexia nervosa have also displayed this phenomenon, although the relationship between diet and activity is complicated by their disorder (Hebebrand et al., 2003). Studies of this phenomenon in rats have demonstrated that this increased energy expenditure and decreased caloric intake may exacerbate starvation at its extreme (Hebebrand et al., 2003). Despite the potential risk this behavior poses, it has persisted throughout evolutionary history, observed in non-human primates and even humans (Weed et al., 1997; Hebebrand et al., 2003). The persistence of this energetically costly behavior suggests a selective advantage; the leading hypothesis proposes that this behavior serves as a foraging response, increasing movement to aide in the search for food calories and overcome the deficit (Weed et al., 1997;

Hebebrand et al., 2003).

The majority of research concerning this change in movement in in obesity has been restricted to non-human animals (Tou and Wade, 2002), and studies in obese humans are limited in depth. The main objective of this study was to determine how NEAT and REE respond to caloric restriction in obese individuals, and if changes in NEAT and REE are determinants of weight loss success and/or maintenance of this weight loss. Obese individuals enrolled in the University of Michigan Health System's Weight Management Program (WMP) were included in this study. This two-year intervention includes an initial phase of intensive energy restriction and resultant weight loss, followed by a maintenance phase in which efforts are focused on maintaining or continuing weight loss, albeit at a more moderate pace.

Evolution of obesity

Obesity is a recent phenomenon in human evolutionary history (Ulijaszek and Lofink, 2006). While the prevalence of obesity in the United States was estimated to be 3% at the end of the 19th century (Helmchen and Henderson, 2004), it currently stands around 35% (Flegal KM, Carroll MD, Kit BK, Ogden CL, 2012). There are many factors contributing to obesity, including interactions between the environment and genes (Wells, 2006). The rapidly changing environment of the United States has been deemed "obesogenic," as it favors the accumulation of excess weight (Swinburn et al., 1999). Industrialization has significantly altered human lifestyles, as manual labor has been largely reduced by technological developments. Given this decrease in habitual physical activity and simultaneous increase in caloric intake, many individuals require less energy for maintenance than that which they consume (Wells, 2006). The result of this is a chronic state of positive energy imbalance, with excess energy stored as adipose tissue.

This obesogenic environment does not match the conditions under which humans evolved (Leonard, 2010). Humans gradually developed large, metabolically active brains, and for most of human evolutionary history, attaining and extracting sufficient energy to feed the human brain and body while surviving to reproduce was of greater concern than the accumulation of excess weight (Leonard et al., 2007). Many hypotheses exist for the mechanisms by which the human body adapted to operate efficiently, leading to obesity in our modern environment (Speakman, 2013). The "thrifty gene" hypothesis has been long supported as the mechanism by which obesity arose; per this hypothesis, the human body maximized energetic efficiency and stored excess energy during times of feast for utilization during times of famine – famine which now does not often manifest (Neel, 1962). Recent findings have disputed the selective force of this mechanism and suggest instead that obesogenic genes emerged as a consequence of selection for other advantageous genes or through genetic drift, in either case lacking a maladaptive consequence in the environment in which they evolved (Speakman, 2013). Regardless of this mechanistic uncertainty, the recent rise in obesity can be largely attributed to a mismatch of genetics and environment (Speakman, 2013).

Dynamics of Energetics: Components, Determinants, and Interdependence

As described, the modern day obesity epidemic sits as a byproduct of efficient bodies living in an energy-rich world. Understanding the dynamics of the resultant imbalance requires consideration of the overall energy equation. This equation depends on inputs and outputs, i.e. energy consumption and energy expenditure. While calorie consumption consists only of the energy absorbed by ingested food, energy expenditure consists of three major components: physical activity, resting energy expenditure, and the thermic effect of food (**Figure 1**).

Physical activity consists of voluntary activity and non-exercise activity thermogenesis (NEAT). In a sedentary lifestyle, voluntary activity contributes very little to overall total energy expenditure; involuntary NEAT makes a larger contribution (Redman et al., 2009). Resting energy expenditure constitutes up to 60% of total energy expenditure, the majority of which is directly related to body mass (Levine and Kotz, 2005). The thermic effect of food (TEF) makes up the smallest proportion of total energy expenditure. TEF accounts for the energy expended in digesting, absorbing, and storing food; it contributes just 6 to 12% of an individual's total energy expenditure and varies little within an individual (Levine and Kotz, 2005).

Given the great complexities of consumption and expenditure, our interest lies in those components that exhibit the greatest interdependence, as these may account for the significant variation observed between individuals attempting weight loss. Available energy may affect how this energy is expended; likewise, energy expenditure may affect the type and amount of food energy consumed. Altering one side of the energy equation impacts the dynamics and outcomes of the other side of the equation. During energy restriction, as with caloric restriction in a clinical weight loss program, these dynamics may explain how the body accepts or resists body weight change and how this can be utilized to successfully reduce excess weight.

The change observed in physical activity, including voluntary exercise and non-exercise activity thermogenesis (NEAT), with caloric restriction has been studied but not fully understood (Martin et al., 2007; Redman et al., 2009). Voluntary exercise may increase or decrease with caloric restriction based on the individual's behavioral choices; therefore, in understanding the innate effects of caloric restriction on physical activity, measurement of NEAT may be preferable. Given NEAT's contribution to inter- and intra- individual variations in total energy expenditure, and its combined biological and environmental determination, changes in NEAT

might be an important result of caloric restriction and predictor of weight loss success (Levine and Kotz, 2005).

A seemingly contradictory change in movement with caloric restriction was first observed in rats in 1954 and has since been investigated across mammals and found in our close primate relatives (Hebebrand et al., 2003; Levine and Kotz, 2005). Curiosity surrounding this phenomenon, in which mammals facing an energy deficit spontaneously increase their energy expenditure through increased movement, led to a "foraging response" hypothesis (Jones et al., 1990). This hypothesis states that the increased movement serves as an innate mechanism to increase the opportunity for food acquisition. This increased movement dissipated with extended caloric restriction, as energy stores depleted with weight loss in the rats (Levine and Kotz, 2005). Similarly, this increased expenditure with severe caloric restriction is observed in patients with Anorexia nervosa, though the association in this condition is complicated by additional psychological complications of a "drive for thinness" (Hebebrand et al., 2003).

