2020

Energy Compensation with Exercise is not Dependent on Dose

H. Michael Hays
University of Kentucky, apmike32@yahoo.com
Digital Object Identifier: https://doi.org/10.13023/etd.2020.127

STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's thesis including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

H. Michael Hays, Student

Dr. Kyle Flack, Major Professor

Dr. Robin Shoemaker, Director of Graduate Studies

ENERGY COMPENSATION WITH EXERCISE IS NOT DEPENDENT ON DOSE

THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Nutrition and Food Systems in the College of Agriculture, Food and Environment at the University of Kentucky

By

H. Michael Hays, B.A., B.S.

Lexington, Kentucky

Director: Dr. Kyle Flack, Ph.D., R.D., L.D, Professor of Dietetics and Human Nutrition

Lexington, Kentucky

2020

ABSTRACT OF THESIS

ENERGY COMPENSATION WITH EXERCISE IS NOT DEPENDENT ON DOSE

Background: Exercise induced weight loss is often less than expected due to a coordinated set of compensatory mechanisms that serve to maintain energy homeostasis. The extent to which exercise frequency, duration, intensity and exercise energy expenditure (ExEE) influences the compensatory response to an exercise-induced energy deficit (energy compensation) is controversial. Determining how these variables impact energy compensation would help health care providers prescribe exercise with greater probability of creating a sustained negative energy balance and subsequent weight loss.
Methods: 44 Overweight/obese men and women (BMI=25-35kg/m^2) aged 18 to 40 years were randomized to perform aerobic exercise 2 or 6 days/week or into a sedentary control group for 12 weeks. Changes in body composition and rates of energy expenditure at rest and during physical activity were assessed. Exercise sessions were evaluated for duration, intensity, and ExEE. Energy compensation was determined by comparing changes in bodily energy stores to total ExEE and expressed as both % energy compensated (compensation index, CI) and total energy compensated (kcal).
Results: No differences in energy compensation (CI or total energy compensated) were observed between groups exercising two or six days per week. ExEE, time spent exercising per week, or exercise intensity did not influence CI or total energy compensated. Greater fat mass was lost (-1.77 kg) when weekly ExEE exceeded 2,000 kcal compared to under 2,000 kcal (-0.41 kg, $p<0.05$), ExEE predicted % fat mass loss ($p<0.05$) when controlling for total energy compensated.
Conclusion: Greater exercise intensity, frequency, ExEE or exercise duration do not promote greater energy compensation when expressed as CI or total energy compensated. When energy compensated is held constant, greater ExEE promote fat mass loss. ExEE over 2,000 kcal/week is needed to overcome the compensatory response and reduce fat mass.

KEYWORDS: Aerobic exercise, Exercise Dose, Weight loss, Energy Compensation, Obesity

H. Michael Hays

04/10/2020

ENERGY COMPENSATION WITH EXERCISE IS NOT DEPENDENT ON DOSE

By

H. Michael Hays

Kyle Flack, PhD, RD, LD
Director of Thesis

Robin Shoemaker, PhD
Director of Graduate Studies

04/10/2020

Table of Contents

LIST OF TABLES

LIST OF FIGURES

Chapter One: Introduction

Background

Obesity is one of the largest epidemics plaguing affluent societies with nearly 40% of the U.S adult population classified as obese [1]. Obesity is a risk factor for some of the most serious health complications including cardiovascular disease, hypertension, certain cancers and type II diabetes [2]. Greater mortality rates with obesity have estimates of life expectancy reduced by 6-7 years with up to 300,000 deaths attributed to obesity annually in the US. Increased healthcare costs and loss of workplace productivity associated with obesity have additionally placed an insurmountable strain on the US. economy [3, 4]. Obesity has been attributed to a variety of factors, with lifestyle choices creating a positive energy balance, i.e., when energy consumed is greater than energy expended, cited as the largest contributor [5].

A large body of work bares proof of physical activity (PA), often increased by leisure-time exercise training, as the main factor of nutrient energy partitioning [6-10]. Energy partitioning simply refers to what becomes of macronutrients once they are absorbed. If one is engaged in regular PA, energy is delegated to repairing and refueling the body rather than storage as adipose tissue. [6-9, 11, 12]. Additionally, most individuals have the ability to exercise for prolonged periods of time at intensities 2 -to -16-fold above resting rates of energy expenditure [13]. As such, single bouts of exercise can result in energy

expenditures of 250-2500 kcal and, when repeated across days, can lead to the significant negative energy balance needed for weight loss [13-15]. This has led to many using exercise training as a cost-effective solution to reverse and prevent obesity and the resulting comorbidities [16].

Unfortunately, weight loss in response to exercise is often much less than expected [17]. Indeed, some report no changes in weight between a sedentary control group and exercise group after 4 weeks of exercise [18], while others demonstrate similar weight loss between groups expending different amounts of energy through an intervention [19, 20]. The reason for these perplexing results are most likely due to a phenomenon referred to as energy compensation.

In an effort to maintain energy homeostasis, the body is equipped with both metabolic and behavioral mechanisms that aggressively retain and replenish bodily energy stores, during an energy deficit. Increases in energy intake are commonly assumed to be the primary compensatory response when exercising to create a negative energy balance, with some reporting a positive relationship between energy expenditure and energy intake [20-22]. The extent to which exercise dose, in terms of frequency, duration, intensity and exercise energy expenditure (ExEE) has on energy compensation is controversial. One thought is that greater energy expenditures with exercise promote greater energy intake and, as such, is a futile weight loss strategy [20, 22]. However, a recent investigation determined groups expending 3,000 or 1,500 kcal/week compensate similarly (about 1,000 kcal per week), causing only the 3,000 kcal group to have significant weight loss after 12-weeks [23]. This demonstrates

greater energy expenditures do not promote greater compensation, rather, are needed to overcome the obligatory compensatory response of about 1,000 kcal/week. Determining the extent to which exercise impacts compensatory outcomes would help health care providers prescribe exercise with greater probability of creating a negative energy balance and subsequent weight loss. With obesity and co-morbidities on the rise, it is imperative to discover novel weight loss and maintenance strategies to mitigate the deleterious consequences obesity has on individuals and on society at large.

Problem Statement

Obesity afflicts every modern society on the planet. With limited success combating the disease pharmacologically and with bariatric surgery being an expensive and often risky operation, it is of the upmost importance we find efficient and sustainable weight loss practices. Exercise and diet are unequivocally the most cost effective and easily implemented solution to combat obesity; however, weight loss results differ drastically between individuals, likely due to variations in the compensatory response to an exercise-include energy deficit. A limitation for prescribing exercise to induce weight loss is the lack of consensus about its role in subsequent energy compensation. The roles exercise variables, such as frequency, duration, intensity and energy expenditure contribute to maintaining a negative energy balance warrants further exploring. The present study aims to fill this gap.

Aims

1. Demonstrate less frequent exercise evokes a reduced compensatory response compared to frequent exercise.

2. Demonstrate fat mass loss is influenced by exercise dose (intensity, ExEE and time spent exercising per week).

Hypothesis

1. Less frequent exercise (2 days/week) will evoke a reduced compensatory response compared to frequent exercise (6 days/week). This hypothesis is based on the notion that fewer exercise sessions could result in less episodes of compensatory eating and/or fewer insults on the biological mechanisms promoting energy homeostasis.

2. Greater exercise dose will lead to greater fat mass loss when controlling for energy compensated. This hypothesis is based on previous literature indicating that when energy compensation is equivocal, greater exercise expenditures are needed to overcome the compensatory response to produce significant weight loss.

Chapter Two: Literature Review

Introduction

Obesity epidemic

Obesity is one of the largest epidemics plaguing affluent societies with nearly 40% of the U.S adult population classified as obese [1]. Obesity is a risk factor for some of the most serious health complications including cardiovascular disease, hypertension, certain cancers and type II diabetes [2].Increased healthcare costs and loss of workplace productivity associated with obesity have additionally placed an insurmountable strain on the US. economy [3, 4]. Obesity has been attributed to a variety of factors, with lifestyle choices creating a positive energy balance, i.e., when energy consumed is greater than energy expended, cited as the largest contributor [5]. A novel theory explaining modern obesity describes the epidemic arising from changes in 20th century socio-environmental conditions such as reduced pathogenic disease, decreased physical activity and improved nutrition leading to excess maternal energy stores and subsequent hyperplasia of fetal pancreatic beta cells and adipocytes [24]. By the late 20th century, a “metabolic tipping point” was reached in which hyperinsulinemia, relative overabundance of adipocytes and persistent inactivity gave a nutrient sequestering advantage to adipocytes garnering the obesity crisis [24]. By 1978, the average amount of daily energy Americans consumed began to exceed energy expended [25, 26]. By 2006, the average American diet contained an extra 218 kilocalories (kcal) per day [25]. This increase in daily energy intake can certainly contribute to the obesity epidemic, although likely

only part of the problem. Comparing the energy intake of Americans in 1909 to 1960, those in the former era actually consumed more energy, yet had much lower rates of obesity [25]. Early in the 20th century, roughly 40% of the U.S. population worked as a farmer and nearly 73% of jobs involved manual labor [27]. Most of the population walked to destinations with motorized vehicles being owned only by the wealthy. Simply put, people were far more physically active 100 years ago and consequently required a greater energy intake. Therefore, the drastic spike in obesity rates are likely due to both greater energy consumption and less physical activity (PA). In the 1950's, scientists demonstrated PA not only effects energy expenditure, but is the major modifiable determinant of energy intake [28]. A large body of work bares proof of PA, often increased by leisure-time exercise training, as the main factor of nutrient energy partitioning [6-10]. Energy partitioning simply refers to what becomes of macronutrients once they are absorbed. If one is engaged in regular PA, energy is delegated to repairing and refueling the body rather than storage as adipose tissue. [6-9, 11, 12]. Additionally, most individuals have the ability to exercise for prolonged periods of time at intensities 2 -to -16-fold above resting rates of energy expenditure [13]. As such, single bouts of exercise can result in energy expenditures of 250-2500 kcal and, when repeated across days, can lead to the significant negative energy balance needed for weight loss [13-15]. This has led to many using exercise training as a cost-effective solution to reverse and prevent obesity and the resulting comorbidities. Unfortunately, weight loss in response to exercise is often much less than expected [17]. Indeed, some report no changes in weight

between a sedentary control group and exercise group after 4 weeks of exercise [18], while others demonstrate similar weight loss between groups expending different amounts of energy through an intervention [19, 20]. The reason for these perplexing results are most likely due to a phenomenon referred to as energy compensation.

What is Energy compensation

One of the most important biological functions of the body is its ability to maintain homeostasis in an ever-changing environment. There are many examples of this including maintaining acid/base balance, blood glucose, body water/electrolyte equilibrium and hormonal regulation. Another often overlooked regulatory process is energy homeostasis, where the human body is working to maintain energy balance. Like other acts of maintaining homeostasis, the ability to maintain energy balance can be viewed as an evolutionarily conserved mechanism, specifically in place to retain bodily energy stores to preserve reproductive function, a useful survival strategy in times of famine [29]. Unfortunately, maintaining energy homeostasis is not advantageous for most individuals living in developed nations today who desire a negative energy balance to induce weight loss. Compensatory responses working against the sustained negative energy balance needed for weight loss may be biological/ metabolic (reduced resting metabolic rate and non-exercise activity thermogenesis) or behavioral (increased energy intake, decreased physical activity) and provoked by either prolonged energy restriction (ER) or exercise [17, 22, 30, 31].

Mechanisms for Metabolic Energy Compensation

Negative energy balance achieved through exercise or ER can cause involuntary perturbations to metabolic processes that are at least partially sufficient to counter an exercise or dietary induced energy deficit. These involuntary metabolic changes include decreases in resting metabolic rate (RMR) and brown adipose tissue activation (BAT), and increased skeletal muscle work efficiency [29].

Resting Metabolic Rate

RMR is the rate at which the human body expends energy at complete rest, often conceptualized as kcal/24 hours [32]. RMR is the largest component (50-70%) of total energy expenditure (TEE), while fat-free mass (FFM) accounts for 60-70% of its variance [33]. During prolonged periods of energy restriction and subsequent weight loss, the body responds by reducing RMR to conserve energy and regain energy balance [29]. Decreases in serum catecholamine levels are one mechanism behind RMR reductions with weight loss, controlling the fraction of glucose oxidized for energy or stored in the body as glycogen or adipose tissue [34]. Changes in RMR could also act as a mediating variable in the positive relationship between FFM and appetite [35]. RMR is positively associated with FFM, meal size and fasting levels of hunger whereas a greater amount of FFM provokes greater energy expenditure and energy intake [36]. This is observed with obese individuals who have greater amounts of FFM to support the large amounts of adipose tissue they harbor, prompting greater

energy intakes in obese than non-obese individuals [36]. This is one reason obese individuals often have more difficulty in tolerating energy restriction.

Skeletal Muscle Work Efficiency, Non-Resting Energy Expenditure

Non-resting energy expenditure is energy expended through PA or exercise. Non-volitional reductions in non-resting energy expenditure during an energy deficit are accomplished by increasing skeletal muscle work efficiency, that is, reducing the energy expended per unit of FFM for a given work load [37, 38]. Improvements in skeletal muscle work efficiency can be caused by increasing hypothalamic – pituitary – adrenal (HPA) axis activity and decreasing hypothalamic – pituitary – thyroid (HPT) axis activity [29]. Hypercortisolemia from increased HPA axis activity results in reductions FFM and greater energy stored as adipose tissue [39]. Attenuations in HPT axis activity due to leptin reductions after weight loss reduces active thyroid hormone (T3) [34], which normally promotes energy expenditure by increasing heart rate, blood pressure and muscle ATP consumption through stimulating the production of muscle ATPase [29].

Increasing the ability of skeletal muscle to oxidize fat over glucose is another mechanism working to improve skeletal muscle work efficiency with weight loss [38, 40]. A 20% increase in skeletal muscle efficiency as a result of a 10% decrease in body weight alters gene expression involved with lipid and carbohydrate metabolism to increase free fatty acid oxidation [37, 38]. Specifically , a downregulation of phosphofructokinase 1 (PFK-1) and fructose-bisphosphate aldolase C (AldoC) are observed, while genes involved in fatty acid

oxidation such as 3-hydroxyacyl-CoA dehydrogenase (HADHsc) and fatty acid binding protein 4 (FABP4) are upregulated [40]. These changes in gene expression cause skeletal muscle to be less reliant on glucose and reduce activity induced energy expenditure as a mechanism to attenuating further weight loss [40]. Shifts in macronutrient utilization can also be assessed by calculating respiratory quotient (RQ, the ratio of CO_2 produced to O_2 consumed during respiration). RQ indicates the predominant macronutrient one is utilizing for fuel, as an RQ of 1 indicates the metabolism of pure glucose, 0.818 indicates protein and 0.696 indicates fatty acid oxidation [41]. Most RQ values are between these values, indicating mixed macronutrient usage. Often, a decrease in RQ follows weight loss, indicating a greater proficiency for fat oxidation, which often follow reductions in resting and TEE [29].

Brown Adipose Tissue Activation

BAT-induced thermogenesis is regulated production of heat, which is influenced by environmental temperature and diet [29]. Brown adipose tissue (BAT) contains the enzyme Uncoupling Protein 1 (UCP1) which is responsible for uncoupling mitochondrial substrate oxidation and releasing energy as heat instead of forming ATP [29]. BAT is highly innervated and vascular, responding to cold weather, changes in body weight and sympathetic nervous stimulation from catecholamines and T3 to generate heat [42, 43]. Reductions in sympathetic nervous system activity (SNS) and T3 after weight loss reduces BAT activation and thus reduce resting and TEE [34]. As little as 25 grams of BAT

becoming minimally active would be sufficient to account for declines in energy expenditure beyond what is predicted after weight loss [44].

Behavioral energy compensation mechanisms

Behavioral compensatory mechanisms are volitional responses to an energy deficit, that is, those in which we have control over, modulated by certain neurobehavioral mechanisms [45]. Behavioral compensatory mechanisms include increases in energy intake and decreases in voluntary PA/exercise engagement, with the former being the primary compensatory mechanism responsible for maintaining energy homeostasis when exercising for weight control [22].

Increases in energy intake

An energy deficit influences the desire to eat through the activation/deactivation of certain regions of the brain [46].Greater energy intake in response to a negative energy balance can be caused by changes in neuronal signaling in response to food [46]. Brain areas that are more active in response to visual food vs. non-food cues following weight loss include areas of the limbic and reward system whereas parts of the brain associated with executive and decision-making functions are decreased [47, 48]. This causes the rewarding properties of food to take precedent over inhibitory control to drive eating behavior [49].

Fluctuations in appetite regulating hormones have long been attributed to increases in appetite and decreases in satiety during a negative energy balance, either from ER or exercise [50]. The “hunger hormones” can either be orexigenic

(ghrelin) or anorexigenic (leptin, insulin, GLP-1, pancreatic peptide, peptide YY) [51]. A rise in ghrelin can cause greater appetite, whereas decreases in the anorexigenic hormones lower feelings of satiety after a meal, both of which can leading to over indulging [52].