Studies of NEAT in obese patients undergoing caloric restriction have failed to observe an increase in spontaneous physical activity with long-term caloric restriction (Redman et al., 2009). However, changes in NEAT with shorter term caloric restriction have not been extensively studied. Given the progressive adaptations to caloric restriction and weight loss before stabilization, objectively measuring NEAT progressively through weight loss will offer a better understanding. As some studies have associated NEAT with resting energy expenditure (Levine and Kotz, 2005), studying NEAT in concert with resting energy expenditure will offer a better understanding of the complex variations of expenditure with changes in intake.

The effect of caloric restriction on resting energy expenditure has been widely studied (Martin et al., 2007; Redman et al., 2009). As expected, resting energy expenditure generally

decreases during caloric restriction, with most of this decrease attributable to loss of body mass (Redman et al., 2009). However, changes in REE and their association with lean body mass may vary (Major et al., 2006; Senechal et al., 2010). Indeed, a "set point" theory has been supported by findings that the decrease in REE is not entirely explained by a decrease in body mass, suggesting that the body "defends" a set body weight with further metabolic and behavioral adaptations to decrease REE per unit of lean body mass as well (Prentice and Jebb, 2004). The relationship between caloric restriction and resting energy expenditure is still not fully understood despite extensive study.

Even with caloric restriction, the thermic effect of food has exhibited little effect on total energy expenditure (Levine and Kotz, 2005). Though the amount and form of energy consumed in a calorically restricted diet leads to a decrease in the thermic effect of food, the small contribution it makes to total energy expenditure makes this decrease relatively insignificant (Levine and Kotz, 2005). Therefore, the thermic effect of food was excluded from this analysis.

Predictions

In measurement of spontaneous physical activity, I hypothesized that NEAT would increase with the onset of caloric restriction. Given the previous observation of a decrease in total REE and REE in respect to lean body mass with weight loss through caloric restriction, I also hypothesized that REE would decrease. Overall, I expected to find that the extent to which NEAT and REE change would predict who would successfully lose weight and maintain weight loss. I predicted that individuals who decreased NEAT would initially lose less weight and regain more of their lost weight, while those who increased NEAT would have better success in losing and maintaining weight loss. I further hypothesized that those who showed the greatest

decrease in REE would initially lose less weight and would eventually regain more of that weight, while those who maintained or decreased their REE to a lesser extent would have better success in initial weight loss and weight maintenance.

Methods

Program overview

Participants were recruited from the University of Michigan Weight Management Program (WMP), a two-year clinical behavioral and lifestyle intervention for obese adults. Program participants were offered the opportunity to participate in this research study, aiming to understand the psychoneurobiological factors that contribute to successful weight loss and long-term weight maintenance. This study was approved by the University of Michigan Institutional Review Board (IRBMED HUM00030088).

The program includes three components: rapid weight loss, transition to conventional foodstuffs over 4-6 weeks, and continued nutrition education and counseling to promote sustained change during the remainder of the 2-year program (Rothberg et al., 2013) (**Figure 2**). Rapid weight loss is achieved with an 800 to 1200 kilocalorie diet, via total meal replacement shakes (HMR®, Boston, MA) to promote 15% weight loss (3-6 months), followed by a transition to conventional foodstuffs over 4-6 weeks. The Registered Dietitian individualizes the meal plan to meet the energy needs and preferences of the participant. During the period of transition and throughout weight maintenance, participants are encouraged to increase physical activity to an equivalent of 60 minutes of moderate physical activity on at least 4 days per week.

Participants meet regularly with a physician and Registered Dietitian. Participants are seen weekly by the dietitian during the first 4 weeks and then monthly thereafter; they are seen monthly by the physician during the first 12 weeks and then every 3 months thereafter, for a total

of 26 and 11 visits, respectively. Physicians are responsible for monitoring changes in co-morbid health conditions, adjusting medications and reviewing adverse events and continued management. These regular visits serve to track weight loss progress and help participants adjust lifestyle behaviors in order to achieve their weight loss goals.

Study Population

Obese (BMI>30kg·m^{-2}) men and non-pregnant, non-lactating women, age 18 to 85 years and seeking clinical weight management support, were recruited for this study. Individuals with weight changes greater than 5 kg within the previous six months, eating disorders other than over-nutrition, or with unstable heart, lung, gastrointestinal, rheumatic or psychiatric diseases were excluded from the research study. 533 obese individuals have enrolled in the program to date.

Assessments

As a component of clinical care, all participants were routinely assessed for blood pressure, heart rate, and anthropometric measurements (height, weight, calculation of BMI, waist circumference, hip circumference and waist/hip ratio). In addition, current state of hunger was assessed on a visual analog scale at each clinical visit with the dietitian or physician. As part of the research component, participants had the option to elect additional assessments at specified points in the program, including those which comprise this analysis: body composition, resting energy expenditure, and habitual physical activity.

Body composition and resting energy expenditure (REE) were assessed at baseline, after 15% weight loss, and at program completion to determine where weight was lost and the

consequential effect of weight loss on overall body composition. Body composition was measured via dual-energy x-ray absorptiometry (Lunar Prodigy ADVANCE Plus; GE Healthcare, United Kingdom), a validated gold standard for body composition measurement (Gotfredsen et al., 1986). REE was determined via indirect calorimetry (TrueOne 2400; Parvo Medics, Sandy, UT), the standard method for determining energy expenditure from oxygen consumption and carbon dioxide production.

Habitual physical activity was assessed at various time points throughout the program. Participants were fitted with activity monitors (SenseWear Armband "mini", BodyMedia, Pittsburgh, PA) and instructed to wear them continuously for at least seven days, excluding water activities. The tri-axial accelerometer and additional sensors (galvanic skin response, near-body temperature, skin temperature, and heat flux) allow measurement of activity and intensity (metabolic equivalents, METs) in free-living conditions, yielding data for each minute during which the monitor is worn (**Table 1**).

Analysis

Participants with REE assessments at baseline and after intensive weight loss were included in analysis (**Figure 3**). Due to delayed inclusion of habitual activity monitoring and the ongoing nature of this clinical program, few subjects with physical activity assessments have completed the program. Thus, two participant subsets were included. The major aim, to determine the change in NEAT with caloric restriction and the effect of this change on weight loss, was studied using the NEAT subset. Participants in the NEAT subset had valid activity monitor data (≥22 hours of wear/day for ≥3 days) at baseline and within the first 60 days of weight loss, in addition to REE data at baseline and after weight loss. The supporting aim, to

determine the change in REE with caloric restriction and weight loss as a component of total energy expenditure, was studied using the REE subset. Participants in the REE subset completed REE assessments at baseline, after intensive weight loss, and at program completion.

All data presented as mean±standard error of the mean. Significance was assigned as $p<0.05$. Associations between primary outcome variables were assessed via Pearson correlations. The effects of time and sex were assessed via repeated measures ANOVA. SAS Analytics versions 9.2 and 9.3 (Cary, NC), as well as SPSS versions 21.0 and 22.0 (IBM, Armonk, New York) were utilized for statistical analyses.

Results

Non-Exercise Activity Thermogenesis (NEAT)

Sixteen of the 533 study participants (9 female, 7 male) completed habitual activity monitoring at baseline and within 60 days of diet initiation, in addition to REE assessments at baseline and after 15% weight loss, and were included in this analysis (**Figure 3**). Baseline subject characteristics did not differ by sex (**Table 1**). Both women and men achieved the program goal of 15% weight loss with caloric restriction (**Figure 4**).

The change in NEAT observed with initial caloric restriction differed by sex ($p=0.044$; $p=0.047$ when adjusted for wear time). NEAT decreased in women while NEAT increased in men (**Figure 5**). Total activity duration also decreased in women and increased in men (**Figure 6a**). The proportion of total activity represented by each activity intensity (NEAT, moderate, vigorous, and very vigorous) did not change with the diet in women or men ($p>0.05$ all) (**Figure 6b**). The initial changes in NEAT observed in women and men were not correlated with percent weight loss following caloric restriction (**Figure 7a**). Change in NEAT with diet initiation was

not correlated with changes in REE during weight loss (R^2=0.095). Change in REE was not correlated with percent weight loss during caloric restriction (**Figure 7b**) and moderately correlated with percent lean mass lost (R^2=0.208). NEAT and hunger assessment were not correlated at baseline (R^2=0.015) or with caloric restriction (R^2=0.000). In addition, the change in NEAT with caloric restriction was not correlated with baseline hunger assessment (R^2=0.104) or the change in hunger over the same time period (R^2=0.081).

Of the 16 participants, REE (absolute and adjusted for body mass) decreased in 12 (7 female, 5 male) and increased in 4 (2 female, 2 male) participants (**Figure 8**). Of the 11 participants with body composition assessments at baseline and after weight loss, REE adjusted for fat free mass did not change (p=0.194). Absolute REE at baseline did not differ between participants whose REE decreased and participants whose REE increased with caloric restriction (2100±158 vs. 1684±125 kilocalories/day, p=0.171). However, baseline REE adjusted for body mass was higher in those whose REE decreased than in those whose REE increased (19±1 vs. 15±1 kilocalories$\cdot$kg$^{-1}\cdot$day^{-1}, p=0.011). Change in physical activity with initial caloric restriction differed by REE response to weight loss (p=0.019; p=0.007 when adjusted for wear time): physical activity decreased in participants whose REE increased, while physical activity increased in participants whose REE decreased (**Figure 9**).

Resting Energy Expenditure (REE)

Fifty-four participants (19 female, 35 male) completed REE assessments at baseline, after intensive weight loss, and at program completion. Females and males were divided into groups based on their success as maintaining weight loss at program completion; participants who continued to lose weight or maintained their weight within 2% of their weight after intensive loss

were categorized as successful, while those who regained over 2% of their weight after intensive loss were categorized as regained. Baseline subject characteristics did not differ by sex or success group (**Table 3**).

Initial intensive weight loss success did not predict weight maintenance success. Baseline REE, REE adjusted for body mass, and change in REE or adjusted REE with intensive weight loss ($P>0.05$ all) were also unrelated to weight loss maintenance success. Change in REE during initial intensive weight loss was moderately correlated with change in REE during weight maintenance ($R^2=0.206$) and from baseline to program completion ($R^2=0.208$). Further, change in REE adjusted for body mass was moderately correlated with change in adjusted REE during weight maintenance ($R^2=0.226$) but not from baseline to program completion ($R^2=0.152$).

Discussion

Change in NEAT with introduction of the total meal replacement diet varied by sex; NEAT decreased in women and increased in men. These changes were not associated with the extent of weight loss during the intensive weight loss period, nor with the change in hunger reported during this period. Change in REE with achievement of the program's 15% weight loss goal varied among individuals; while the majority decreased their REE with weight loss, REE increased in one-quarter of included participants. Changes in NEAT and REE were not significantly correlated with each other, or with initial weight loss success due to total meal replacement. Analysis of a set of individuals who have completed the program showed a moderate association between baseline REE and success of weight loss maintenance.

Evaluation of Hypotheses

I originally hypothesized that NEAT would increase with caloric restriction, by means of the foraging hypothesis which has been proposed for increased movement with reduced energy consumption in various mammals (Weed et al., 1997; Tou and Wade, 2002; Hebebrand et al., 2003). Instead, there was a sex difference in the change in NEAT: while men did increase their NEAT with the initiation of the diet, women decreased their NEAT. Maintenance of the proportion of total activity contributed by each intensity shows that the increase in men was not due to a shift from more moderate and vigorous activity to more NEAT, nor due to a shift from NEAT to more moderate and vigorous activity in women. Further, a lack of correlation between change in hunger assessment and change in NEAT in both the females showing a reduction in NEAT and the males showing an increase in NEAT suggests an alternative mechanism for observed changes in NEAT.

The study that presented the initial proposition of the foraging hypothesis also found a sex difference in the change in movement with caloric restriction; however, in this case, it was found that female rats increased their activity more than males (Jones et al., 1990). More recent findings have shown the opposite, that female rats have a more conservative metabolic response to caloric restriction than do males (Valle et al., 2005). In humans, this more conservative response on the part of the female has also been displayed; a study of the opposite approach – caloric excess – showed that all of the individuals who displayed the least dramatic increases in NEAT were also female (Levine et al., 1999). The differential effect of caloric restriction on NEAT might be explained by differences in hormones between women and men. For example, estrogen has been noted to have a variety of effects on non-reproductive behaviors in women, including activity (Morgan et al., 2004). The low estrogen levels of this post-menopausal

population of women, then, may have contributed to the decline in NEAT.

In addition, this sex difference in change in NEAT may be explained by the different type of lifestyle change which occurs for women and men with a dietary change. Women of this age group are likely to typically spend time preparing meals for their family; with the meal replacement diet, they may exhibit a decline in NEAT due to the reduced preparation time needed for meal replacement shakes and thus the reduced duration of this low energy activity. However, this explanation does not apply to the increase in NEAT in men, as shake preparation could only minimally add to their NEAT. Further information about the participants' lifestyles is required.