The endocannabinoid system (ECS) is a widespread neuromodulatory system that plays important roles in central nervous system (CNS) development, synaptic plasticity, immunity, and energy homeostasis [53, 54]. The ECS is comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids. The two most well-studied endocannabinoids are the arachidonic acid derivatives, N-arachidonoylethanolamide (AEA) and 2-acachidonoylglycerol (2-AG) and come from multiple organs and tissues including the brain, muscle and adipose tissue [55]. AEA serves as an orexigenic factor in hunger-driven, homeostatic feeding, while 2-AG is implicated in the motivational value of food [55].

AEA and 2-AG are endogenous agonists of the canonical cannabinoid receptors, CB1R and CB2R, G protein coupled receptors that are widely distributed throughout the body [55]. CB1R is heavily concentrated in organs and tissues associated with energy homeostasis including the brain, liver, pancreas, GI tract, muscle and adipose tissue, whereas CB2R is primarily involved with immunity [55]. Activation of CB1R receptors in the hypothalamus increases consumption of food and is suppressed by the satiety signaling hormone leptin [56]. In the reward centers of the brain (mesolimbic system), CB1R activation

enhances reward driven consumption of highly palatable food [57-59]. In the periphery, CB1R binding by endocannabinoids increases energy storage via stimulation of fat mass hyperplasia, glucose uptake and lipogenesis in adipocytes [60], initiation of lipogenesis in the liver [61], and increased insulin secretion from the pancreas [62]. In addition to favoring energy storage, CB1R activation can also reduce energy expenditure by decreasing BAT-induced thermogenesis [63] and glucose uptake into skeletal muscle [64]. Increasing plasma glucose and insulin suppresses the amount of endocannabinoids found in circulation, but not in insulin resistant individuals, which may be implicative in the overeating associated with type II diabetes or pre-diabetes [65]. Interestingly, the more visceral adipose tissue an individual has the greater the concentration of 2-AG, but not AEA found in circulation [66, 67]. Given the role 2-AG has on activating energy storage mechanisms in the periphery and its ability to promote the consumption of highly palatable foods, its role in the progression of obesity and other metabolic syndrome components seems probable.

Reductions in physical activity

Another proposed behavioral change during a negative energy balance is engaging in less non-exercise physical activity (NEPA). Limiting the amount of time spent doing unstructured physical activity may counter the energy expended during exercise or the negative energy balance created via energy restriction [68]. Experiencing muscle soreness or mental fatigue after a rigorous bout of exercise may lead one to engage in more sedentary behaviors such as taking the elevator instead of climbing the stairs.

Exercise and Energy balance:

Exercise is a common therapy for weight loss with the American College of Sports Medicine recommending 225 minutes of moderate physical activity per week for adults seeking weight loss [69]. However, exercise-induced weight loss, based on the energy expended during exercise, is often much less than one would expect due to the compensatory mechanisms working to maintain energy balance discussed above. Increases in energy intake are commonly assumed to be the primary compensatory response when exercising to create an energy deficit [21, 22]. Edholm *et al*. was the first to establish a positive relationship between energy expenditure and energy intake [70, 71]. His research suggested activity levels and energy intake formed a J-shaped curved, where inactive and highly active individuals have the greatest energy intakes with moderately active individuals having the lowest. Subsequent research has backed this claim that greater energy expenditures promote greater energy intake, implying excessive exercise is a futile weight loss strategy [20, 72]. However, disagreement exists in the notion that greater amounts of exercise energy expenditure (ExEE) cause an equivalent increase in energy intake. A recent investigation determined groups expending 3,000 or 1,500 kcal/week compensate similarly (about 1,000 kcal per week), causing only the 3,000 kcal group to have significant weight loss after 12-weeks [23]. This finding was replicated in another trial where overweight individuals exercising either 6 days per week (expending 2,753 kcal/week) or 2 days per week (1,490 kcal/week) compensated similarly, with only the group exercising at the greater dose losing significant amount of body fat mass [73].

Exercise plays a role in regulating appetite hormones and subsequent energy compensation. Many have shown single bouts of exercise do not alter circulating concentrations of hunger hormones [74, 75], while chronic exercise can improve the satiety response to a meal [76, 77] leading to reductions in energy intake [78, 79]. Additionally, obese individuals often present with leptin and insulin resistance, causing lower and less pronounced feelings of satiety [80]. Exercise improves leptin sensitivity, promoting greater hormone/receptor binding to stimulate satiety even when decreasing concentrations of leptin [81, 82].

An emerging field of interest with regards to exercise and subsequent energy consumption involves investigating potential psychological mechanisms. Post-exercise eating behavior can be influenced by the extent to which exercise is experienced as autonomous (enjoyable, valued) or controlled (forced, internal and external pressures) [83]. Feelings about exercise have such a strong implication on food intake just reading about “tiring” physical activity leads to more snacking as opposed to reading about “fun” physical activity [84]. Exercising because you “have” to rather than because you “want to” also influences eating behaviors, as individuals who self-impose physical activity are more prone to consume a “food reward” post-exercise compared with individuals who possess more self-determined regulation for exercise [85]. In alliance with this, compared to individuals in a controlled exercise setting, individuals who have more choice over exercise mode, intensity, duration, time of session and music played during exercise consume less energy post-exercise [86]. Exercise

autonomy also leads to consuming less energy from “unhealthy” food choices post-exercise [86]. It therefore appears the notion that exercise causes compensatory increases in energy intake is multi-layered and influenced by attitudes regarding the exercise bout itself.

The implications exercise has on metabolic energy expenditure is mixed. Many studies demonstrate greater post exercise oxygen consumption (EPOC) following single bouts of exercise can increase RMR for up to 48 hours [87-89]. However, determining exercise’s long-term effects on RMR is more mottled. It can be argued that a negative energy balance created from exercise would elicit reductions in RMR (metabolic compensation). Couple this with homeostatic signals promoting over-eating and you have a feedback loop primed to protect from losing body mass, abolishing the negative energy balance created through exercise [90]. The change in one’s RMR after aerobic and/or resistance exercise appear to depend on how long after the final exercise bout RMR is measured and if changes in FFM is controlled for [91]. Long-term exercise studies consisting of predominantly aerobic interventions for maximizing fat loss showed significant decreases in RMR greater than would be expected from losses in FFM alone [92-94].

With the role the ECS plays in energy consumption and storage, it is logical to hypothesize that increased energy expenditure will lead to increased plasma concentrations of endocannabinoids to replace lost energy stores. Indeed, engaging in 30-90 minutes of moderate intensity exercise increases plasma levels of AEA immediately post exercise [95, 96]. The rise of

endocannabinoids in response to exercise appears to be intensity and modality dependent. When heart rate reaches 75% of maximal level, plasma AEA increases significantly form baseline, where no significant increases are witnessed with lower or near maximal intensities [96]. Exercise protocols utilizing intense isometric muscle contractions significantly increase circulating levels of 2-AG but not AEA, and may have something to do with endocannabinoids role in decreasing pain sensations [97]. Overall, engaging in moderate intensity, longer duration exercises will increase AEA while short bursts of exercise, as in a strength training regimen, will garner increases 2-AG. However, these increases in endocannabinoids may not lead to greater energy intake post exercise as expected. The rise in AEA following exercise may affect only the periphery and not the brain, as perceived feelings of hunger are not positively correlated with increases in AEA [98]. This may be related to in AEA's ability to increase muscle glucose uptake, improving insulin sensitivity and mitochondrial biogenesis [99]. In order to mitigate the post-exercise desire to replenish energy expended it may be beneficial to engage in interval training protocols over moderate intensity or strength training especially if an individual has significant visceral adipose tissue, as individuals with greater amounts of visceral adipose tissue have greater amounts of plasma 2-AG [66].

There are many different exercise modalities that may influence the degree of energy compensation. An investigation of how exercise mode may influence individual responses to exercise is of great interest to the health

community in order to develop optimal exercise prescriptions resulting in a minimal compensatory response and therefore maximize weight loss.

Summary of Research Related to Physical Activity and Energy Balance

Source	Study Design	Exercise protocol	Study Population*	Primary Findings
Werle et al. [80]	Cross sectional analysis demonstrating compensatory eating after reading/thinking about engaging in physical activity	N/A	78 women; 45 men; healthy, age 38.7 ± 16 years; BMI 26.37 ± 4.78 kg/m²	Reading about physical activity leads participants to compensate by eating more snacks and if the exercise is perceived as tiring.
Fenzl et al. [81]	Randomized, two-armed trial determining if labeling an exercise bout affects immediate post-exercise food intake in individuals who self-impose exercise	20-minute Moderate intensity bicycle ergometer ride	45 women; 51 men; healthy, age 26.1 ± 9.4, recruited from a college campus	Self-imposed exercisers ate more food after exercise when the bout was labeled “fat-burning” compared to “endurance”
Beer et al. [82]	Randomized between subject yoked design investigating the role choice in exercise has on subsequent energy consumption.	30-60 minutes of aerobic training on either a bike or treadmill	38 men and 20 women; healthy, age 22 ± 4; BMI 23 ± 2.3 kg/m²; VO2 max 52.7 ± 6.4	Greater energy intake after exercise performed under the no-choice condition (587 ± 344 kcal vs. 399 ± 290 kcal)
Johannsen et al. [89]	2-armed longitudinal design determining if diet restriction with exercise helps preserve FFM and maintain RMR.	90 min/d of circuit or aerobic training for 40 weeks	7 men; 9 female; obese, age 33 ± 10; BMI 49.4 ± 9.4 kg/m²	% BW lost was 38 ± 8%, 83% of that being fat mass. RMR decreased out of proportion to decrease in body mass.
Cedernaes et al. [94]	Crossover design comparing alterations to endocannabinoids after sleep deprivation and exercise	30-minute moderate intensity bicycle ergometer ride per each intervention	16 men; age 22.9 ± 0.66 years, healthy, BMI 22.9 ± 0.46 kg/m²	Plasma concentrations of AEA increased after exercise but did not cause increases in hunger.

***Units listed as means ± SD**

High intensity interval training and compensation

High intensity interval training (HIIT) is characterized by brief, intense bouts of near maximal effort exercise performed at ≥ 80% of maximum heart rate or the equivalent VO_2 max separated by recovery periods in a work to rest duration of ≥ 1:1 [100]. Sprint interval training (SIT) is another form of HIIT and is performed at intensities equal to or superior to one's VO_2 max [101]. HIIT is equally effective, or superior to moderate intensity continuous training for improving various health variables including increasing VO_2 max [102], increased capacity for oxidative phosphorylation in skeletal muscle [103], improving insulin resistance [104] and reducing body fat mass [101, 103]. HIIT is associated with increased NEPA and thus an increase in total daily energy expenditure (TDEE), which may lead to less energy compensation [105, 106]. HIIT may also reduce the compensatory response to exercise by reducing food intake and appetite sensations post exercise due to a rise in a potent anorectic peptide called corticotrophin releasing factor (CRF) [107, 108]. In rats infused with a CRF antagonist, hard exercise had no effect on food intake nor did it reduce body weight opposed to exercised rats without the CRF antagonist who decreased food intake and body weight [108]. Among humans, exercise-induced hunger and desire to eat decreases after HIIT when compared to moderate intensity interval training (MIIT), specifically causing less wanting and consumption of high fat

foods post-exercise [109]. These changes in macronutrient preference may be one reason HIIT elicits greater reductions in fat mass even if energy expenditure is less than or equal to MIIT. [109]. HIIT may also preferentially influence metabolic compensation by provoking greater EPOC and thus increasing TEE [110, 111]. It therefore appears HIIT has an advantage over traditional moderate intensity aerobic exercise by favoring less energy compensation. However, research on HIIT and weight loss is mixed possibly due to the variability of HIIT protocols (HIIT vs. SIT) [101]. When compared to moderate intensity exercise, HIIT requires nearly half the exercise time to burn equivalent amounts of energy [109]. With leisure time shrinking in modern societies, having the ability to shorten training time while maintaining increases in energy expenditure is of great value. Future research may investigate specific variables in a HIIT program that may be modified to attenuate the compensatory response to HIIT, such as different intensities of the work intervals, durations, frequency, and individual factors such as gender, age, and training status.

Summary of Research Related to HIIT and Compensation

Source	Study Design	Exercise Protocol	Study Population*	Primary Findings
Schubert et al. [102]	RCT, Investigating the effects of different interval training on RMR	SIT or HIIT, 4 weeks	30 healthy men and women, age 28.8 ± 7.6 years	SIT protocol significantly increased RMR after four weeks
Rivest et al. [104]	RCT Investigating the role CRF plays in the anorexia induced by exercise	40 minutes high intensity running	Male Wistar rats roughly 200 grams in weight	Exercised rats ate less food when injected with saline than resting animals or CRF antagonist
Alkahtani et al. [105]	2-armed Crossover design Comparing the effect of moderate and high intensity interval training on eating behavior and compensation	4 weeks of HIIT (3x/week) and 4 weeks of MIIT (3x/week)	10 sedentary males; age 29 ± 3.7; BMI 30.7 ± 3.4 kg/m²	HIIT decreased desire to eat, liking of high fat non-sweet food and overall fat consumption

*** Units listed as means ± SD**

Resistance training and compensation

Resistance training (RT) is a form of exercise whereby external weights provide progressive overload to skeletal muscles in order to make them stronger often resulting in hypertrophy [112]. Most individuals envision loads> 80% max and fewer repetitions (5-9) per set best for increasing muscle strength whereas lower loads (50-70% max) and more repetitions (9-20) best for muscular

endurance [112]. RT lowers blood lipids and blood pressure, promotes skeletal muscle maintenance/growth, improves blood glucose levels, insulin sensitivity and is effective for fat mass loss [113]. Because RT acts to preserve FFM during weight loss it may eliminate or attenuate metabolic compensatory responses such as the drop in RMR often seen with energy-restriction or aerobic exercise-induced weight loss [112]. Indeed, increases in RMR with RT and protocols using both RT and aerobic training increases RMR compared to aerobic exercise alone [114]. When controlling for ExEE, there appears to be a sex effect when assessing differences in compensatory increases in energy intake between RT and aerobic exercise, whereas only men are more prone to compensatory increases in energy intake after RT compared to after aerobic exercise [115]. Resistance training does lead to different changes in body composition compared to aerobic exercises [116] and compensatory increases in energy intake in men may have to do with the anabolic nature of RT and the subsequent gains in lean muscle mass when combined with adequate protein intake [117, 118]. Therefore, compensatory eating with RT may be due to muscle growth and repair and less to do with replenishing energy stores to maintain energy balance.

Summary of Research Related to Resistance Training and Compensation

Source	Study Design	Exercise protocol	Study population*	Primary findings
Dolezal et al. [110]	RCT Comparing changes in RMR, body fat, max aerobic power and strength between exercise modalities	10 weeks, 3x/week Aerobic (AT), concurrent (CT) or RT	30 physically active, healthy men, age 20.1 ± 1.6 years	Greater increases in RMR in RT and CT compared to AT. Greater decreases in body fat in CT compared to RT and AT
Cadieux et al. [111]	3-armed Crossover design to evaluate the effects of exercise modality on EI, TEE, NEAT	RT, AT and control for 4 days /week, 6 weeks	8 men and 8 women; healthy, sedentary, age 21.9 ± 2.6	When controlling for ExEE, no differences in energy compensation except in males after resistance training (1567 ± 469; 1255 ± 409 kcal, respectively)

*** Units listed as means ± SD**

Aerobic training and compensation

Aerobic exercise is continuous exercise performed at submaximal intensity and involves large groups of skeletal muscles [30]. Aerobic exercise attenuates risk for coronary artery disease, obesity, depression and diabetes [119]. Aerobic exercise has long been prescribed to combat obesity because of the large acute energy deficit it can elicit. Despite this, the magnitude to which aerobic exercise precisely impacts energy compensation and thus weight loss is

debatable and highly individualistic [120]. Some have indicated greater ExEE produced with high volume aerobic exercise is positively correlated with increases in energy compensation resulting in no significant differences in weight loss compared to a moderate volume exercise protocol expending less energy [20]. Others have demonstrated an acute bout of aerobic exercise has little effect on immediate energy intake [121, 122], inducing changes in “hunger hormones” and alterations in substrate oxidation in muscle and liver correlated to the post-exercise decrease in hunger and food intake [123, 124]. A negative energy balance induced by exercise can provoke these responses due to increased SNS activation in the hypothalamus by hunger hormones and the endocannabinoids favoring energy consumption [50, 52, 55, 125].

Compensatory responses to aerobic exercise are extremely idiosyncratic with some achieving drastic weight loss and others actually gaining weight [126]. Success of an aerobic exercise protocol may have to do with one’s baseline body fat percentage, whereas obese individuals may be more successful at decreasing fat mass while maintaining lean mass compared to their lean counterparts [127]. In this light, body fat may serve as an energy buffer to mitigate compensatory eating and to improve weight loss [127]. This may be why energy compensation first presents 2-4 weeks after establishing an exercise induced negative energy balance in obese individuals [21, 128].

Alternatively, a recent study demonstrated individuals expending 1,500 kcal or 3,000 kcal per week in aerobic exercise saw no differences in energy compensation (roughly 1,000 kcal extra per week) indicating greater amounts of

aerobic exercise do not produce more energy compensation. Rather, a large exercise dose is needed to overcome the compensatory response to promote significant fat mass loss [23], which has been replicated in a separate trial where aerobic exercise expenditures of 2,753 and 1,490 kcal per week resulted in similar energy compensation [73]. This is at odds with Rosenkilde et. al, who demonstrated that expending either 1,800 or 3,600 kcal during exercise per week produced nearly identical energy deficits after 12-weeks due to the greater energy compensation among the 3,600 kcal group [20]. Results from the large E-MECHANIC study (Examination of Mechanisms of Exercise-Induced Weight Compensation) offers additional insight with high-volume group (ExEE of 20 kcal/kg body weight) compensating significantly more than the low-volume group (eight kcal/kg body weight); however, weight loss was greater in the 20 kcal/kg group compared to the eight kcal/kg (-1.6 vs. -0.4, respectively, P=0.02) [129]. These results partially support both findings, that greater exercise energy expenditures are needed to produce weight loss, and those of Rosenkilde et. al, that greater ExEE instigates greater compensation. The ExEE of E-MECANIC study participants was about 1760 and 700 kcal per week for the 20 and eight kcal/kg groups respectively, much lower than the energy expenditures of [23, 73]. The larger dose (3,000 vs 1,800 kcal/week) and larger differences in ExEE between groups (1,800 kcal) Rosenkilde et. al used may explain some of the discrepancies [20]. It is possible that there may be a point at which greater levels of ExEE do not additionally contribute to weight loss, rather, disproportionately influence energy compensation. Future research may benefit from assessing the

compensatory responses to 4,000-5,000 kcal per week to investigate this possibility.

Summary of Research Related to Aerobic Training and Compensation

Source	Study Design	Exercise protocol	Study population*	Primary findings
Rosenkilde et al. [24]	RCT examining effects of increasing doses of aerobic exercise on body composition, AEB and compensation	MOD (300 kcal/d) or HIGH (600 kcal/d) for 13 weeks	61 males, age 20-40, healthy, sedentary, moderately overweight	Similar body fat loss was obtained regardless of exercise dose with the greater dose inducing a greater degree of compensation
Flack et al. [70]	2-arm randomized trial comparing compensation to exercise energy expenditures of 1,500 and 3,000 kcal/wk	Aerobic exercise expending 300 or 600 kcal/exercise session, 5 days/wk, 12 weeks	10 males and 26 females, age 18-49, sedentary, BMI 25-35 kg/m^2	Similar energy compensation occurs in response to both ExEE groups, rendering greater fat mass loss in 3,000 kcal/wk group
Lim et al. [125]	Cross sectional study comparing the effects of basic military training on body composition in obese recruits	Aerobic exercise 3x/week Circuit training 2x/week for 20 weeks	40 healthy males, age 18.9 ± 1, BF > 24% of total body weight	20 weeks of basic military training was effective at decreasing body fat mass and maintaining FFM in obese subjects

*** Units listed as means ± SD**

Diet and Energy balance:

Creating the necessary energy deficit to experience significant weight loss is also often accomplished through dietary energy restriction. Similar to exercise, this negative energy balance can induce the same compensatory response to maintain energy homeostasis. Unlike energy compensation exhibited with a negative energy balance, humans tend not to compensate for increases in energy intake, that is, they fail to increase energy expenditure upon increasing energy intake [130]. This becomes problematic when coupled with the energy dense, palatable, and convenient food environment of modern society. However, timing between meals may be one malleable variable to attenuate this response. When examining subsequent energy intake after a low-energy preload to produce an acute energy deficit, individuals compensate for at least 100% of the energy deficit when the time interval to the next meal is roughly 30 minutes [130]. Spacing the next meal to 2 hours individuals only compensate 60% of the low-energy preload [130]. Similar to an energy deficit with exercise, restricting food intake can lead to metabolic adaptations to further imped weight loss. Studies performed in a controlled environment producing a 10% weight loss in obese or normal weight individuals promote a decrease in RMR and TEE of 3-4 kcal per kg of FFM [38, 131].

Intermittent fasting (IF) has been growing in popularity for its ability to restrict energy intake and limit compensatory responses [132]. IF encompasses periods of voluntary abstinence from food and drink and can be followed in a variety of different designs [133]. In studies involving individuals with obesity, 24-

hour total energy restriction or 75% energy restriction improves subsequent postprandial glucose and lipid metabolism while inducing a 30% energy deficit over 3 days [132]. Resting and meal-induced thermogenesis do not change in either a 24-hour total energy restriction or 75% restriction protocol, indicating a lack of metabolic compensatory response to the energy deficit [132]. Although initial research using IF to combat obesity is promising, many of the studies include few individuals for short periods of time.

Recent research has examined the extent to which foods and beverages alter hunger and the desire to eat in order to inhibit future eating. One of the techniques explored is to design nutrient dense “satiating” foods that decrease the return of hunger after eating and inhibit future energy intake [134]. These foods are often high in fiber and protein and enhance satiety in an acute manner [134] but fail to attenuate the long term compensatory increases in energy intake needed to promote significant weight loss [135]. The popularity of diets such as the ketogenic, high protein or carbohydrate cycling in promoting significant weight loss is well documented, but all successful diets have one thing in common: maintaining an energy deficit. The degree to which type of diet promotes the least amount of compensatory eating and metabolic adaptations to maintain the greatest energy deficit needs further exploration.

Summary of Research Related to Diet and Energy Balance

Source	Study Design	Diet protocol	Study population*	Primary findings
Leibel et al. [129]	3-arm crossover study comparing metabolic adaptations in obese and non-obese when exposed to an energy deficit and surplus.	Dietary formula (40% fat, 45% carb, 15% pro) at 800 kcal/d or 5,000-8,000 kcal/day self-selected food	11 obese women, 7 obese men, and 7 normal weight women, 16 normal weight men age 29 ± 10 years (obese) 26 ± 10 (normal weight)	Maintenance of a reduced or elevated body weight is associated with compensatory changes targeted at returning to initial weight in both obese and normal weight individuals
Antoni et al. [130]	3-arm crossover study looking to characterize the early metabolic responses to varying degrees of IF over 24 hours (0%, 75% or 100% ER)	75% or 100% ER for 24 hours and ad libitum feeding day	6 female and 8 male, overweight or obese, aged 36 ± 17.2	ER alters post prandial glucose/lipid metabolism with partial ER producing more favorable results including incomplete energy compensation
McCrickerd et al. [132]	4-arm crossover study looking at the role sensory characteristics of food influence appetite regulation and portion size selection.	Once daily iso-energetic fruit drink of varying sensory contexts consisting of either thin/low creamy, thin/high creamy, thick/low creamy, thick/ high creamy	24 male and 24 female, healthy, age 20.8 ± 5.3 years, BMI 22.5 ± 2.8 kg/m²	Women consume smaller portions of a drink when its sensory characteristics indicate it will be satiating (thick texture)

*** Units listed as means ± SD**

Protein and compensation

The ideal conditions for body weight loss are sustained satiety despite a lower energy intake, [136, 137] and sustained metabolic energy expenditure despite body weight loss [137, 138]. High-protein diets are a popular strategy for weight loss, based on the idea dietary protein helps spare muscle protein degradation and elicits greater satiating effects compared to other macronutrients [139]. The satiating effects of eating protein are partly due to slowing gastric emptying. When protein is infused intra-duodenally, the digestive system responds by increasing pyloric motility and stifling antral and duodenal movement [140, 141]. Oral ingestion of protein in healthy adults slows gastric emptying rates to reduce plasma ghrelin and increase insulin, CCK and GLP-1 concentrations, which all play a role in satiety signaling [141]. Macronutrients are seldom ingested alone but evidence does show greater postprandial plasma concentrations of CCK and GLP-1 (satiety hormones) and lower ghrelin after ingestion of yogurt containing a greater percentage of protein than a comparable yogurt with less [142]. When comparing gastric emptying of fat and carbohydrate, high-fat or high-carbohydrate meals have similar gastric emptying half times, both faster than protein, indicating protein may be the crucial macronutrient responsible for slowing gastric emptying and thus influencing appetite and satiety [143, 144]. Ratings of hunger and desire to eat tend to be attenuated by a high-protein drink compared to iso-volumetric drinks containing less protein and greater amounts of fat and carbohydrate. Even when energy content is controlled for, the high-protein option reduces ratings of hunger and desire to eat and slows

gastric emptying several hours after consumption [144]. The ability of a high-protein diet to mitigate lean muscle mass losses body fat loss is also plausible. When combined with resistance exercise, a high-protein diet consisting of 2g per kg body weight spaced evenly throughout the day paired with a slight energy deficit can alter body composition and preserve lean mass [145, 146]. Preserving lean mass during weight loss would serve to maintain RMR (attenuate metabolic compensation) compared to equivocal weight loss where FFM is decreased [147].

Summary of Research Related to Protein and Energy Compensation

Source	Study Design	Diet protocol	Study population*	Primary findings
Blom et al. [140]	Single blind crossover design investigating the satiating effects of a high-protein breakfast compared to a high-carbohydrate meal.	Isoenergetic dairy breakfast differing in protein and carbohydrate content	15 males, healthy, age 18-26 years, BMI 19-25 kg/m²	High-protein breakfast decreased postprandial ghrelin concentrations more and for longer duration than a high-carbohydrate breakfast.
Giezenaar et al. [142]	Double-blind crossover design determining the effects of adding or substituting carb or fat to whey protein on gastric emptying, gut hormones, appetite and energy intake	(Pro/carb/fat) 14g/28g/12.4g (280 kcal) 70g/28g/12.4g (504 kcal) 70g/0g/0g (280 kcal)	13 males, healthy, age 18-30 years, BMI 24 ± 3.6 kg/m²	Substitution of whey protein with carbohydrate and fat accelerated gastric emptying. High-protein mixed macronutrient drink increased gut hormone and insulin responses
Hector et al. [144]	Randomized double-blind trial comparing impact of protein quality on rates of muscle protein synthesis and lipolysis	Energy-restricted diet consisting of either 1.3 g/kg protein or 0.7g/kg protein. The high-protein group either received 27g whey protein or 27g soy twice/day for 14 days	19 men and 21 females, healthy, age 35-65, BMI 28-50 kg/m²	Whey protein supplementation attenuated the decline in postprandial rates of muscle protein synthesis compared to soy when in energy deficit.

***Units listed as means ± SD**

Ketogenic diet

The ketogenic diet is a high-fat diet with 80-90% of energy derived from fat. [148]. With so little dietary glucose, the body and brain depend on the utilization of fat for fuel. Consumption of a ketogenic diet is characterized by elevated levels of ketone bodies, primarily β-hydroxybutyrate, which represent an alternative energy source to glucose and can increase feelings of satiety [148, 149]. In fact, some argue it's a better energy source compared to glucose due to ketones having a greater inherent energy [150], causing greater heart contractility while utilizing less oxygen in animal models [151]. The health benefits promoted by a ketogenic diet are improvements in epilepsy [152, 153], weight loss [154], cognitive improvements in Parkinson's and Alzheimer's disease[155, 156], decreased fasting insulin and lower blood glucose levels [148]. The ketogenic diet is a popular strategy to fight obesity based on its efficacy in promoting satiety while maintaining an energy deficit [157-159]. This is accomplished through interactions between circulating ketones and hormonal mediators of appetite in the periphery and the brain [160]. Under normal circumstances, the preferred fuel source for the brain is glucose; however, it can utilize β-hydroxybutyrate to meet its energy needs, which is roughly 20% of TEE [161]. Most of the body (excluding red blood cells) can utilize free-fatty acids (FFA's) from endogenous adipose tissue as an energy source further decreasing the need to feed. Compensatory eating is therefore less likely to take place and subsequent altered weight maintenance is easier to achieve when the body is using fat and its metabolites for fuel. Weight loss from a ketogenic diet is

primarily due to fat mass reductions, and may often lead to increases in FFM [154]. Unlike other diet-induced weight loss protocols, no significant reductions in RMR, circulating leptin or postprandial release of CCK occur while on an energy restricted ketogenic diet [154, 160]. The lack of metabolic compensation on a ketogenic diet could be due to the increased energy demands of undergoing gluconeogenesis in the absence of dietary glucose [149, 154], despite upregulating fatty-acid oxidation that often promotes metabolic compensation with energy restriction [29, 37].

Summary of Research Related to Ketogenic Diet and Energy Compensation

Source	Study Design	Diet protocol	Study population*	Primary findings
Mohorko et al. [152]	Longitudinal intervention examining the effects of a 12-week ketogenic diet on physiological, psychological and biochemical changes in the body	12-week energy-restricted ketogenic diet	13 men and 25 women, obese, aged 37 ± 7 years, BMI 36.1 ± 5.6 kg/m²	Significant weight loss, reductions in plasma insulin and leptin and decreased snacking with ketogenic diet
Sumithran et al. [158]	RCT examining the effects of ketosis on different factors involved with appetite regulation	10-week energy-restricted ketogenic diet	Healthy, overweight/obese men and postmenopausal women, age 54 ± 10.9	Ketogenic diet induced significant weight loss while suppressing ghrelin and ratings of hunger
Johnstone et al. [155]	3-arm crossover study comparing the hunger, appetite and weight loss responses to a high-protein ketogenic diet and high protein normal carb diet	High protein ketogenic diet vs. high-protein normal carbohydrate diet for 65 days	17 healthy men, age 20-65, BMI >30 kg/m²	High-protein ketogenic diet reduced hunger and lowered food intake compared to high protein normal carbohydrate diet

***Units listed as means ± SD**

Low energy meal replacement

Countless “low calorie” foods appear in every aisle of the supermarket including brownies and potato chips, where food manufacturers aim to attenuate the energy density of these foods without changing the palatability and sensory

experience of eating [162]. Designing low energy foods and beverages that satisfy hunger and do not lead to later compensation would greatly improve obesity rates throughout the modern world. Although these foods often do not completely accomplish this goal, promising research does exist. When a meal is given to an individual 60 minutes after ingesting either a low-energy preload (100 kcal beverage) or a high-energy control beverage (300 kcal), individuals consume 80 kcal more in the low-energy preload scenario, which constitutes only 40% of the 200 kcal removed from the control beverage [162]. When exposed to the same control preload containing an additional 200 kcal, individuals do not alter their next meal energy intake compared to the 300 kcal preload, demonstrating our lack of ability to completely compensate for decreases or increases in energy intake [162]. In addition to only a partially compensating to a low-energy preload in the following meal, there appears to be no such compensation the rest of the day, whereas participants consumed the least amount of energy on the low energy meal day and most on the high energy day (Low energy: 2172 ± 93; Control: 2323 ± 73 High energy: 2500 ± 84) [162]. Individuals are good at compensating with later food intake in response to smaller quantities of familiar energy-dense foods, like chocolate. Although when energy density is reduced while keeping volume and sensory characteristics constant, the satiety is improved to attenuate the increase in energy consumption compared to control [134]. Adding volume without adding energy to a meal may also attenuate food intake, demonstrated in studies where individuals who consume 500ml of water immediately prior to a meal ingest significantly less

energy in the subsequent meal than individuals consuming no water [163, 164]. Taking advantage of the body's inability to perfectly compensate for lost energy may be easier to accomplish by incorporating more reduced energy options into one's diet.

Summary of Research Relate to Low Energy Meal Replacement and Energy Compensation

Source	Study Design	Diet protocol	Study population	Primary findings
McCrickerd et al. [162]	Single blind crossover study testing the satiety responses to a 200kcal reduction/addition to a soy beverage	Three iso-volumetric soymilk test drinks varying in energy (100 kcal, 302 kcal and 500 kcal)	29 males, healthy, non-obese, age 21-37 years, BMI 18-28.6 kg/m²	Adult men were more sensitive to energy dilution than energy addition to a familiar beverage
Dennis et al. [163]	RCT to determine if pre-meal water consumption facilitates weight loss among overweight/ obese middle-aged adults through reductions in energy intake at subsequent meals	12-week energy-restricted diet, 500 ml H_20 prior to each meal (3 times per day) or diet alone	48 male and females, age 55-75 years, BMI 25-40 kg/m²	Combining a weight loss diet with consuming 500ml H_2O prior to meals leads to significant weight loss compared to diet alone

Genetic variability and energy compensation

The large inter-individual differences in weight gain under equal conditions of excess energy intake that has been reported in several overfeeding studies

points to genetic variability playing a major role in obesity development [165, 166]. Since the mapping of the human genome, the search for a genetic cause of obesity has been underway. The genetic etiology can be classified as either monogenic or polygenic [167]. Monogenic obesity describes individuals who carry a rare gene variant that is directly linked to drastic changes in adiposity and exhibit a nearly one – to – one relationship between genotype and phenotype [168, 169]. Monogenic obesity can be classified as syndromic or non-syndromic, with non-syndromic characterized by changes in leptin/melanocortin pathways leading to hyperphagia [170]. Syndromic, on the other hand, is obesity occurring in the clinical context of a specific genetic disorder such as found in individuals with Prader-Willi syndrome [171]. Homozygote carriers of non-syndromic mutations are rare but directly lead to early-onset extreme obesity [167]. Heterozygous variations in the same pathway account for a greater number of obesity cases, with environmental factors influencing the expression of these genes [170]. Polygenic obesity is attributed to the collaborative presence of multiple DNA mutations in several genes, each having a relatively small effect on obesity probability [169]. Recent advancements have identified hundreds of polygenic variants playing a role in obesity with environment, age, sex and lifestyle choices interacting to influence phenotypic expression [172].