I also hypothesized that initial response of NEAT to caloric restriction would predict weight loss and, further, weight loss maintenance success. Though this study population did not include individuals with habitual activity monitoring who have completed the two-year program, weight loss success within the first phase of intensive weight loss did not differ by change in NEAT during weight loss. This is likely due to the program design for all individuals to achieve 15% weight loss with the total meal replacement diet. Though there is variation of actual loss in this period, ranging from 6% to 30% of baseline weight lost, this variation did not differ by the initial change in NEAT. Changes in NEAT, if maintained in either direction from the baseline level, may exhibit a greater effect on weight loss maintenance after the intensive dietary intervention is complete and individuals partake in personalized plans to maintain weight loss and achieve other goals by program completion.

Observed variance of changes in REE and REE adjusted for body mass with caloric restriction also deviated from my hypothesis. Since REE is largely controlled by body mass, and lean body mass in particular, REE was expected to decrease with weight loss. However, my

inconsistent findings are in agreement with previous research displaying great variance in how weight loss via caloric restriction affects REE (Redman et al., 2009; Senechal et al., 2010). The relationship between change in REE and physical activity is contrary to what I would have expected: physical activity initially increased in those whose REE decreased, while physical activity decreased in those whose REE increased with weight loss. Physical activity during caloric restriction may help to preserve lean body mass and allow individuals with reduced energy intakes to better maintain their REE with weight loss (Thompson et al., 1996; Bryner et al., 1999). However, my results suggest that increased physical activity with weight loss was paired with declines in REE. Further, there was no difference in the loss of lean body mass between individuals whose REE decreased and increased. This suggests that REE and physical activity may not be closely related through lean body mass as predicted, though the limited sample size makes this conclusion tentative on a larger study population.

Finally, I hypothesized that baseline values of NEAT and REE, as well as changes in NEAT and REE with caloric restriction and concurrent weight loss, would predict weight loss and weight maintenance success. As previously described, predictions for weight loss during the intensive weight loss phase were limited by the homogeneity of program and outcome during this phase. Though variation in the extent of weight loss was apparent, this variation may not be sufficient to distinguish effects of NEAT and REE on weight loss success. Predictions for weight loss maintenance with the population included in REE analyses offer greater potential for deviation in success, given the transition to a diet of regular whole foods and the incorporation of physical activity at each participant's will and action. Yet, baseline values and initial changes in NEAT and REE still did not strongly predict the success of long-term maintenance at program completion. Though NEAT and REE do contribute greatly to energy balance, this suggests that

they are not the most significant factors in predicting who will experience the greatest success in weight management in this population.

Limitations

The sample sizes available for this study were largely limited by the availability of data over the time course of the program. Though the Investigational Weight Management Program was initiated in 2009, habitual activity monitoring was not included in data collection until late 2011. Thus, few individuals who consented to activity monitoring have progressed to program completion. This limited the availability of physical activity data at each of the prescribed program time points, especially those during and after the weight maintenance phase. Though this limitation prevented the direct comparison of NEAT and weight maintenance success, inclusion of individuals with REE at this final time point provided another population subset for long-term weight management analyses.

As a clinical research program, this study was also largely limited by inherent challenges of data collection in a free-living population. Adherence to the established clinical visit schedule, along with the assessments conducted at set time points during the schedule, was difficult to achieve, especially given the long duration of this program at two years. This not only affected the real time at which physician and dietitian visits, habitual activity monitoring, and REE assessments occurred but also the individuals' compliance to attendance and performance of the assessments. One of the most notable effects of this limitation for participant inclusion was the variance of time points at which habitual activity monitoring occurred. As a result, there was not a set of individuals with activity monitoring at each determined time point during weight loss, or a consistent set within that interval; alignment of monitoring data by days from diet initiation

addressed this limitation to allow selection of 16 individuals with activity data at two time points.

Despite these limitations, studying the effects of caloric restriction in individuals involved in a clinical weight management program allows for research in a realistic environment. The same limits to data collection which limited subject inclusion allow for better understanding of practices that may improve weight management program success, from personalized weight loss methods to practices for improved participant retention. Two years of data collection with regular assessments by a physician and registered dietitian allow study of program progress at multiple intermediate time intervals.

Future Directions

In the context of this study, continued data collection is important to increase the sample size and obtain full time course data. Attaining a more complete set of physical activity data throughout weight loss and maintenance will allow us to track the progression of NEAT during this extended weight management program. As more individuals with activity monitoring data reach program completion, we will be able to determine if the initial changes in NEAT observed in this study predict weight outcomes.

Further analysis of the activity data collected will allow us to better understand the types and dynamics of activities constituting this categorization of NEAT. Analyzing data on body position during time attributed to NEAT will allow us to break down NEAT into that which occurs while lying down, sitting, and standing. Such analysis will give better insight into the types of activities constituting NEAT in this population, if this breakdown changes with caloric restriction and weight loss, and if an individual's breakdown of type of NEAT is a factor in predicting weight loss and loss maintenance. In addition, separating NEAT by time of the day

and day of the week (weekdays vs. weekends) will provide additional insight into the patterning of NEAT and the effects that different patterns may have on weight loss and weight loss maintenance success.

Finally, given the modulation of leptin on energy expenditure, and observed associations of leptin with NEAT and REE (Levine and Kotz, 2005; DeLany et al., 2014), assessing circulating leptin levels will allow us to determine what role leptin plays in the modulation of energy dynamics and weight in this population.

Conclusion

While on a very low calorie diet intended for rapid intensive weight loss, NEAT decreased in obese women and increased in obese men. The increase observed in men follows that which is observed in many calorically restricted mammals; however, the lack of correlation between NEAT and hunger assessment does not support the foraging hypothesis for the relationship between caloric restriction and increased movement. I expected that changes in not only NEAT but REE, the largest component of energy expenditure, would predict success in weight loss and weight loss maintenance. Neither of these hypotheses was strongly supported, suggesting that studying the components of energy expenditure alone may not be useful in predicting weight loss success.

Further data collection is needed to expand the sample size, attain NEAT data throughout weight loss and weight loss maintenance, and better understand the types and trends of activity constituting NEAT. Indications of a difference in NEAT response to caloric restriction between females and males suggest a need for sex-specific weight management recommendations. Though I did not find a relationship between NEAT and weight loss success, focusing on

maintaining or even increasing NEAT in females may have successful implications for longer term weight management.