Although genetic makeup clearly plays a role in obesity, the extent to which is controversial, and more studies are needed to uncover the exact role biology plays in the obesity epidemic. Currently, research is focusing on

metabolic phenotypes, the melanocortin system, and variants in the fat mass and obesity-associated gene.

Spendthrift and thrifty phenotype

Individuals can be classified as either “thrifty” or “spendthrift” metabolic phenotypes depending on changes in TEE after 24 hours of fasting and a subsequent 6-week overfeeding period [173]. TEE during the 24-hour fast is used to predict the extent of weight loss during energy restriction, in that the less TEE drops the more weight one loses [174]. Individuals who experience the smallest increases in TEE after overfeeding have the greatest decrease while fasted (thrifty metabolic phenotype), whereas individuals with the smallest decrease in TEE after fasting have the greatest increase after overfeeding (spendthrift phenotype) [174-176]. A smaller decrease in TEE after fasting is indicative of less metabolic compensation and correlated with less weight gain after 6 months of living normally [175]. Individuals who increase TEE the most during overfeeding are those who gain the least amount of weight, especially in fat mass [173]. The greater increase in TEE during overfeeding indicates metabolic “spend thriftiness” in short-term overfeeding and is therefore somewhat protective of weight gain while the thrifty phenotype is more prone to metabolic compensation [173]. The recent discovery of the hormone fibroblast growth factor 21 (FGF21) has given a possible explanation on how the thrifty phenotype is expressed. FGF21 is an energy homeostasis hormone that is upregulated in response to low-protein/high energy diets mediating increases in energy expenditure potentially through diet induced thermogenesis [177, 178].

Individuals with smaller increases in FGF21 after 24h of a low-protein/high energy diet gained more weight during a six-month intervention than individuals with larger increases in FGF21. These results indicate persons with a dampened FGF21 response have a “thrifty” metabolism and measuring FGF21 responses to a low protein diet may help predict an individual’s susceptibility to future weight gain [178].

Summary of Research Related to Spendthrift and Thrifty Phenotypes

Source	Study Design	Diet protocol	Study population*	Primary findings
Hollstein et al. [172]	2-arm crossover study investigating whether energy expenditure responses to 24 h of fasting or overfeeding would predict weight gain in lean individuals	High energy, low-protein diet (2%), 6 weeks	7 males, healthy, age 31 ± 12 years, BMI 20.5 ± 1.6 kg/m²	Subjects with a lower 24-h energy expenditure decrease during fasting and greater increase during overfeeding gain less weight
Reinhardt et al. [173]	Longitudinal trial analyzing changes in 24-hr energy expenditure in obese individuals after fasting and overfeeding and implications on weight loss in a subsequent energy restricted diet	50% energy restricted liquid diet, 20 weeks What about overfeeding group?	7 men and 5 women, healthy, age 33.7 ± 8.6, BMI 38 ± 6.3 kg/m²	Smaller reduction in 24-h energy expenditure during fasting and larger increase to overfeeding predicted more weight loss over 6 weeks of underfeeding
Schlogl et al. [174]	Inpatient crossover design determining whether 24-h energy expenditure responses to dietary extremes will identify phenotypes associated with weight regulation	Low-protein, high-fat and high-carbohydrate overfeeding and a control energy balanced standard diet	27 men and 10 women, healthy, age 36.1 ± 9.6, BMI 26.1 ± 4	A larger reduction in energy expenditure during fasting, a smaller energy expenditure response during overfeeding in low protein diet and a larger response to overfeeding in high carbohydrate overfeeding correlated with weight gain

***Units listed as means ± SD**

MC4R genotypes

The melanocortin system consists of several agonists, two antagonists and five receptors [179]. The agonists are all derived from pro-opiomelanocortin (POMC) in the anterior pituitary gland [180, 181]. The two antagonists of the receptor are Agouti and Agouti-related peptide (AgRP) [179]. The melanocortin receptors mediate diverse actions but the melanocortin 4 receptor (MC4R), expressed primarily in the central nervous system, is of interest in regards to obesity [179]. The MC4R is a G-protein coupled receptor that binds the agonist α-melanocyte stimulating hormone. This receptor/hormone binding is involved in feeding behavior, metabolism and other biological functions [179]. Defects in eight independent genes involved in neural function of the paraventricular nucleus and in the leptin/melanocortin pathway have been identified, promoting monogenic obesity through hyperphagia [182]; however, these homozygotes are rare and do not explain the majority of obesity phenotypes. The emergence of polygenic predisposition to obesity is often related to the central nervous system's control of body weight regulation [183]. A single nucleotide polymorphism (SNP) near the MC4R (SNP rs17782313) is associated with increased feelings of hunger [184, 185], increased snacking [184], decreased satiety [185], and increased total fat and protein intake [184, 186]. The degree to which a specific MC4R phenotype affects hyperphagia is directly related to how well the receptor works or how many are present. Mutations that result in a complete loss of function cause the more severe forms of obesity [187]. MC4R

genotype also affects the extent to which a weight loss intervention remains successful. Individuals with decreased MC4R signaling, despite normal weight loss during an intervention, have more difficulty maintaining weight loss [188]. This could be due to MC4R's impact on metabolic compensation, with mutations causing decreased energy expenditure as evidenced in obese Pima Indian and Hispanic individuals [189, 190]. Although these mutations of the MC4R are obesogenic, others confer protection. Two such mutations protect individuals from severe obesity and abdominal adiposity by making MC4R less sensitive to its antagonist, AgRP, that results in a weaker orexigenic signal [191, 192], and by making it more sensitive to its agonist [191, 193]. Individuals with decreased functioning of the MC4R receptors are not only more prone to overeating but also experience greater metabolic compensatory responses to weight loss making weight loss maintenance especially difficult.

Summary of Research Related to MC4R Genotypes and Energy Compensation

Source	Study Design	Gene Polymorphism	Study population	Primary findings
Stutzmann et al. [183]	Epidemiological study in French and Swiss population comparing genotype with eating behavior traits	Rs17782313 (MC4R) and rs1421085 (FTO)	N = 17,527 French obese/normal weight children and adults and Swiss class III obese adults	The Rs17782313 allele (MC4R) may modulate eating behavior in both obese adults and children
Valladares et al. [184]	Epidemiological study examining the relationship between MC4R gene variant with childhood obesity and eating behavior	Rs17782313	N = 489 Chilean children and their parents	The rs17782313 variant is significantly associated with satiety responsiveness to a meal (P = 0.01) and enjoyment of food (P = 0.03)
Reinehr et al. [187]	Longitudinal intervention study comparing weight changes after lifestyle intervention in children with mutations in the MC4R gene	Loss of function mutation of MC4R compared to normal	226 male and 288 female children, healthy, age 5-16 years, BMI 24-29 kg/m² enrolled into a 1-year lifestyle intervention	Children with MC4R mutation leading to loss of receptor function were able to lose weight as normal but had greater difficulties maintaining weight loss

FTO genotype

As recently as 2007, the function of the fatso gene (FTO) [194] was unknown [195]. Today, FTO is known as the fat mass and obesity associated

gene and is responsible for coding a protein known as alpha-ketoglutarate-dependent dioxygenase. Complete or partial inactivation of the FTO gene in mice protects from obesity but increases mortality [196, 197], whereas over-expression leads to increases in food intake and subsequent obesity [198]. In humans, complete FTO deficiency is associated with growth retardation, multiple malformations and premature death, indicating its essential role in normal development of the central nervous system [199]. FTO is highly expressed in the hypothalamus and plays a large role in controlling feeding behavior and energy expenditure [195, 200, 201]. Initially, SNPs in the FTO gene were thought to show a direct association with type II diabetes, however, upon further analysis, the relationship between FTO SNPs and type II diabetes was facilitated by an association with BMI [202]. The association between FTO SNPs and the risk of being overweight or obese has been confirmed in several different populations [202, 203]. FTO is linked to deficits in Fe (II) and 2-oxoglutarate oxygenase [200]. These enzymes catalyze oxidative reactions on multiple substrates using non-heme iron as a co-factor and oxyglutarate as a co-substrate [200]. The main enzyme FTO codes for that can cause dysregulation of metabolism-regulating oxygenases is a single-stranded DNA demethylase involved in nucleic acid repair or modification processes [200, 204]. Therefore, FTO expression has a role in regulating genes dealing with metabolism possibly through epigenetic mechanisms [200]. FTO may pose as a transcriptional coactivator that enhances activation of certain enhancer binding proteins dealing with the development and maintenance of fat tissue, with dysregulation in this process causing obesity

[205]. The obesity predisposing FTO variant is associated with increased energy and fat intake in both children and adults [206]. Certain FTO variants are also associated with diminished satiety and increased feelings of hunger [207]. Energy homeostasis is extremely sensitive and any variation in FTO, combined with dietary/physical activity habits can substantially impact body composition. The wide disparity in FTO genotypes is one possible explanation for the varying degrees of energy compensation individuals experience in response to exercise and energy restriction and the degrees of success maintaining a reduced weight.

Summary of Research Related to FTO Genotype and Energy

Compensation

Source	Study Design	Gene Polymorphism	Study population	Primary findings
Cecil et al. [200]	Genome wide association study analyzing the role FTO variants play in modulating specific components of energy balance in children	Rs9939609 FTO variant	N = 2726 Scottish children, healthy, age 4-10 years	FTO variant (rs9939609) doesn't appear to be involved in regulating energy expenditure but may have a role in the control of food intake and choice
Wardle et al. [201]	Cohort study examining the association between alleles of FTO known to increase obesity risk and measures of habitual appetitive behavior	Rs9939609 FTO variant	N = 3337 United Kingdom children from TEDS cohort	FTO variant (rs9939609) associated with increased adiposity due to reduced satiety responsiveness
Church et al. [204]	3-armed longitudinal study analyzing the role over/under expression of FTO plays on energy expenditure and adiposity	FTO variants Which variant? The other studies you listed the specific one. Or was it the whole gene?	Mice generated to globally express either one (n=17) or two additional copies of FTO gene (n=17) or wild-type control (n=16).	Mice with over expression of FTO had a dose-dependent increase in fat mass resulting from increased food intake. These mice also developed glucose intolerance

Conclusion

In humans, homeostatic regulation of an energetic state is regulated by a sensory feedback system that attempts to preserve stability through the concerted amendment of both energy intake and energy expenditure. The disruption of this metabolic homeostasis is reflected by adaptations in body weight, with a positive or negative energy balance leading to weight gain or loss, respectively. Many Americans with obesity strive to maintain a negative energy balance needed for weight loss, yet the majority of these efforts lead to less than desirable outcomes. Unfortunately for these individuals, energy balance regulation favors defending against an energy deficit over surplus. It can be argued survival rather than sustainability is the evolutionary authority, where periods of energy deficit are protected by a hardwired system that prevents starvation to promote species continuation. For most of human existence this was an instrumental system that ensured our survival but in the modern age of convenience, abundant energy-dense food and sedentary lifestyles, the once necessitous and rigid compensatory mechanisms are playing a role in the rising obesity trend. To be fair, our current biological makeup took millions of years to evolve and expecting it to change in response to half a century of living in an obesogenic society is outlandish. Obesity has reached epidemic proportions along with related comorbidities, thus finding novel, applicable therapies to remedy the situation is imperative and will likely involve individual, environmental and societal interventions.

The most intuitive way to expend energy is by performing some form of physical activity. Exercise comes in many forms and intensities, ranging from aerobic cardiovascular bouts to anaerobic resistance training sessions to modalities utilizing both such as HIIT protocols. No matter the modality, the ability to sustain a prolonged energy deficit will determine how successful an exercise protocol is at reducing fat mass. There does appear to be a limit on total energy compensation of about 1,000 kcal per week when expending as much as 3,000 kcal/week, indicating greater expenditures may be needed to overcome this compensatory response[23, 73]. Although there is some evidence that greater energy expenditures, beyond that of 3,000 kcal per week, elicit a greater compensatory response than a lower dose [20]. It therefore appears additional research is needed to determine the optimal dose of weekly or per session energy expenditure needed to best produce weight loss without instigating a greater compensatory response.

An interesting psychological aspect to exercise and subsequent food consumption comes in the role “choice” and “implied exertion” may play. If you give people structured choices in exercise modality, music, intensity and duration they are more inclined to view exercise as enjoyable and not seek food rewards post physical activity [86]. The same is true when initial thoughts about an exercise protocol are more positive than negative. If someone thinks a workout will be hard and gruesome, they are more likely to seek a reward for completing such a task. The opposite happens when they view a workout as beneficial and enjoyable [85].

In a perfect world, we could promote satiety and maintain metabolic rate while in a negative energy balance by modifying our food choices and quantities. A high-protein diet may be able to accomplish such a feat. The satiety inducing effects amino acids is well known, but consuming increased amounts of protein may also spare lean muscle degradation leading to maintained metabolic rate during weight loss [137]. Incorporating resistance training with a high protein/energy restricted diet may be a potent mechanism for promoting maximal fat mass losses while increasing/maintaining FFM [145].

Further elucidation on the role the hunger hormones and endocannabinoids play in the dysregulation of appetite witnessed in obesity is a novel area of interest. Larger amounts of visceral adiposity are positively correlated with insulin resistance and increased 2-AG both fostering a metabolism favoring energy storage and potentially leading to greater difficulty in achieving a healthy body composition through exercise and dieting. More research in this field my lead to novel pharmacological treatments for obesity that may be use in conjuncture with exercise or ER.

The role genetics play in obesity phenotypes with regards to energy compensation is controversial and not well understood. Although a few monogenic genotypes are directly related to increases in adiposity, these only account for a small percentage of individuals who are morbidly obese [167]. More research is needed to understand polygenic relationships amongst genes and the environment, how to identify these relationships, and if this could lead to personalized weight loss therapies [208].

Overall, understanding how best to limit energy compensation while maintaining an energy deficit is of importance in combating obesity. The answer may lie in a coupling paradigm where all the reputable facts and empirically supported theories across multiple disciplines unite to form a common groundwork for explanation and more effective weight loss treatments.

Chapter Three: Materials and Methods

Research Design

This study was a randomized, controlled trial that included a 12-week exercise intervention of either six sessions (days) per week, two sessions per week, or a sedentary control group (no exercise) blocked on sex. Participants were randomized upon completion of all baseline assessments with no blinding of assignment to interventions as participants and research staff needed to monitor weekly exercise sessions to ensure compliance. Participants were assessed for outcome measures at baseline and immediately after the intervention.

Subjects

A total of 52 participants aged 18 to 49 years volunteered and were randomized into one of three groups during this longitudinal, randomized, controlled trial. Of these, 44 participants completed the study (32 women), with six (four women) withdrawing for personal reasons and two female participants being excluded for non-compliance. Inclusion criteria included participants having a body mass index (BMI) ranging from 25-35 kg/m^2, non-diabetic, no medications, not pregnant were between the ages of 18-49 and were inactive (not engaging in any form of exercise for the previous 6 months). We defined exercise as purposeful, leisure time physical activities performed to improve health and/or weight status. This was determined during screening when participants were asked of their exercise behaviors and were excluded if they

reported engaging in any exercise over the previous six months. The lack of exercise behaviors of the current sample was validated by accelerometry, as baseline seven-day vigorous physical activity (VPA) values were well below the recommended 75 minutes per week for every participant (Table 1). The study was an open enrollment with staggered start dates for participants between the winter of 2018 and continued until recruitment goals were met (spring of 2019) in and around Lexington, Kentucky. Participants were a sample who responded to recruitment media including printed brochures and flyers and online advertisements placed on University of Kentucky's Center for Clinical and Translational Science (CCTS) website. This study was approved by the University of Kentucky Institutional Review Board and is registered with ClinicalTrials.gov identifier: NCT03413826.