As we address the modern obesity epidemic, improved understanding of the dynamics of obesity and obesity treatment strategies is important. The public health burden of obesity has become increasingly apparent, and developing effective strategies to counter this burden will continue to gain importance. Looking to our human evolutionary past to understand the energetics of obesity and treatment can help us to develop the best, personalized strategies for weight management given our genetic adaptations and environmental influences.

Tables and Figures

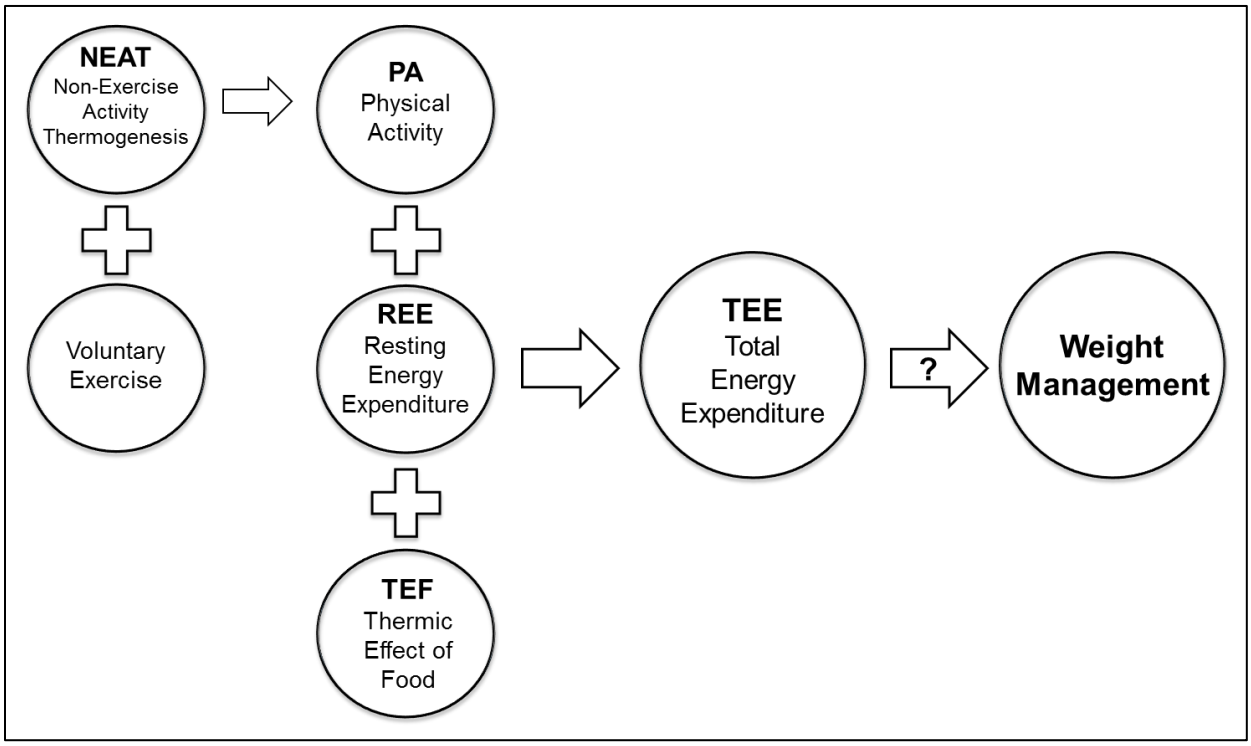

Figure 1. Resting Energy Expenditure (REE) and Non-Exercise Activity Thermogenesis (NEAT) contribute to Total Energy Expenditure (TEE), the dynamics of which may predict weight management success

Figure 2. Program design

Table 1. Activity intensity was defined by metabolic equivalents (METs)

Metabolic Equivalents (METs)	Activity Intensity
<1.5	Sedentary
≥1.5 and <3.0	NEAT
≥3.0 and <6.0	Moderate
≥6.0 and <9.0	Vigorous
≥9.0	Very Vigorous

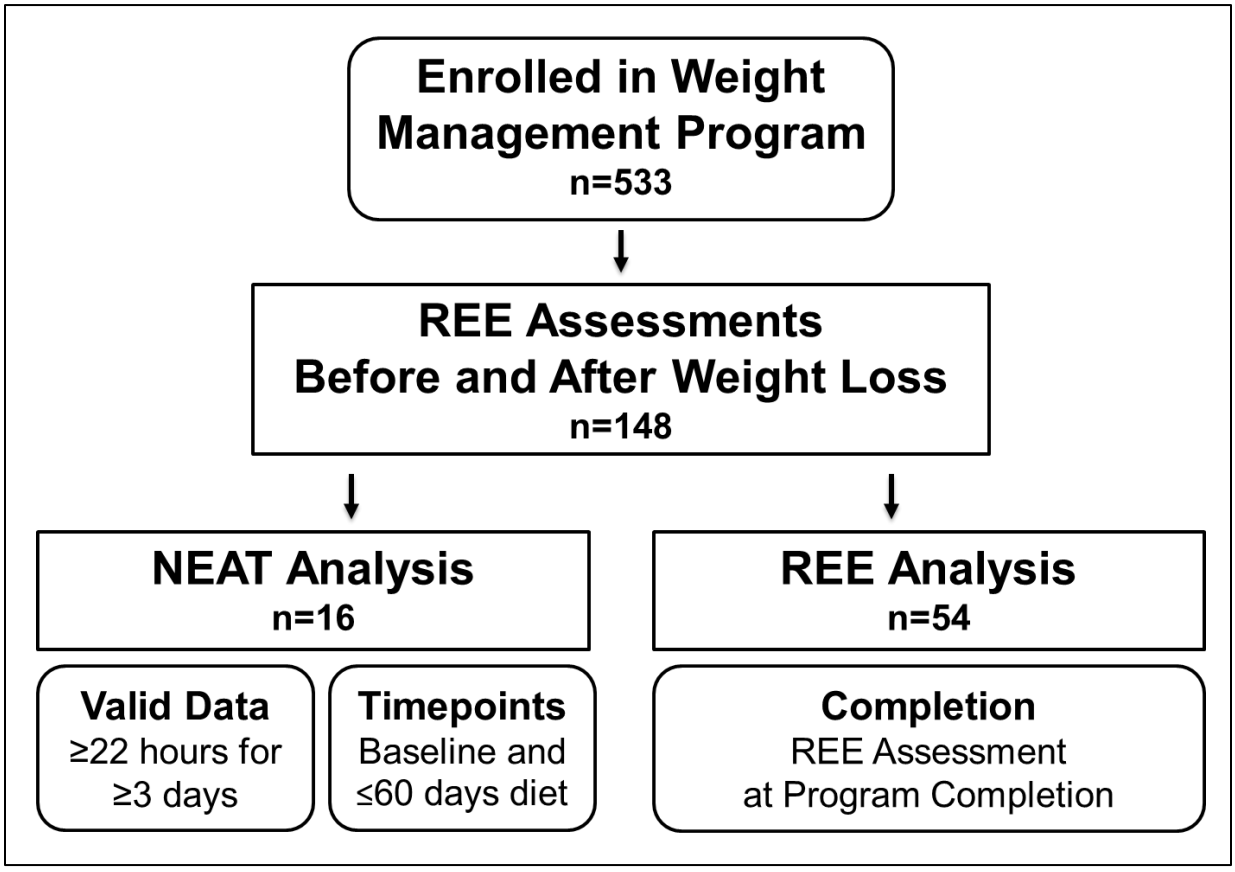

Figure 3. Participants with resting energy expenditure (REE) assessments before and after weight loss were included in analysis; from these 148 individuals, two subsets were created: 1) one with valid activity monitoring data at baseline and on diet and 2) an additional supporting subset with REE assessment at 3 time points

Table 2. NEAT analysis: Baseline subject characteristics

	Females n = 9	Males n = 7
Age (yrs)	51 ± 4 (32-64)	53 ± 3 (39-65)
Weight (kg)	102.6 ± 5.7 (86.0-132.1)	126.0 ± 8.4 (95.0-157.9)
BMI (kg/m^2)	39.0 ± 1.8 (33.7-50.4)	38.7 ± 1.6 (32.8-43.2)
White, Non-Hispanic	8 (89%)	6 (86%)
White, Hispanic/Latino	0 (0%)	1 (14%)
Black or African American	0 (0%)	0 (0%)
Native Hawaiian or Pacific Islander	1 (11%)	0 (0%)

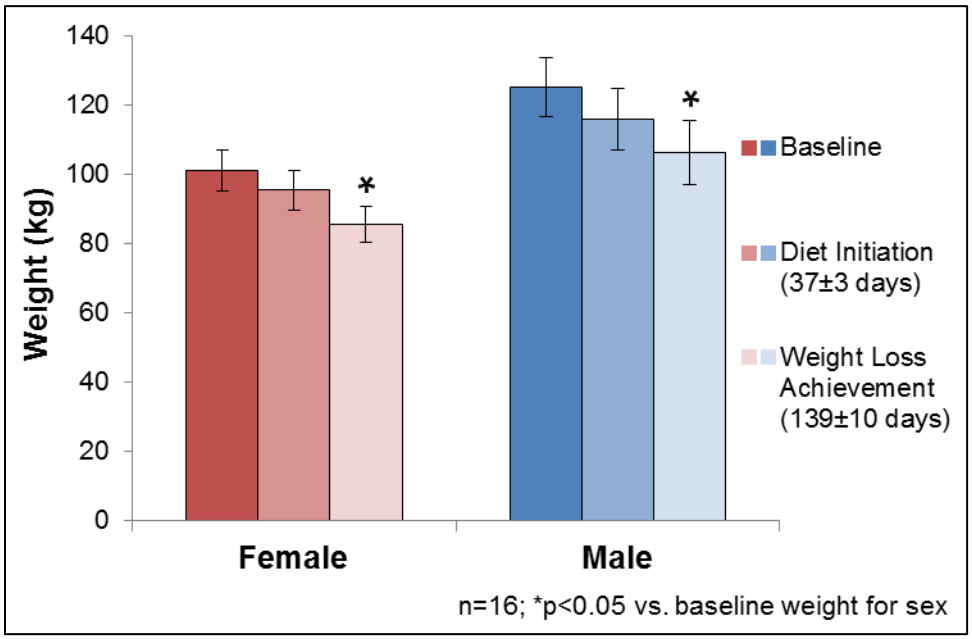

Figure 4. Participants achieved the program goal of 15% weight loss with a very low calorie diet

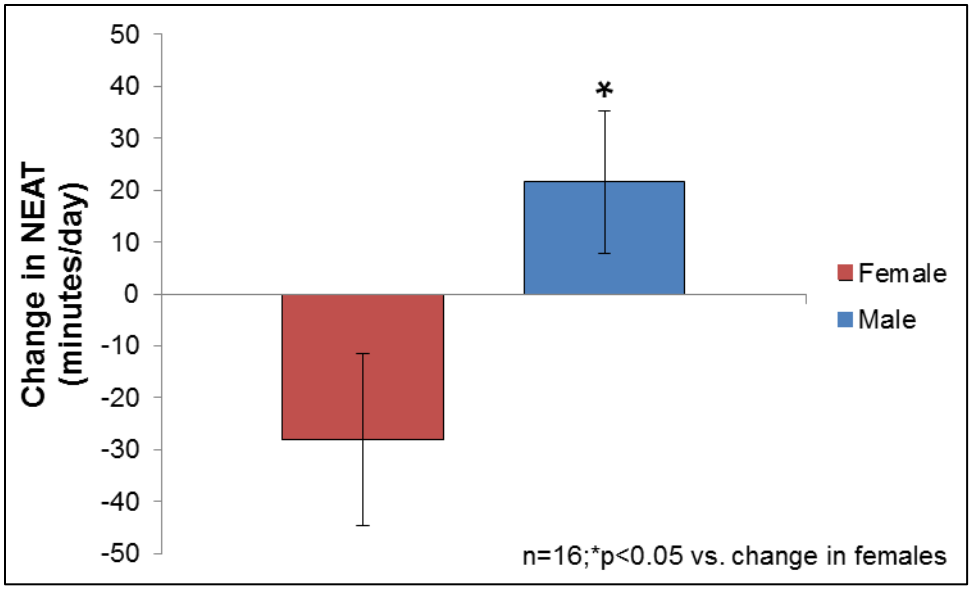

Figure 5. NEAT decreased in women (range -112 to 66 minutes) and increased in men (range -1 to 76 minutes) with initial caloric restriction