Procedures

During the initial screening and consenting visit, participants provided their written informed consent and were screened of eligibility criteria, completing a physical activity readiness questionnaire (PARQ), health history questionnaire, and screened on their dieting, weight loss history, and physical activity behaviors. Participants were provided an ActiGraph Accelerometer (Pensacola, Fla) to wear for the following seven days to objectively assess physical activity prior to completing baseline testing. Subsequent visits included assessments for resting metabolic rate, rate of energy expenditure during exercise, and body composition, (all detailed below).

Assessments

Physical activity

Habitual, free-living physical activity was measured using an ActiGraph accelerometer (GT3X+ model; Pensacola, Florida) at baseline to verify participants were not engaging in exercise. Participants were instructed to wear the monitor at the hip using the provided belt during all hours awake except when bathing or swimming. Data were cleaned of non-wear time, defined as consecutive strings of zeros greater than 20 minutes. An epoch of 10 seconds was used for data collection as a shorter epoch is more suitable to reflect bout duration under free-living conditions of sedentary individuals [209]. These data were used to determine participants' weekly minutes of vigorous physical activity (VPA) using the Crouter et.al algorithm, and Freedson cut-points. VPA was used over the more typical moderate to vigorous physical activity (MVPA) to determine exercise behavior as VPA is a better measure of purposeful exercise opposed to activities like walking across a large college campus (as many participants were obligated to do) which can be counted as MVPA but did not fit our definition of "exercise".

Rate of Energy Expenditure

A graded exercise treadmill test was used to determine each participant's rate of energy expenditure at five different heart rate zones. Oxygen consumed

and CO_2 produced were analyzed by indirect calorimetry (VMAX Encore Metabolic Cart, Vyaire Medical, Mettawa, IL), which included an integrated 12-lead ECG for monitoring heart rate and used in conjunction with the Trackmaster TMX428 Metabolic cart interfaced treadmill. Upon completion of a five-minute warm-up walking at 0% grade and 3.0 mph, the treadmill grade increased to 2.5% for three minutes. The treadmill grade was then increased every three minutes to produce an approximately 10-beat per minute increase in heart rate from the previous stage with the speed fixed at 3.0 mph. The test continued until a heart rate of 85% heart rate reserve (HRR) was attained or the participant felt they could no longer continue. Rate of energy expenditure (kcal per minute) was determined from the amount of oxygen consumed and CO_2 expired using the Weir equation [210]. The average rate of energy expenditure during the last 30 seconds of each stage of the test was regressed against the heart rate averaged over the last 30 seconds of the corresponding stage to calculate the rate of energy expenditure at different heart rates. Heart rate zones were calculated based on the HRR formula as (220-age)-resting heart rate * zone % + resting heart rate. Heart rate zone 1 ranged from 50-59% HRR, zone 2 corresponded to 60-69% HRR, zone 3 was 70-79% HRR, zone 4 was 80-89% HRR, and zone 5 was 90% or greater. Energy expenditure in kcal/min was averaged across each heart rate zone for determination of energy expenditure per minute for each zone. This test was completed at baseline and again at six-weeks to recalculate energy expenditure to take improvements in cardiorespiratory fitness into account.

Body Composition

Body composition was measured using a GE Lunar iDXA machine prior to the exercise test. The iDXA technique allows the non-invasive assessment of soft tissue composition by region with a precision of 1-3% [211]. Lunar iDXA was used pre and post intervention to determine changes in FM and FFM of each participant. A total body scan was conducted with participants lying supine on the table and arms positioned to the side. Most scans were completed using the thick mode suggested by the software. All scans were analyzed using GE Lunar enCORE Software (13.60.033). Automatic edge detection was used for scan analyses. The machine was calibrated before each scanning session, using the GE Lunar calibration phantom.

Resting Energy Expenditure

Resting Energy Expenditure (REE) was measured using indirect calorimetry (Quark RMR; Cosmed USA, Chicago, IL) with a ventilated canopy. Calibrations were performed on the flow meter using a 3.0-L syringe and on the gas analyzers using verified gases of known concentrations before each test. On the day of the test, participants were instructed to come into the lab having fasted for 12 hours, engaged in no physical activity and drinking nothing but water. After 30 minutes of quiet rest in the supine position in a dimly lit, temperature-controlled room between 22 and 24 C, REE was measured for 30 minutes. The test was monitored to ensure participants remained awake and between 0.8 and

1.2% feCO_2. Criteria for a valid REE was a minimum of 15 minutes of steady state, determined as a <10% fluctuation in oxygen consumption and <5% fluctuation in respiratory quotient. The Weir equation [210] was used to determine REE from the measured oxygen consumption and CO_2 production. Participants completed the baseline REE assessment prior to the exercise test and 36-72 hours after their final exercise session of the intervention. Fat-free mass (FFM) is the predominate determinant of REE due to its metabolic activity, explaining 53% to 88% of the variance in REE [212, 213]. For this reason, REE (raw value) was divided by FFM (kg, from DXA) at each time point to standardize REE. This is consistent with previous literature and the definition of metabolic compensation, i.e. mass-independent reductions in energy expenditure [131, 214, 215].

Compensation

To calculate compensation for the energy expended during the exercise program, the accumulated energy balance (AEB) was calculated from pre-post changes in fat mass (FM) and FFM as body composition changes reflect long-term alterations in energy balance [20]. Gains of 1kg FM and 1kg FFM were assumed to reflect 12,000 kcal and 1,780 kcal, respectively [216]. Losses of 1kg FM and 1kg FFM were assumed to equal -9,417 and -884 kcal, respectively [217]. Exercise energy expenditure (ExEE) was calculated from the training-induced energy expenditure (TrEE) with the addition of 15% excess post-exercise energy expenditure [218]. The REE that would have occurred during the

exercise sessions (REE x 1.2) was subtracted so not to include it twice. Thus, ExEE = (TrEE x 0.15) + (TrEE – training duration x (REE x 1.2)) [20]. Compensation in response to the increase in ExEE was assessed as described by Rosenkilde [20], with the compensation index (CI) calculated as (ExEE + AEB)/ExEE x 100%. When the CI equals zero, AEB equals -1*ExEE, or changes in the energy equivalent of FM and FFM equal energy expended during exercise. Positive compensation suggests that changes in body composition indicate a negative energy balance that was less than expected based on ExEE, whereas negative compensation indicates a greater than expected negative energy balance. ExEE, AEB, and CI could be calculated only for those participants who completed the study as both a pre- and post-treatment data points were needed to calculate these variables.

$$\text{Compensation Index (CI, \% kcal compensated for)} = \frac{\text{exercise energy expenditure (ExEE)} + \text{accumulated energy balance (AEB)}}{\text{ExEE}} \text{ X } 100$$

Note: AEB is a negative number when bodily energy stores decrease, positive when gaining

Exercise Intervention

Participants were provided a Polar A-300 heart rate monitor (watch and chest strap, Kempele, Finland) for the duration of the 12-week intervention and instructed to engage in aerobic exercise (excluding swimming) either two or six days per week. Participants in the control group were instructed to remain sedentary and were offered the exercise intervention after post-testing, 12-weeks

later. Those in the exercise groups returned to the lab weekly to meet a researcher and download their exercise sessions using the PolarFlow™ software, which allowed research staff to monitor and track compliance. If a participant was not 90% compliant (completed 90% of expected exercise sessions per month) they were dropped from the study. The downloaded exercise session reports provided the amount of time spent in each heart rate zone, which allowed for the calculation of total energy expended during each exercise session based off individual rates of energy expenditure averaged across each heart rate zone calculated from the graded exercise test with indirect calorimetry performed at baseline and again at week six. Participants in the two-day per week group were instructed to perform two long exercise sessions per week between 90 and 120 minutes at a self-selected intensity provided they were in at least HRR zone 1. Participants in the six-day per week group were instructed to keep their sessions between 40 and 60 minutes per session with the same intensity guidelines as the two-day group. Individuals were instructed to only engage in exercise per intervention group assignment. Participants were provided feedback each week on their time and energy expenditure of each session of the prior week. All participants were instructed not to purposely change dietary habits during the intervention.

Statistical Analysis

Baseline participant characteristics and exercise training-induced variables (ExEE, AEB, and CI) were tested for group differences using T-tests.

Our primary outcomes were CI, total energy compensated, and percent body fat loss with interest in how these variables related to exercise dose defined as sessions per week (randomized group), ExEE per week, time spent exercising per week, and exercise intensity (% time spent exercising in HRR zones 3-5). Differences in primary outcomes were tested via repeated measures two-way ANOVA to determine differences between groups, over time, and group by time interactions with gender and age included as covariates. Additional ANCOVA analyses were performed assessing changes over time and between groups for changes in body weight and fat mass, both as percent change and raw values. Linear regression analyses were used to predict CI and percent FM loss using exercise group (exercise frequency), time spent exercising per week, ExEE per week, and exercise intensity as independent variables. Additional regression analysis was used to predict percent change in FM using the dosing variables and total energy compensation. All analyses were performed in IBM SPSS Version 26 (IBM corporation, Armonk, New York). ***Power Analysis:*** A previous study [23] demonstrated significant differences (1.7 kg) in body fat loss in groups exercising at 3,000 kcal per week vs. 1,500 kcal per week for 12 weeks. Using an 80% power and 95% confidence level, 13 participants per group were needed to detect a significant change in body fat loss from baseline to post intervention with a standard deviation of 2.3.

Chapter 4: Results

Baseline characteristics are presented in Table 1, with no differences in BMI, age, VPA, RMR/kg FFM, RQ, or VO_2 max between groups. Participants in the two-day per week group expended on average 745.33 ± 61.04 kcal per session, while the six-day per week group expended 460.37 ± 26.04 kcal per session, mean ± SE, which was different ($P<0.01$) between groups as expected. All exercise training-induced variables are presented in Table 2, with differences in weekly ExEE, time spent exercising, and percent body fat loss between groups. Neither CI or total kcal compensated per week were different between groups. Figure 1 presents a plot of individual CI values, indicating a large individual variation and a mean CI of 50%. Both total and percent body fat and body weight changed (decreased) over time for the six-day per week group but not in the two-day per week group or control. These changes held when controlling for age and gender (ANOVA) and when controlling for baseline values (ANCOVA). The control group gained 0.98 ± 0.79 kg (4.20 ± 2.82 percent) body fat, which was significantly different ($P<0.04$) from both exercise groups. The increases in total body weight of the control group (0.40 ± 0.99 kg and 0.78 ± 1.19 percent) was not significantly different from either exercise group. These results did not change when covarying for baseline body fat or total mass, sex, or age. Changes RQ and REE were not different between groups or over time when assessed as raw values or per kg FFM.

Linear regression results predicting CI are presented in Table 3, demonstrating none of the dosing variables (exercise frequency [randomized

group], duration, intensity, and ExEE) predicted CI. Similar results are presented in table 4, whereas none of the dosing variables predicted total energy compensated. Linear regression results predicting changes in percent FM are presented in Table 5. Exercise duration, and intensity did not independently predict percent FM loss when accounting for energy compensation. The only dose variable that predicted percent FM change was weekly ExEE. Table 6 further supports the aforementioned results demonstrating greater FM is lost when weekly ExEE exceeded 2,000 kcal compared to under 2,000 kcal, with no differences in CI or total energy compensated between these retrospectively split groups.

Figure 1. Plot of CI values.

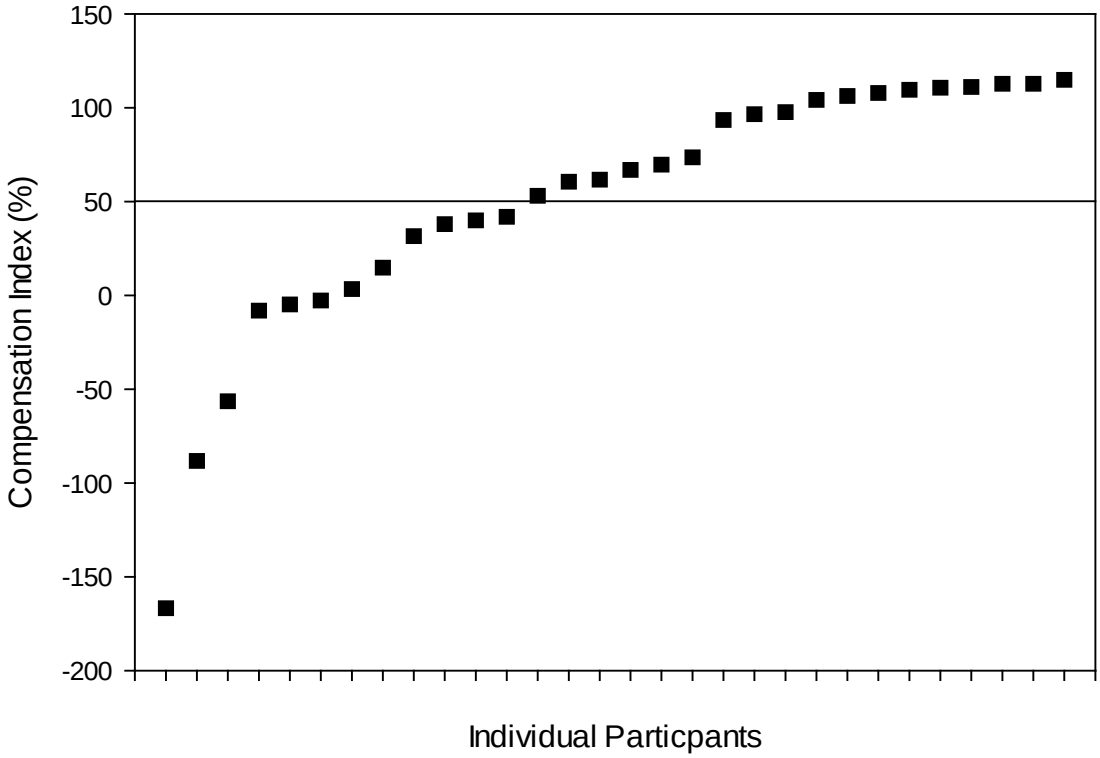

Figure 1. Compensation Index values. Each point represents an individual participant. Y values are compensation index (CI) expressed as a percentage (% kcal compensated for). The solid black line is the mean.

Table 1. Demographics, vigorous physical activity, and metabolic rates of the study participants at baseline (included all randomized participants).

	6 days per week group N = 19	**2 days per week group N = 20**	**Control N = 14**
Sex (% female)	68.4	85.0	78.8
Age (years)	29.32 ± 7.2	28.56 ± 5.85	26.00 ± 7.80
BMI[1]	29.0 ± 2.87	30.51 ± 3.47	29.36 ± 2.87
VPA[2]	9.08 ± 12.88	8.57 ± 17.45	12.91 ± 19.87
REE/Kg FFM[3]	31.52 ± 4.76	33.86 ± 4.75	33.37 ± 4.62
RQ[4]	0.93 ± 0.10	0.90 ± 0.09	0.92 ± 0.06
VO^2 Peak[5]	39.76 ± 4.56	38.45 ± 2.57	39.95 ± 4.84

Data are mean ± SD

[1]Body Mass Index, kg/m2

[2]VPA: Minutes of vigorous physical activity assessed objectively assessed via accelerometery using Freedson cut points

[4]RQ: Respiratory quotient, CO2 produced/O2 consumed during resting energy expenditure test.

[3]REE/Kg FFM: Resting energy expenditure per kg FFM, in kcal per 24 hours, assessed from indirect calorimetry and calculated via the Weir equation from O2 consumed and CO2 produced.

[5]VO2 Peak: Estimated from sub-maximal exercise test, ml/kg/mi

Table 2. Resulting data from the exercise intervention between groups that exercised. Data are mean ± SE, only individuals who completed exercise intervention

	6 days per week group N=15	2 days per week group N=17	All participants N=32
Exercise Time/week[1] *	320.5 ± 20.40	188.8 ± 12.00	249.41 ± 16.85
% Time in Zone 3-5[2]	47.73 ± 6.13	52.31 ± 4.62	50.32 ± 3.69
% Time in Zone 1-2[3]	52.11 ± 5.68	47.69 ± 4.62	49.67 ± 3.69
ExEE/week[4] *	2,753.5 ± 144.9	1,490.7 ± 122.1	2,041.68 ± 150.8
Kcal compensated/week[5]	1309.86 ± 274.5	715.42 ± 268.6	961.39 ± 198.7
Total exercise time[6]	3,944.2 ± 242.8	2,265.4 ± 143.4	2,992.9 ± 202.2
Total ExEE[7]	33,091 ± 2,112.8	17,562 ± 1,547.7	24,291 ± 1,895.0
Total Kcal compensated[8]	15,718 ± 3,294.1	8,585.0 ± 3,223.0	11,537 ± 2,384.2
AEB[9]	-16,789 ± 3,589.8	-8,977.3 ± 3,515.3	-12,363 ± 2,586.7
CI[10]	55.43 ± 10.16	49.31 ± 20.56	50.25 ± 12.27
Kg weight loss[11] *	-1.04 ± 0.45^	-0.76 ± 0.60	-0.59 ± 0.38
% weight loss[12] *	-1.48 ± 0.64^	-0.84 ± 0.66	-1.09 ± 0.45
Kg body fat loss[13]	-1.82 ± 0.39^	-0.64 ± 0.44	-0.58 ± 0.34
% body fat loss[14]	-7.70 ± 2.04^	-1.86 ± 1.27	-4.43 ± 1.30
Delta REE/kg FFM[15]	1.06 ± 0.94	-1.45 ± 1.08	-0.38 ± 0.81
Delta RQ[16]	-0.11 ± 0.06	-0.09 ± 0.07	-0.09 ± 0.04

*Significantly different between groups, P ≤ 0.05
^Significant change over time (change different from zero) P ≤ 0.05.