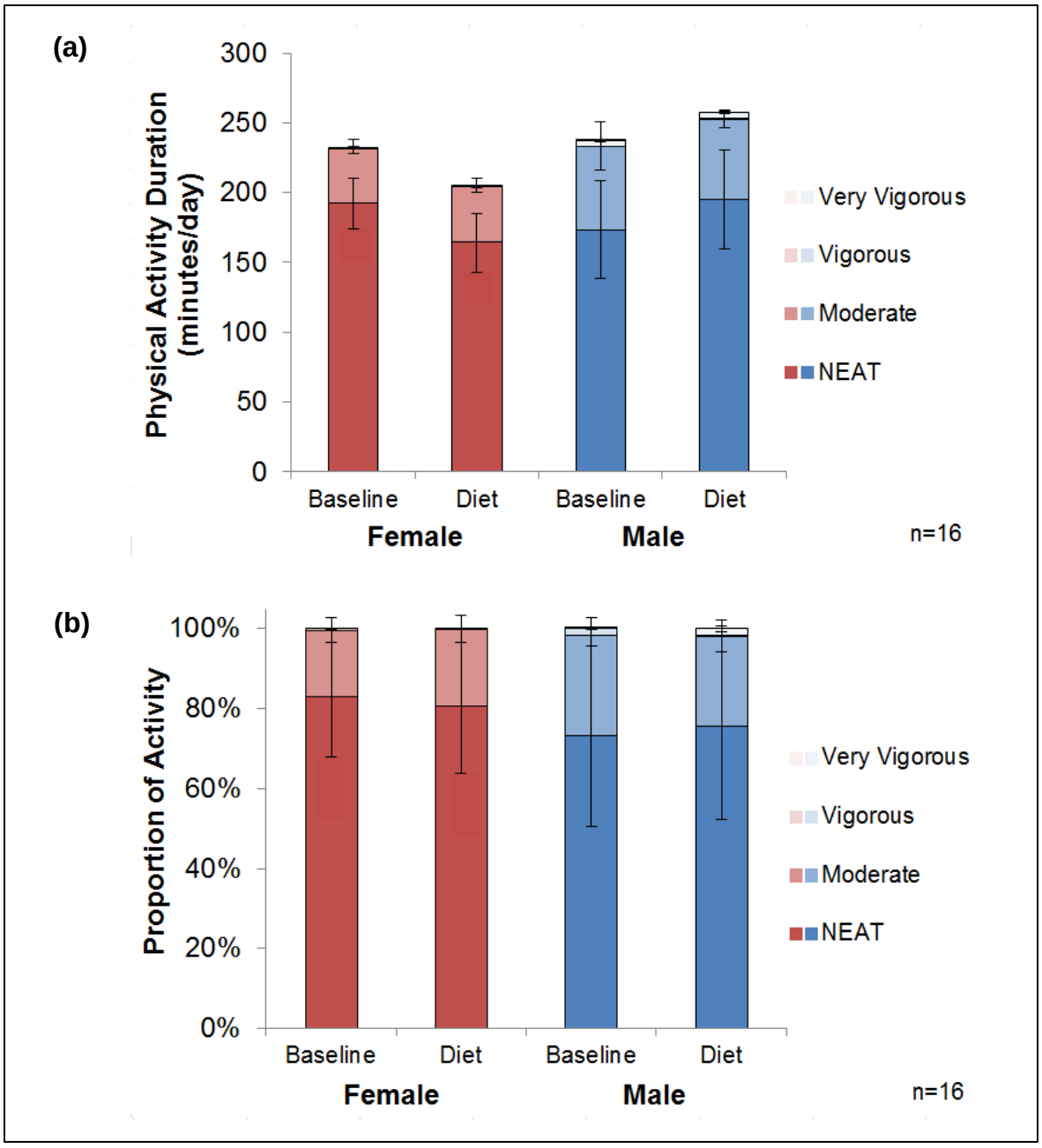

Figure 6. (**a**) Changes in habitual physical activity differed by sex; (**b**) Proportion of total activity constituted by each intensity did not change in women or men

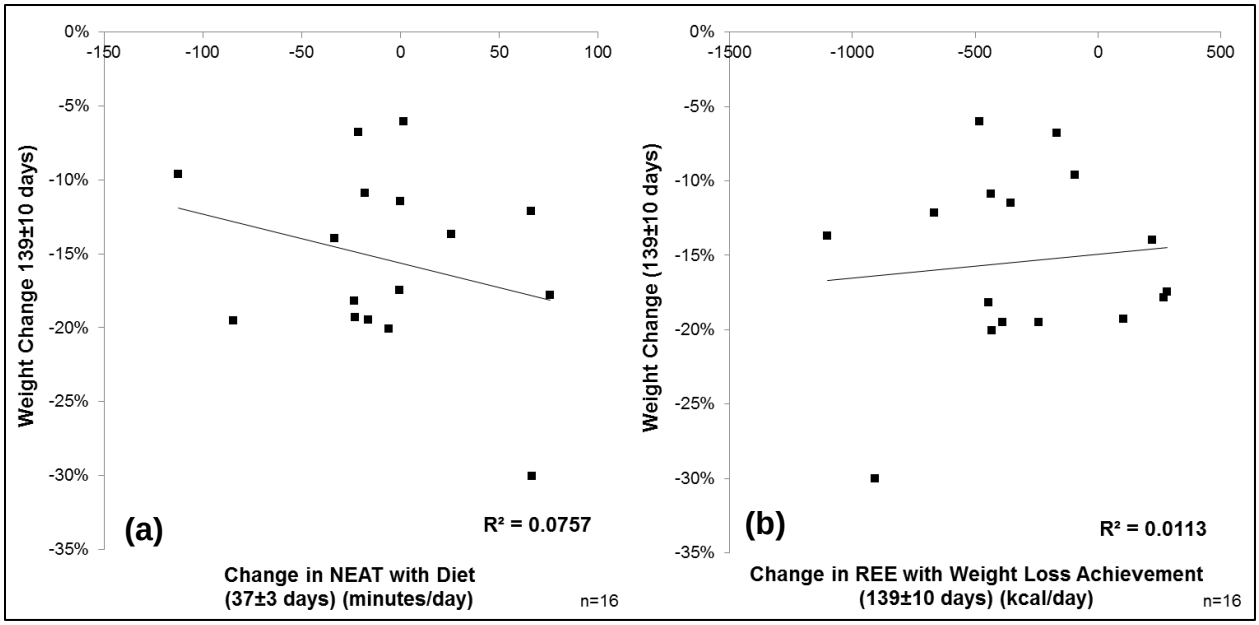

Figure 7. Weight change was not correlated with changes in **(a)** NEAT with diet or **(b)** REE with weight loss achievement

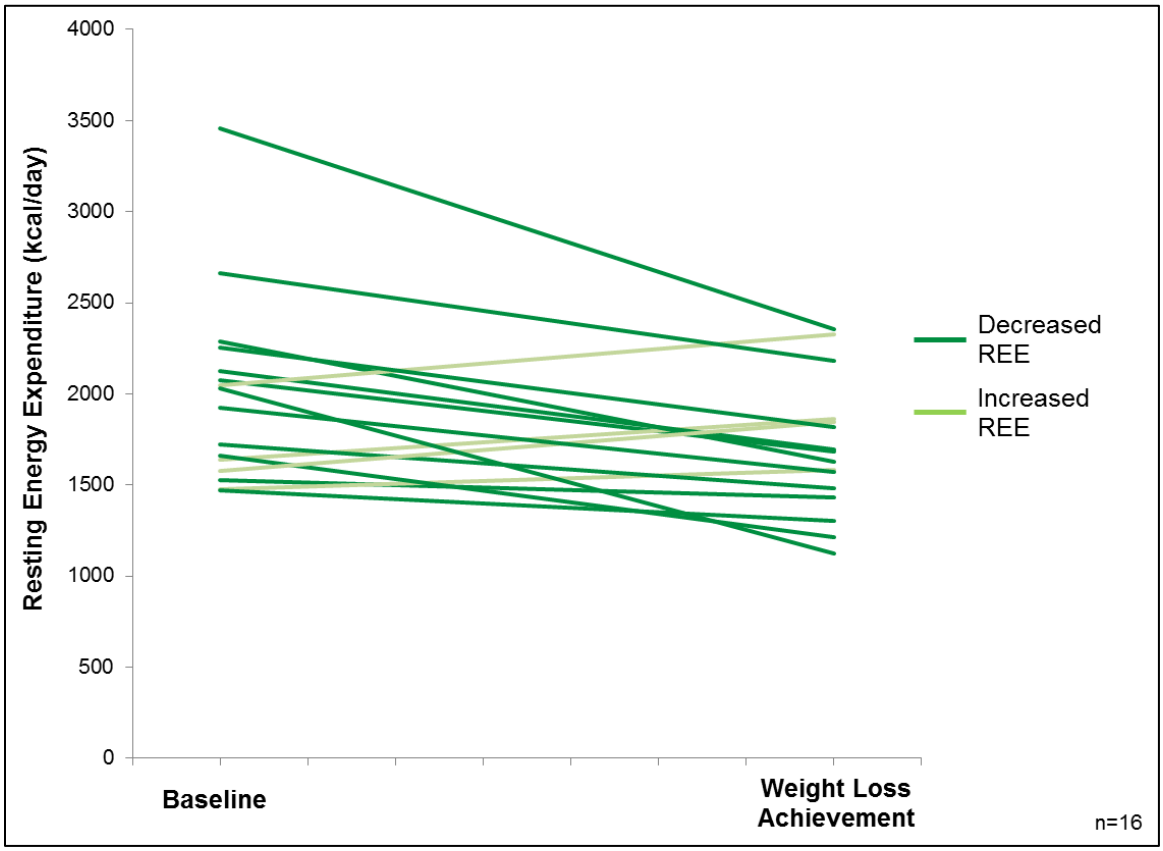

Figure 8. REE decreased in most participants

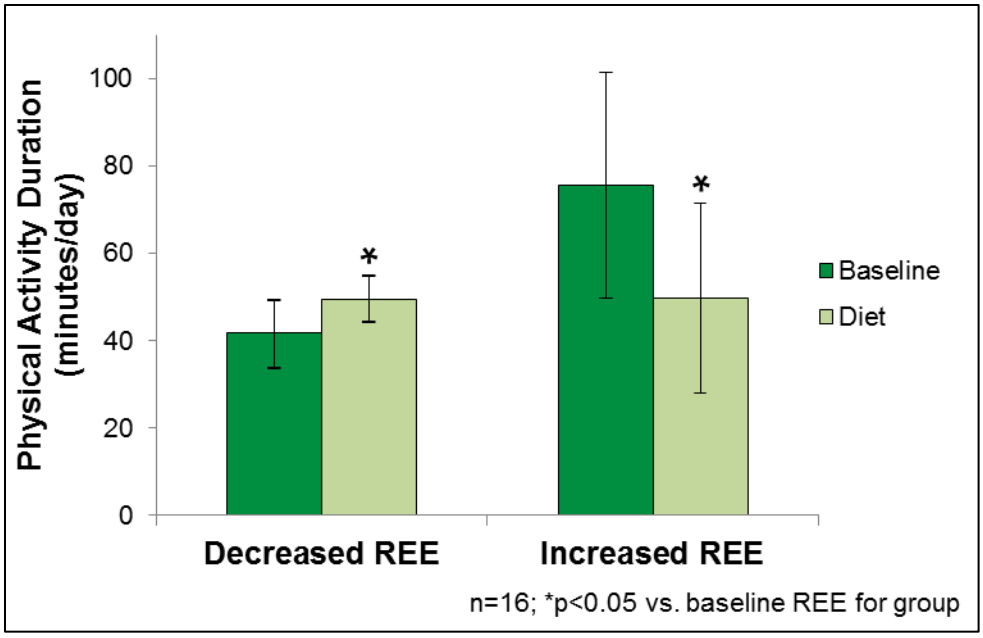

Figure 9. Physical activity increased with caloric restriction in participants who decreased their REE with weight loss and physical activity decreased in participants who increased their REE

Table 3. REE analysis: Baseline subject characteristics

	Females n = 19		Males n = 35	
	Success n = 7	**Regain** n = 12	**Success** n = 19	**Regain** n = 16
Age (yrs)	52 ± 2 (42-60)	51 ± 3 (29-64)	51 ± 2 (33-63)	54 ± 1 (42-64)
Weight (kg)	102.8 ± 5.1 (88.7-124.9)	106.4 ± 6.0 (83.3-155.1	130.2 ± 3.8 (107-166.5)	127.1 ± 3.3 (114.0-164.0)
BMI (kg/m^2)	39.9 ± 1.3 (36.6-45.9)	39.9 ± 1.7 (30.9-50.1)	39.4 ± 1.2 (35.0-54.9)	39.8 ± 0.8 (35.7-48.3)
White, Non-Hispanic	5 (71.4%)	12 (100%)	16 (84.2%)	12 (93.7%)
White, Hispanic/Latino	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black or African American	2 (28.6%)	0 (0%)	3 (15.8%)	1 (6.3%)
Native Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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