Note: control group (N = 12) increased % weight change (+0.78 ± 1.19) and kg body weight (+0.40 ± 0.99) which was not different from exercise groups. The control group increased % fat change (+4.20 ± 2.82) and kg fat change (+0.98 ± 0.79) both different from 2- and 6-day groups (P<0.05).

[1]Exercise Time/week: amount of time (in minutes) spent exercising per week
[2]% Time in Zone 3-5: Percentage of time exercising spent in heart rate zones 3, 4 or 5 (70-100% heart rate reserve).
[3]% Time in Zone 1,2: Percentage of time exercising spent in heart rate zones 1 or 2 (50-69% heart rate reserve).

[4]ExEE/week: Exercise energy expenditure (in kilocalories) per week.
[5]Kcal compensated/week: Energy (in kilocalories) compensated for each week calculated by adding accumulated energy balance (AEB) and total exercise energy expenditure (ExEE) together and dividing by 12.
[6]Total exercise time: total amount of time spent exercising during the entire 12-week intervention, in min.
[7]Total ExEE: total exercise energy expenditure of the 12-week intervention, in kcal
[8]Total Kcal compensated: total amount of kcal compensated, calculated by adding AEB and total ExEE together.
[9]AEB: Accumulated energy balance, calculated from changes in bodily energy stores (changes in fat and lean mass) converted to kilocalorie equivalents.
[10]CI: percentage of kilocalories compensated for, calculated as (ExEE + AEB) / ExEE)
[11]Kg weight loss: kg of total body weight lost after the 12-week intervention
[12]% weight loss: kg of weight loss / baseline body weight in kg
[13] Kg body fat loss: kg of body fat lost after the 12-week intervention
[14]% body fat loss: kg of body fat loss / baseline body fat in kg
[15]Delta REE/kg FFM: changes in resting energy expenditure per kg of FFM from baseline to post (post value minus baseline value)
[16]Delta RQ: changes in respiratory quotient during rest from baseline to post (post value minus baseline value).

Table #3 Regression model predicting changes in compensation index with exercise intensity, ExEE, time spent exercising, and exercise group as independent variables

Effect	β	SE	P
Intercept	68.357	45.719	0.147
% Time in zone 4-5[1]	-0.554	1.050	0.603
Average ExEE/week[2]	-0.002	0.030	0.953
Average exercise time/week[3]	-0.175	0.226	0.953
Exercise group[4]	29.088	51.619	0.578

P ≤ 0.05

[1]% Time zone 4-5 - Percentage of time exercising spent in heart rate zones 4 to 5 (80-100% heart rate reserve)

[2]Average ExEE/week – Exercise energy expenditure per week

[3]Average time spent exercising per week – Amount of time (in minutes) spent exercising per week

[4] Exercise group – Low frequency (2 times per week) and high frequency (6 times per week)

Table #4 Regression model predicting changes in total calories compensated between exercise intensity, ExEE, time spent exercising and exercise group

Effect	β	SE	P
Intercept	5738.435	8441.341	0.503
% Time in zone 4-5[1]	-150.240	192.388	0.442
Average ExEE/week[2]	3.342	5.687	0.562
Average exercise time/week[3]	-39.064	42.961	0.372
Exercise group[4]	8613.149	9472.673	0.372

P ≤ 0.05

[1]% Time zone 4-5 - Percentage of time exercising spent in heart rate zones 4 to 5 (80-100% heart rate reserve)

[2]Average ExEE/week – Exercise energy expenditure per week

[3]Average time spent exercising per week – Amount of time (in minutes) spent exercising per week

[4] Exercise group – Low frequency (2 times per week) and high frequency (6 times per week)

Table #5. Regression Model predicting 12-week body fat change using exercise intensity, ExEE, total energy compensated and time spent exercising as independent variables

Effect	β	SE	P
Intercept	2.640	1.571	0.106
% Time in zone 4-5[1]	.088	.036	0.24
Average ExEE/week[2]	-0.09	0.001	0.00
Average exercise time/week[3]	0.19	0.008	0.16
Total calories compensated	0.000	0.000	0.000

P ≤ 0.05

[1]% Time zone 4-5 - Percentage of time exercising spent in heart rate zones 4 to 5 (80-100% heart rate reserve)

[2]Average ExEE/week – Exercise energy expenditure per week

[3]Average time spent exercising per week – Amount of time (in minutes) spent exercising per week

Table #6. Kilocalories compensated, ExEE, and CI Retroactively split into under and over 2,000 kcal burned per week with exercise

		N	Mean	SE	Max	P
Kilocalories compensated/week[1]	Under 2,000 kcal/week	15	858.2652	225.74631	2039.63	
	Over 2,000 kcal/week	14	1071.8860	339.85811	2885.11	
	Total	29	961.3925	198.68406	2885.11	0.600
Average ExEE/week[2]	Under 2,000 kcal/week	15	1484.0703	185.63382	3642.9	
	Over 2,000 kcal/week	15	2599.2911	123.58551	3659.45	
	Total	30	2041.6807	150.75241	3659.45	*0.00
Compensation index[3]	Under 2,000 kcal/week	15	59.1020	20.96639	114.96	
	Over 2,000 kcal/week	15	41.4059	13.15720	109.65	
	Total	30	50.2539	12.27163	114.96	0.481
12-week body fat change (kg)	Under 2,000 kcal/week	15	-.4067	.44195	1.42	
	Over 2,000 kcal/week	15	-1.8953	.36854	.44	
	Total	30	-1.1510	.31470	1.42	*0.015

***Significant between group difference (P < 0.05)**

[1]Kilocalories compensated/week: Energy (in kilocalories) compensated for each week calculated by adding accumulated energy balance (AEB) and total exercise energy expenditure (ExEE) together and dividing by 12.

[2]Average ExEE/week: Exercise energy expenditure (in kilocalories) per week.

[3]Compensation index: Percentage of kilocalories compensated for, calculated as (ExEE + AEB) / ExEE)

Chapter 5: Discussion

The current study hypothesized that less frequent exercise (2 days/week) would evoke a reduced compensatory response compared to frequent exercise (6 days/week). This was based on the notion that fewer exercise sessions could result in less episodes of compensatory eating and/or fewer insults on the biological mechanisms promoting energy homeostasis. The obesogenic environment modern societies embrace shows no indications of regressing and as such, obesity rates will continue to rise. Understanding the most effective way to engage in exercise to limit the body's compensatory response normally working to maintain energy homeostasis would be a valuable weight-loss treatment. Compensatory responses that defend against a negative energy balance can be separated into two types, behavioral or automatic [22]. Automatic compensatory responses are those in which humans have no control over, such as lowering metabolic rate, when faced with an energy deficit. Behavioral compensatory responses are those in which people do have control over, such as increasing energy intake, which many proclaim to be the primary compensatory response protecting against a negative energy balance induced by exercise [22]. Limiting the compensatory responses provoked by exercise would make it a more viable obesity treatment option. Little is known about how different aspects of an exercise program influence subsequent compensatory responses. The present investigation provides insight into some of these questions, with the primary finding that energy compensation is not influenced by

exercise frequency, intensity, duration, or energy expenditure, rather, greater energy expenditures (near 2,000 kcal per week) are needed to overcome this compensatory response to produce significant reductions in fat mass.

The present study failed to reject the null hypothesis that less frequent exercise would conjure a reduced compensatory response. Rather, the present study demonstrated no differences in energy compensation when engaging in 2 or 6 sessions of aerobic exercise per week. The current findings indicate that individuals compensate for approximately 50% of the kcal they expend through exercise, regardless of exercise dose. Exercise dose in this case refers to frequency (number of sessions per week), duration of exercise (time spent engaged in exercise), exercise intensity (percent time spent exercising in heart rate zones 3-5) and ExEE. None of these variables influenced the compensatory response when including each as an independent variable in regression models predicting compensation index (CI) or total kcal compensated. In agreement with Flack et al. [23], the current investigation demonstrated the compensatory response when controlling for ExEE was not different between groups (mean of 961 kcal compensated/week). When dividing participants into groups either expending over or under 2,000 kcal/week (mean= 2041 kcal/week) only the group with greater ExEE lost significant amounts of body fat, indicating greater energy expenditures are able to partially mitigate the compensatory response to an exercise-induced energy deficit to produce reductions in body fat. This is at odds with Rosenkilde et. al, who demonstrated that expending either 1,800 or

3,600 kcal during exercise per week produced nearly identical energy deficits after 12-weeks due to greater CI observed in the 3,600 kcal group [20].

The current study did successfully reject the null hypothesis of our second hypothesis, demonstrating greater exercise dose produces greater FM loss when controlling for energy compensated. This hypothesis was based on previous literature indicating that when energy compensation is equivocal, greater exercise expenditures are needed to overcome the compensatory response to produce significant weight loss [23]. ExEE was the only dosing variable that predicted percent FM loss when controlling for energy compensation (CI and total energy compensated). The finding that percent FM loss decreased as time spent exercising and ExEE increased supports what we deduced from the between group differences and regression models predicting CI as discussed earlier, that greater energy expenditures do not result in greater energy compensated for and thus needed to create the negative energy balance needed for FM loss.

Although exercise frequency caused equivocal obligatory compensatory responses, the answer to why may lie in the sedentary nature of the participants. A number of epidemiological studies have concluded that prolonged sitting is a significant risk factor for cardiovascular disease (CVD), obesity and mortality even in individuals who obtain the recommended physical activity levels (150 min per week moderate intensity or 75 min per week vigorous) [219-222]. Outside of the exercise intervention, subjects in the current study spent minimal time engaged in vigorous physical activity with the vast majority of their time spent

sedentary, giving credence to the idea of too much time spent idle can cause exercise resistance. More frequent exposures to exercise in the six day per week group may have countered their otherwise inactive lifestyle; however, the two day per week group, despite exercising188 minutes per week, saw no significant decreases in FM.

The current study demonstrated the average weekly ExEE for all participants was 2041 ± 150 kcal with no significant decreases in percent FM. Our results indicate that if the two day per week group expended 2753 ± 145 kcal per week as in the six-day group, they would have also decreased percent FM. This notion would also be supported in that exercise intensity did not influence FM loss, so the longer duration/ lower intensity sessions that would need to be performed by the two day per week group to match the ExEE of the six day per week group would seem to be a viable way to produce FM loss. However formerly sedentary, obese individuals would have a difficult time expending roughly 1,400 kcal per session, necessitating a greater number of sessions per week.

An additional finding from the current study is REE or RQ do not significantly contribute to the compensatory response induced with exercise [23]. These results seem to dismiss the role automatic metabolic compensatory responses have on the overall compensatory response; however, these findings may be indicative of methodological inadequacies. Work by Weigle et al demonstrated that after weight loss, REE was 97% of that predicted, while non-resting energy expenditure was only 76%, indicating the energy conserving

metabolic effects occurred primarily through non-resting energy expenditure [223]. Assessing skeletal muscle efficiency during exercise along with total energy expenditure would further elucidate metabolic adaptations occurring in response to a negative energy balance.

The study does present limitations. Although lower frequency exercise did not show improvements in body composition, the effects of prolonged time spent sedentary may have played a significant role in this finding, which may have been different among participants. Having all individuals engage in light physical activity (> 8,000 steps/day and sitting less than 10 hours per day) on days they are not performing vigorous physical activity may help mitigate the negative metabolic effects caused by a sedentary lifestyle [224-226]. Use of doubly labeled water would be the most accurate method to evaluate energy expenditure and energy intake from comparing expected to actual body composition changes. Energy intake of the participants is not known, and we can only assume most of the energy compensated came from increases in energy intake. The use of ab libitum energy intake in a controlled setting would help lessen known under-reporting of food consumption that often occurs in self-reported dietary intake. Also, tracking food intake could help determine if dietary changes occurred throughout the study despite being told to eat their normal diet. As noted previously, the present study only assessed REE and resting RQ to deduce metabolic compensatory response. Additional assessments of the thermic effect of food and skeletal muscle efficiency would be valuable to include in future studies. Additionally, stage of menstrual cycle was not accounted for

among female participants, which could have influenced the calculated ExEE during the 12-week intervention. The unsupervised nature of the exercise sessions may also be considered a limitation as participants could have exercised longer without recording, although we have no reason to believe this to be true. Finally, out of the 44 participants who completed the study, 40 were Caucasian (one Pacific Islander, one Asian, two African American), thus limiting the generalizability to the entire population. The study was not designed to detect sex differences and included majority female participants; thus, sex effects cannot be drawn.

Conclusion

In conclusion, the present study demonstrates individuals do not increase their energy compensation with greater doses of exercise, which is in alignment with Flack et al. [23]. Participants compensated similarly, both when considering participants in the randomized groups (2 vs. 6 days/week) and ExEE groups (under or over 2,000 kcal/week). Only greater energy expenditures predicted fat loss, indicating the greater dose of the six day per week group was needed to overcome this compensatory response. The American College of Sports Medicine recommends 225 minutes per week of moderate exercise to induce weight loss, however, in the current study, the average weekly exercise time for all participants was 249 minutes with no significant changes in FM. The six-day per week group exercised more than 320 minutes per week in order to

experience significant decreases in body fat, therefore exercise recommendations for weight loss may need to be closer to 300 minutes per week instead of 225.

References

1. Cooksey-Stowers, K., M.B. Schwartz, and K.D. Brownell, *Food Swamps Predict Obesity Rates Better Than Food Deserts in the United States.* Int J Environ Res Public Health, 2017. **14**(11).
2. Heymsfield, S.B., et al., *Establishing energy requirements for body weight maintenance: validation of an intake-balance method.* BMC Res Notes, 2017. **10**(1): p. 220.
3. Tremmel, M., et al., *Economic Burden of Obesity: A Systematic Literature Review.* Int J Environ Res Public Health, 2017. **14**(4).
4. Wang, Y.C., et al., *Health and economic burden of the projected obesity trends in the USA and the UK.* Lancet, 2011. **378**(9793): p. 815-25.
5. Wright, S.M. and L.J. Aronne, *Causes of obesity.* Abdom Imaging, 2012. **37**(5): p. 730-2.
6. Thyfault, J.P. and R. Krogh-Madsen, *Metabolic disruptions induced by reduced ambulatory activity in free-living humans.* J Appl Physiol (1985), 2011. **111**(4): p. 1218-24.
7. Bergouignan, A., et al., *Effect of physical inactivity on the oxidation of saturated and monounsaturated dietary Fatty acids: results of a randomized trial.* PLoS Clin Trials, 2006. **1**(5): p. e27.
8. Bergouignan, A., et al., *Physical inactivity differentially alters dietary oleate and palmitate trafficking.* Diabetes, 2009. **58**(2): p. 367-76.
9. Dube, J.J., et al., *Exercise-induced alterations in intramyocellular lipids and insulin resistance: the athlete's paradox revisited.* Am J Physiol Endocrinol Metab, 2008. **294**(5): p. E882-8.
10. Romijn, J.A., et al., *Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration.* Am J Physiol, 1993. **265**(3 Pt 1): p. E380-91.
11. Hamilton, M.T., et al., *Role of local contractile activity and muscle fiber type on LPL regulation during exercise.* Am J Physiol, 1998. **275**(6): p. E1016-22.
12. Hamilton, M.T., D.G. Hamilton, and T.W. Zderic, *Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease.* Diabetes, 2007. **56**(11): p. 2655-67.
13. Hulton, A.T., et al., *Energy expenditure in the Race Across America (RAAM).* Int J Sports Med, 2010. **31**(7): p. 463-7.
14. Vanhees, L., et al., *Importance of characteristics and modalities of physical activity and exercise in defining the benefits to cardiovascular health within the general population: recommendations from the EACPR (Part I).* Eur J Prev Cardiol, 2012. **19**(4): p. 670-86.
15. Westerterp, K.R., *Control of energy expenditure in humans.* Eur J Clin Nutr, 2017. **71**(3): p. 340-344.

16. Santos, I., et al., *Prevalence of personal weight control attempts in adults: a systematic review and meta-analysis.* Obes Rev, 2017. **18**(1): p. 32-50.
17. Thomas, D.M., T.K. Kyle, and F.C. Stanford, *The gap between expectations and reality of exercise-induced weight loss is associated with discouragement.* Prev Med, 2015. **81**: p. 357-60.
18. Church, T.S., et al., *Exercise without weight loss does not reduce C-reactive protein: the INFLAME study.* Med Sci Sports Exerc, 2010. **42**(4): p. 708-16.
19. Kraus, W.E., et al., *Effects of the amount and intensity of exercise on plasma lipoproteins.* N Engl J Med, 2002. **347**(19): p. 1483-92.
20. Rosenkilde, M., et al., *Body fat loss and compensatory mechanisms in response to different doses of aerobic exercise--a randomized controlled trial in overweight sedentary males.* Am J Physiol Regul Integr Comp Physiol, 2012. **303**(6): p. R571-9.
21. Blundell, J.E., et al., *Cross talk between physical activity and appetite control: does physical activity stimulate appetite?* Proc Nutr Soc, 2003. **62**(3): p. 651-61.
22. King, N.A., et al., *Metabolic and behavioral compensatory responses to exercise interventions: barriers to weight loss.* Obesity (Silver Spring), 2007. **15**(6): p. 1373-83.
23. Flack, K.D., et al., *Energy compensation in response to aerobic exercise training in overweight adults.* Am J Physiol Regul Integr Comp Physiol, 2018. **315**(4): p. R619-R626.
24. Archer, E., *The childhood obesity epidemic as a result of nongenetic evolution: the maternal resources hypothesis.* Mayo Clin Proc, 2015. **90**(1): p. 77-92.
25. Hall, K.D., *Did the Food Environment Cause the Obesity Epidemic?* Obesity (Silver Spring), 2018. **26**(1): p. 11-13.
26. Hall, K.D., *Metabolism of mice and men: mathematical modeling of body weight dynamics.* Curr Opin Clin Nutr Metab Care, 2012. **15**(5): p. 418-23.
27. Leon, C.B. *The life of American workers in 1915*. 2016.
28. Mayer, J., *Correlation between metabolism and feeding behavior and multiple etiology of obesity.* Bull N Y Acad Med, 1957. **33**(11): p. 744-61.
29. Rosenbaum, M. and R.L. Leibel, *Adaptive thermogenesis in humans.* Int J Obes (Lond), 2010. **34 Suppl 1**: p. S47-55.
30. Thomas, D.M., et al., *Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis.* Obes Rev, 2012. **13**(10): p. 835-47.
31. Stubbs, R.J., et al., *Rate and extent of compensatory changes in energy intake and expenditure in response to altered exercise and diet composition in humans.* Am J Physiol Regul Integr Comp Physiol, 2004. **286**(2): p. R350-8.
32. McMurray, R.G., et al., *Examining variations of resting metabolic rate of adults: a public health perspective.* Med Sci Sports Exerc, 2014. **46**(7): p. 1352-8.
33. Johnstone, A.M., et al., *Factors influencing variation in basal metabolic rate include fat-free mass, fat mass, age, and circulating thyroxine but not sex, circulating leptin, or triiodothyronine.* Am J Clin Nutr, 2005. **82**(5): p. 941-8.

34. Rosenbaum, M., et al., *Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function.* Am J Clin Nutr, 2000. **71**(6): p. 1421-32.
35. Blundell, J.E., et al., *Body composition and appetite: fat-free mass (but not fat mass or BMI) is positively associated with self-determined meal size and daily energy intake in humans.* Br J Nutr, 2012. **107**(3): p. 445-9.
36. Blundell, J.E., et al., *Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation.* Dis Model Mech, 2012. **5**(5): p. 608-13.
37. Rosenbaum, M., et al., *Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects.* Am J Physiol Regul Integr Comp Physiol, 2003. **285**(1): p. R183-92.
38. Goldsmith, R., et al., *Effects of experimental weight perturbation on skeletal muscle work efficiency, fuel utilization, and biochemistry in human subjects.* Am J Physiol Regul Integr Comp Physiol, 2010. **298**(1): p. R79-88.
39. Liebel R, C.S., Rosenbaum M. , *Obesity*, in *The Metabolic and Molecular Bases of Inherited Disease*. 2001, McGraw-Hill: New York. p. 3965-4028.
40. Camps, S.G., et al., *Weight loss-induced changes in adipose tissue proteins associated with fatty acid and glucose metabolism correlate with adaptations in energy expenditure.* Nutr Metab (Lond), 2015. **12**: p. 37.
41. Patel, H. and A. Bhardwaj, *Physiology, Respiratory Quotient*, in *StatPearls*. 2019, StatPearls Publishing
StatPearls Publishing LLC.: Treasure Island (FL).
42. Marlatt, K.L. and E. Ravussin, *Brown Adipose Tissue: an Update on Recent Findings.* Curr Obes Rep, 2017. **6**(4): p. 389-396.
43. Alkemade, A., *Central and peripheral effects of thyroid hormone signalling in the control of energy metabolism.* J Neuroendocrinol, 2010. **22**(1): p. 56-63.
44. Cypess, A.M., et al., *Identification and importance of brown adipose tissue in adult humans.* N Engl J Med, 2009. **360**(15): p. 1509-17.
45. Sumithran, P. and J. Proietto, *The defence of body weight: a physiological basis for weight regain after weight loss.* Clin Sci (Lond), 2013. **124**(4): p. 231-41.
46. Rosenbaum, M., et al., *Energy intake in weight-reduced humans.* Brain Res, 2010. **1350**: p. 95-102.
47. Smith, K.S., et al., *Ventral pallidum roles in reward and motivation.* Behav Brain Res, 2009. **196**(2): p. 155-67.
48. Augustine, J.R., *Circuitry and functional aspects of the insular lobe in primates including humans.* Brain Res Brain Res Rev, 1996. **22**(3): p. 229-44.
49. Rosenbaum, M., et al., *Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli.* J Clin Invest, 2008. **118**(7): p. 2583-91.
50. Schubert, M.M., et al., *Acute exercise and hormones related to appetite regulation: a meta-analysis.* Sports Med, 2014. **44**(3): p. 387-403.
51. Karra, E. and R.L. Batterham, *The role of gut hormones in the regulation of body weight and energy homeostasis.* Mol Cell Endocrinol, 2010. **316**(2): p. 120-8.

52. Cummings, D.E., et al., *A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans.* Diabetes, 2001. **50**(8): p. 1714-9.
53. Lu, H.-C. and K. Mackie, *An Introduction to the Endogenous Cannabinoid System.* Biological Psychiatry, 2016. **79**(7): p. 516-525.
54. Mazier, W., et al., *The Endocannabinoid System: Pivotal Orchestrator of Obesity and Metabolic Disease.* Trends Endocrinol Metab, 2015. **26**(10): p. 524-537.
55. Hillard, C.J., *Circulating Endocannabinoids: From Whence Do They Come and Where are They Going?* Neuropsychopharmacology, 2018. **43**(1): p. 155-172.
56. Di Marzo, V., L. De Petrocellis, and T. Bisogno, *Endocannabinoids Part I: molecular basis of endocannabinoid formation, action and inactivation and development of selective inhibitors.* Expert Opin Ther Targets, 2001. **5**(2): p. 241-65.
57. De Luca, M.A., et al., *Cannabinoid facilitation of behavioral and biochemical hedonic taste responses.* Neuropharmacology, 2012. **63**(1): p. 161-8.
58. Mahler, S.V., K.S. Smith, and K.C. Berridge, *Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward.* Neuropsychopharmacology, 2007. **32**(11): p. 2267-78.
59. Melis, T., et al., *The cannabinoid antagonist SR 141716A (Rimonabant) reduces the increase of extra-cellular dopamine release in the rat nucleus accumbens induced by a novel high palatable food.* Neurosci Lett, 2007. **419**(3): p. 231-5.
60. Vettor, R. and C. Pagano, *The role of the endocannabinoid system in lipogenesis and fatty acid metabolism.* Best Pract Res Clin Endocrinol Metab, 2009. **23**(1): p. 51-63.
61. Osei-Hyiaman, D., et al., *Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity.* J Clin Invest, 2005. **115**(5): p. 1298-305.
62. Juan-Pico, P., et al., *Cannabinoid receptors regulate Ca(2+) signals and insulin secretion in pancreatic beta-cell.* Cell Calcium, 2006. **39**(2): p. 155-62.
63. Verty, A.N., A.M. Allen, and B.J. Oldfield, *The effects of rimonabant on brown adipose tissue in rat: implications for energy expenditure.* Obesity (Silver Spring), 2009. **17**(2): p. 254-61.
64. Liu, Y.L., et al., *Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice.* Int J Obes (Lond), 2005. **29**(2): p. 183-7.
65. Di Marzo, V., et al., *Role of insulin as a negative regulator of plasma endocannabinoid levels in obese and nonobese subjects.* Eur J Endocrinol, 2009. **161**(5): p. 715-22.
66. Bluher, M., et al., *Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity.* Diabetes, 2006. **55**(11): p. 3053-60.
67. Cote, M., et al., *Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men.* Int J Obes (Lond), 2007. **31**(4): p. 692-9.
68. Silva, A.M., et al., *What is the effect of diet and/or exercise interventions on behavioural compensation in non-exercise physical activity and related energy*

expenditure of free-living adults? A systematic review. Br J Nutr, 2018. **119**(12): p. 1327-1345.
69. Donnelly, J.E., et al., *American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults.* Med Sci Sports Exerc, 2009. **41**(2): p. 459-71.
70. Edholm, O.G., *Energy balance in man studies carried out by the Division of Human Physiology, National Institute for Medical Research.* J Hum Nutr, 1977. **31**(6): p. 413-31.
71. Edholm, O.G., et al., *The energy expenditure and food intake of individual men.* Br J Nutr, 1955. **9**(3): p. 286-300.
72. Mayer, J., P. Roy, and K.P. Mitra, *Relation between caloric intake, body weight, and physical work: studies in an industrial male population in West Bengal.* Am J Clin Nutr, 1956. **4**(2): p. 169-75.
73. Flack, K.H., HM; Moreland, J; Long, DE, *Exercise for Weight Loss: Further Evaluating Energy Compensation with Exercise.* Med. Sci. Sport Exerc, 2020. **In reivew**.
74. Dorling, J., et al., *Acute and Chronic Effects of Exercise on Appetite, Energy Intake, and Appetite-Related Hormones: The Modulating Effect of Adiposity, Sex, and Habitual Physical Activity.* Nutrients, 2018. **10**(9).
75. Howe, S.M., et al., *No Effect of Exercise Intensity on Appetite in Highly-Trained Endurance Women.* Nutrients, 2016. **8**(4): p. 223.
76. Martins, C., M.D. Robertson, and L.M. Morgan, *Effects of exercise and restrained eating behaviour on appetite control.* Proc Nutr Soc, 2008. **67**(1): p. 28-41.
77. King, N.A., et al., *Dual-process action of exercise on appetite control: increase in orexigenic drive but improvement in meal-induced satiety.* Am J Clin Nutr, 2009. **90**(4): p. 921-7.
78. Masurier, J., et al., *Effect of Exercise Duration on Subsequent Appetite and Energy Intake in Obese Adolescent Girls.* Int J Sport Nutr Exerc Metab, 2018. **28**(6): p. 593-601.
79. Beaulieu, K., et al., *Does Habitual Physical Activity Increase the Sensitivity of the Appetite Control System? A Systematic Review.* Sports Med, 2016. **46**(12): p. 1897-1919.
80. Maffei, M., et al., *Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects.* Nat Med, 1995. **1**(11): p. 1155-61.
81. Guelfi, K.J., C.E. Donges, and R. Duffield, *Beneficial effects of 12 weeks of aerobic compared with resistance exercise training on perceived appetite in previously sedentary overweight and obese men.* Metabolism, 2013. **62**(2): p. 235-43.
82. Zhao, S., et al., *Partial Leptin Reduction as an Insulin Sensitization and Weight Loss Strategy.* Cell Metab, 2019. **30**(4): p. 706-719.e6.
83. Dimmock, J.A., et al., *Does Motivation for Exercise Influence Post-Exercise Snacking Behavior?* Nutrients, 2015. **7**(6): p. 4804-16.

84. Werle, C.O., B. Wansink, and C.R. Payne, *Just thinking about exercise makes me serve more food. Physical activity and calorie compensation.* Appetite, 2011. **56**(2): p. 332-5.
85. Fenzl, N., K. Bartsch, and J. Koenigstorfer, *Labeling exercise fat-burning increases post-exercise food consumption in self-imposed exercisers.* Appetite, 2014. **81**: p. 1-7.
86. Beer, N.J., et al., *Providing Choice in Exercise Influences Food Intake at the Subsequent Meal.* Med Sci Sports Exerc, 2017. **49**(10): p. 2110-2118.
87. Dolezal, B.A., et al., *Muscle damage and resting metabolic rate after acute resistance exercise with an eccentric overload.* Med Sci Sports Exerc, 2000. **32**(7): p. 1202-7.
88. Binzen, C.A., P.D. Swan, and M.M. Manore, *Postexercise oxygen consumption and substrate use after resistance exercise in women.* Med Sci Sports Exerc, 2001. **33**(6): p. 932-8.
89. Melby, C., et al., *Effect of acute resistance exercise on postexercise energy expenditure and resting metabolic rate.* J Appl Physiol (1985), 1993. **75**(4): p. 1847-53.
90. Dulloo, A.G., et al., *Passive and active roles of fat-free mass in the control of energy intake and body composition regulation.* Eur J Clin Nutr, 2017. **71**(3): p. 353-357.
91. Speakman, J.R. and C. Selman, *Physical activity and resting metabolic rate.* Proc Nutr Soc, 2003. **62**(3): p. 621-34.
92. Westerterp, K.R., et al., *Long-term effect of physical activity on energy balance and body composition.* Br J Nutr, 1992. **68**(1): p. 21-30.
93. Johannsen, D.L., et al., *Metabolic slowing with massive weight loss despite preservation of fat-free mass.* J Clin Endocrinol Metab, 2012. **97**(7): p. 2489-96.
94. Bryner, R.W., et al., *Effects of resistance vs. aerobic training combined with an 800 calorie liquid diet on lean body mass and resting metabolic rate.* J Am Coll Nutr, 1999. **18**(2): p. 115-21.
95. Heyman, E., et al., *Intense exercise increases circulating endocannabinoid and BDNF levels in humans--possible implications for reward and depression.* Psychoneuroendocrinology, 2012. **37**(6): p. 844-51.
96. Raichlen, D.A., et al., *Exercise-induced endocannabinoid signaling is modulated by intensity.* Eur J Appl Physiol, 2013. **113**(4): p. 869-75.
97. Koltyn, K.F., et al., *Mechanisms of exercise-induced hypoalgesia.* J Pain, 2014. **15**(12): p. 1294-1304.
98. Cedernaes, J., et al., *Sleep restriction alters plasma endocannabinoids concentrations before but not after exercise in humans.* Psychoneuroendocrinology, 2016. **74**: p. 258-268.
99. Heyman, E., et al., *The role of the endocannabinoid system in skeletal muscle and metabolic adaptations to exercise: potential implications for the treatment of obesity.* Obes Rev, 2012. **13**(12): p. 1110-24.
100. Weston, M., et al., *Effects of low-volume high-intensity interval training (HIT) on fitness in adults: a meta-analysis of controlled and non-controlled trials.* Sports Med, 2014. **44**(7): p. 1005-17.

101. Viana, R.B., et al., *Is interval training the magic bullet for fat loss? A systematic review and meta-analysis comparing moderate-intensity continuous training with high-intensity interval training (HIIT).* Br J Sports Med, 2019. **53**(10): p. 655-664.
102. Gist, N.H., et al., *Sprint interval training effects on aerobic capacity: a systematic review and meta-analysis.* Sports Med, 2014. **44**(2): p. 269-79.
103. Gillen, J.B., et al., *Interval training in the fed or fasted state improves body composition and muscle oxidative capacity in overweight women.* Obesity (Silver Spring), 2013. **21**(11): p. 2249-55.
104. Earnest, C.P., et al., *Interval training in men at risk for insulin resistance.* Int J Sports Med, 2013. **34**(4): p. 355-63.
105. McNeil, J., et al., *Dose-response effects of aerobic exercise on energy compensation in postmenopausal women: combined results from two randomized controlled trials.* Int J Obes (Lond), 2017. **41**(8): p. 1196-1202.
106. Schubert, M.M., et al., *Impact of 4 weeks of interval training on resting metabolic rate, fitness, and health-related outcomes.* Appl Physiol Nutr Metab, 2017. **42**(10): p. 1073-1081.
107. Boutcher, S.H., *High-intensity intermittent exercise and fat loss.* J Obes, 2011. **2011**: p. 868305.
108. Rivest, S. and D. Richard, *Involvement of corticotropin-releasing factor in the anorexia induced by exercise.* Brain Res Bull, 1990. **25**(1): p. 169-72.
109. Alkahtani, S.A., et al., *Interval training intensity affects energy intake compensation in obese men.* Int J Sport Nutr Exerc Metab, 2014. **24**(6): p. 595-604.
110. Kelly, B., et al., *The impact of high-intensity intermittent exercise on resting metabolic rate in healthy males.* Eur J Appl Physiol, 2013. **113**(12): p. 3039-47.
111. Kiens, B. and E.A. Richter, *Utilization of skeletal muscle triacylglycerol during postexercise recovery in humans.* Am J Physiol, 1998. **275**(2): p. E332-7.
112. Phillips, S.M. and R.A. Winett, *Uncomplicated resistance training and health-related outcomes: evidence for a public health mandate.* Curr Sports Med Rep, 2010. **9**(4): p. 208-13.
113. Tresierras, M.A. and G.J. Balady, *Resistance training in the treatment of diabetes and obesity: mechanisms and outcomes.* J Cardiopulm Rehabil Prev, 2009. **29**(2): p. 67-75.
114. Dolezal, B.A. and J.A. Potteiger, *Concurrent resistance and endurance training influence basal metabolic rate in nondieting individuals.* J Appl Physiol (1985), 1998. **85**(2): p. 695-700.
115. Cadieux, S., et al., *Resistance and aerobic exercises do not affect post-exercise energy compensation in normal weight men and women.* Physiol Behav, 2014. **130**: p. 113-9.
116. Villareal, D.T., et al., *Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults.* N Engl J Med, 2017. **376**(20): p. 1943-1955.
117. Antonio, J., et al., *A high protein diet (3.4 g/kg/d) combined with a heavy resistance training program improves body composition in healthy trained men and women--a follow-up investigation.* J Int Soc Sports Nutr, 2015. **12**: p. 39.

118. Valenzuela, P.L., et al., *Does Beef Protein Supplementation Improve Body Composition and Exercise Performance? A Systematic Review and Meta-Analysis of Randomized Controlled Trials.* Nutrients, 2019. **11**(6).
119. Ruegsegger, G.N. and F.W. Booth, *Health Benefits of Exercise.* Cold Spring Harb Perspect Med, 2018. **8**(7).
120. Schubert, M.M., et al., *Acute exercise and subsequent energy intake. A meta-analysis.* Appetite, 2013. **63**: p. 92-104.
121. Blundell, J.E., et al., *Appetite control and energy balance: impact of exercise.* Obes Rev, 2015. **16 Suppl 1**: p. 67-76.
122. Blundell, J.E. and N.A. King, *Effects of exercise on appetite control: loose coupling between energy expenditure and energy intake.* Int J Obes Relat Metab Disord, 1998. **22 Suppl 2**: p. S22-9.
123. Stensel, D., *Exercise, appetite and appetite-regulating hormones: implications for food intake and weight control.* Ann Nutr Metab, 2010. **57 Suppl 2**: p. 36-42.
124. Hopkins, M., et al., *The relationship between substrate metabolism, exercise and appetite control: does glycogen availability influence the motivation to eat, energy intake or food choice?* Sports Med, 2011. **41**(6): p. 507-21.
125. Fujikawa, T., et al., *The hypothalamic regulation of metabolic adaptations to exercise.* J Neuroendocrinol, 2017. **29**(10).
126. King, N.A., et al., *Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss.* Int J Obes (Lond), 2008. **32**(1): p. 177-84.
127. Lim, C.L. and L.K. Lee, *The effects of 20 weeks basic military training program on body composition, VO2max and aerobic fitness of obese recruits.* J Sports Med Phys Fitness, 1994. **34**(3): p. 271-8.
128. Stubbs, R.J. and M. Elia, *Macronutrients and appetite control with implications for the nutritional management of the malnourished.* Clinical Nutrition, 2001. **20**: p. 129-139.
129. Martin, C.K., et al., *Effect of different doses of supervised exercise on food intake, metabolism, and non-exercise physical activity: The E-MECHANIC randomized controlled trial.* Am J Clin Nutr, 2019. **110**(3): p. 583-592.
130. Almiron-Roig, E., et al., *Factors that determine energy compensation: a systematic review of preload studies.* Nutr Rev, 2013. **71**(7): p. 458-73.
131. Leibel, R.L., M. Rosenbaum, and J. Hirsch, *Changes in energy expenditure resulting from altered body weight.* N Engl J Med, 1995. **332**(10): p. 621-8.
132. Antoni, R., et al., *Investigation into the acute effects of total and partial energy restriction on postprandial metabolism among overweight/obese participants.* Br J Nutr, 2016. **115**(6): p. 951-9.
133. Patterson, R.E. and D.D. Sears, *Metabolic Effects of Intermittent Fasting.* Annu Rev Nutr, 2017. **37**: p. 371-393.
134. McCrickerd, K., L. Chambers, and M.R. Yeomans, *Does modifying the thick texture and creamy flavour of a drink change portion size selection and intake?* Appetite, 2014. **73**: p. 114-20.

135. Halford, J.C. and J.A. Harrold, *Satiety-enhancing products for appetite control: science and regulation of functional foods for weight management.* Proc Nutr Soc, 2012. **71**(2): p. 350-62.
136. Weigle, D.S., et al., *A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations.* Am J Clin Nutr, 2005. **82**(1): p. 41-8.
137. Soenen, S., et al., *Normal protein intake is required for body weight loss and weight maintenance, and elevated protein intake for additional preservation of resting energy expenditure and fat free mass.* J Nutr, 2013. **143**(5): p. 591-6.
138. Westerterp-Plantenga, M.S., et al., *Dietary protein, weight loss, and weight maintenance.* Annu Rev Nutr, 2009. **29**: p. 21-41.
139. Soenen, S. and M.S. Westerterp-Plantenga, *Proteins and satiety: implications for weight management.* Curr Opin Clin Nutr Metab Care, 2008. **11**(6): p. 747-51.
140. Ryan, A.T., et al., *Intraduodenal protein modulates antropyloroduodenal motility, hormone release, glycemia, appetite, and energy intake in lean men.* Am J Clin Nutr, 2012. **96**(3): p. 474-82.
141. Hutchison, A.T., et al., *Acute load-dependent effects of oral whey protein on gastric emptying, gut hormone release, glycemia, appetite, and energy intake in healthy men.* Am J Clin Nutr, 2015. **102**(6): p. 1574-84.
142. Blom, W.A., et al., *Effect of a high-protein breakfast on the postprandial ghrelin response.* Am J Clin Nutr, 2006. **83**(2): p. 211-20.
143. Clegg, M. and A. Shafat, *Energy and macronutrient composition of breakfast affect gastric emptying of lunch and subsequent food intake, satiety and satiation.* Appetite, 2010. **54**(3): p. 517-23.
144. Giezenaar, C., et al., *Acute Effects of Substitution, and Addition, of Carbohydrates and Fat to Protein on Gastric Emptying, Blood Glucose, Gut Hormones, Appetite, and Energy Intake.* Nutrients, 2018. **10**(10).
145. Morton, R., C. McGlory, and S. Phillips, *Nutritional interventions to augment resistance training-induced skeletal muscle hypertrophy.* Frontiers in Physiology, 2015. **6**(245).
146. Hector, A.J., et al., *Whey protein supplementation preserves postprandial myofibrillar protein synthesis during short-term energy restriction in overweight and obese adults.* J Nutr, 2015. **145**(2): p. 246-52.
147. Kraemer, W.J., et al., *Influence of exercise training on physiological and performance changes with weight loss in men.* Med Sci Sports Exerc, 1999. **31**(9): p. 1320-9.
148. Gasior, M., M.A. Rogawski, and A.L. Hartman, *Neuroprotective and disease-modifying effects of the ketogenic diet.* Behav Pharmacol, 2006. **17**(5-6): p. 431-9.
149. Erlanson-Albertsson, C. and J. Mei, *The effect of low carbohydrate on energy metabolism.* Int J Obes (Lond), 2005. **29 Suppl 2**: p. S26-30.
150. Cahill, G.F., Jr. and R.L. Veech, *Ketoacids? Good medicine?* Trans Am Clin Climatol Assoc, 2003. **114**: p. 149-61; discussion 162-3.

151. Kashiwaya, Y., et al., *Control of glucose utilization in working perfused rat heart.* J Biol Chem, 1994. **269**(41): p. 25502-14.
152. van Berkel, A.A., I.J. DM, and J.M. Verkuyl, *Cognitive benefits of the ketogenic diet in patients with epilepsy: A systematic overview.* Epilepsy Behav, 2018. **87**: p. 69-77.
153. Vining, E.P., et al., *A multicenter study of the efficacy of the ketogenic diet.* Arch Neurol, 1998. **55**(11): p. 1433-7.
154. Mohorko, N., et al., *Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults.* Nutr Res, 2019. **62**: p. 64-77.
155. Vanitallie, T.B., et al., *Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study.* Neurology, 2005. **64**(4): p. 728-30.
156. Reger, M.A., et al., *Effects of beta-hydroxybutyrate on cognition in memory-impaired adults.* Neurobiol Aging, 2004. **25**(3): p. 311-4.
157. Johnstone, A.M., et al., *Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum.* Am J Clin Nutr, 2008. **87**(1): p. 44-55.
158. Gibson, A.A., et al., *Do ketogenic diets really suppress appetite? A systematic review and meta-analysis.* Obes Rev, 2015. **16**(1): p. 64-76.
159. Nymo, S., et al., *Timeline of changes in appetite during weight loss with a ketogenic diet.* Int J Obes (Lond), 2017. **41**(8): p. 1224-1231.
160. Sumithran, P., et al., *Ketosis and appetite-mediating nutrients and hormones after weight loss.* Eur J Clin Nutr, 2013. **67**(7): p. 759-64.
161. Mikkelsen, K.H., et al., *Systemic, cerebral and skeletal muscle ketone body and energy metabolism during acute hyper-D-beta-hydroxybutyratemia in post-absorptive healthy males.* J Clin Endocrinol Metab, 2015. **100**(2): p. 636-43.
162. McCrickerd, K., N.B. Salleh, and C.G. Forde, *Removing energy from a beverage influences later food intake more than the same energy addition.* Appetite, 2016. **105**: p. 549-56.
163. Dennis, E.A., et al., *Water consumption increases weight loss during a hypocaloric diet intervention in middle-aged and older adults.* Obesity (Silver Spring), 2010. **18**(2): p. 300-7.
164. Dennis, E.A., K.D. Flack, and B.M. Davy, *Beverage consumption and adult weight management: A review.* Eat Behav, 2009. **10**(4): p. 237-46.
165. Norgan, N.G. and J.V. Durnin, *The effect of 6 weeks of overfeeding on the body weight, body composition, and energy metabolism of young men.* Am J Clin Nutr, 1980. **33**(5): p. 978-88.
166. Tappy, L., *Metabolic consequences of overfeeding in humans.* Curr Opin Clin Nutr Metab Care, 2004. **7**(6): p. 623-8.
167. Reddon, H., J.L. Gueant, and D. Meyre, *The importance of gene-environment interactions in human obesity.* Clin Sci (Lond), 2016. **130**(18): p. 1571-97.
168. Blakemore, A.I. and P. Froguel, *Investigation of Mendelian forms of obesity holds out the prospect of personalized medicine.* Ann N Y Acad Sci, 2010. **1214**: p. 180-9.
169. Hinney, A., C.I. Vogel, and J. Hebebrand, *From monogenic to polygenic obesity: recent advances.* Eur Child Adolesc Psychiatry, 2010. **19**(3): p. 297-310.

170. Choquet, H. and D. Meyre, *Molecular basis of obesity: current status and future prospects.* Curr Genomics, 2011. **12**(3): p. 154-68.
171. Chung, W.K., *An overview of mongenic and syndromic obesities in humans.* Pediatric blood & cancer, 2012. **58**(1): p. 122-128.
172. Hinney, A. and J. Hebebrand, *Polygenic obesity in humans.* Obes Facts, 2008. **1**(1): p. 35-42.
173. Hollstein, T., et al., *Metabolic response to fasting predicts weight gain during low-protein overfeeding in lean men: further evidence for spendthrift and thrifty metabolic phenotypes.* Am J Clin Nutr, 2019.
174. Reinhardt, M., et al., *A Human Thrifty Phenotype Associated With Less Weight Loss During Caloric Restriction.* Diabetes, 2015. **64**(8): p. 2859-67.
175. Schlogl, M., et al., *Energy Expenditure Responses to Fasting and Overfeeding Identify Phenotypes Associated With Weight Change.* Diabetes, 2015. **64**(11): p. 3680-9.
176. Piaggi, P., et al., *Energy expenditure in the etiology of human obesity: spendthrift and thrifty metabolic phenotypes and energy-sensing mechanisms.* J Endocrinol Invest, 2018. **41**(1): p. 83-89.
177. Coskun, T., et al., *Fibroblast growth factor 21 corrects obesity in mice.* Endocrinology, 2008. **149**(12): p. 6018-27.
178. Vinales, K.L., et al., *FGF21 Is a Hormonal Mediator of the Human "Thrifty" Metabolic Phenotype.* Diabetes, 2019. **68**(2): p. 318-323.
179. Tao, Y.X., *The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology.* Endocr Rev, 2010. **31**(4): p. 506-43.
180. Smith, A.I. and J.W. Funder, *Proopiomelanocortin processing in the pituitary, central nervous system, and peripheral tissues.* Endocr Rev, 1988. **9**(1): p. 159-79.
181. Bertagna, X., *Proopiomelanocortin-derived peptides.* Endocrinol Metab Clin North Am, 1994. **23**(3): p. 467-85.
182. O'Rahilly, S. and I.S. Farooqi, *Human obesity as a heritable disorder of the central control of energy balance.* Int J Obes (Lond), 2008. **32 Suppl 7**: p. S55-61.
183. Walley, A.J., J.E. Asher, and P. Froguel, *The genetic contribution to non-syndromic human obesity.* Nat Rev Genet, 2009. **10**(7): p. 431-42.
184. Stutzmann, F., et al., *Common genetic variation near MC4R is associated with eating behaviour patterns in European populations.* Int J Obes (Lond), 2009. **33**(3): p. 373-8.
185. Valladares, M., et al., *Melanocortin-4 receptor gene variants in Chilean families: association with childhood obesity and eating behavior.* Nutr Neurosci, 2010. **13**(2): p. 71-8.
186. Qi, L., et al., *The common obesity variant near MC4R gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women.* Hum Mol Genet, 2008. **17**(22): p. 3502-8.
187. Farooqi, I.S., et al., *Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene.* N Engl J Med, 2003. **348**(12): p. 1085-95.
188. Reinehr, T., et al., *Lifestyle intervention in obese children with variations in the melanocortin 4 receptor gene.* Obesity (Silver Spring), 2009. **17**(2): p. 382-9.

189. Krakoff, J., et al., *Lower metabolic rate in individuals heterozygous for either a frameshift or a functional missense MC4R variant.* Diabetes, 2008. **57**(12): p. 3267-72.
190. Cole, S.A., et al., *Evidence that multiple genetic variants of MC4R play a functional role in the regulation of energy expenditure and appetite in Hispanic children.* Am J Clin Nutr, 2010. **91**(1): p. 191-9.
191. Xiang, Z., et al., *Pharmacological characterization of 40 human melanocortin-4 receptor polymorphisms with the endogenous proopiomelanocortin-derived agonists and the agouti-related protein (AGRP) antagonist.* Biochemistry, 2006. **45**(23): p. 7277-88.
192. Rosmond, R., et al., *A missense mutation in the human melanocortin-4 receptor gene in relation to abdominal obesity and salivary cortisol.* Diabetologia, 2001. **44**(10): p. 1335-8.
193. Stutzmann, F., et al., *Non-synonymous polymorphisms in melanocortin-4 receptor protect against obesity: the two facets of a Janus obesity gene.* Hum Mol Genet, 2007. **16**(15): p. 1837-44.
194. Peters, T., K. Ausmeier, and U. Rüther, *Cloning of Fatso (Fto), a novel gene deleted by the Fused toes (Ft) mouse mutation.* Mammalian Genome, 1999. **10**(10): p. 983-986.
195. Fawcett, K.A. and I. Barroso, *The genetics of obesity: FTO leads the way.* Trends Genet, 2010. **26**(6): p. 266-74.
196. Church, C., et al., *A mouse model for the metabolic effects of the human fat mass and obesity associated FTO gene.* PLoS Genet, 2009. **5**(8): p. e1000599.
197. Fischer, J., et al., *Inactivation of the Fto gene protects from obesity.* Nature, 2009. **458**(7240): p. 894-8.
198. Church, C., et al., *Overexpression of Fto leads to increased food intake and results in obesity.* Nat Genet, 2010. **42**(12): p. 1086-92.
199. Boissel, S., et al., *Loss-of-function mutation in the dioxygenase-encoding FTO gene causes severe growth retardation and multiple malformations.* Am J Hum Genet, 2009. **85**(1): p. 106-11.
200. Gerken, T., et al., *The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase.* Science, 2007. **318**(5855): p. 1469-72.
201. Tung, Y.C., et al., *Hypothalamic-specific manipulation of Fto, the ortholog of the human obesity gene FTO, affects food intake in rats.* PLoS One, 2010. **5**(1): p. e8771.
202. Frayling, T.M., et al., *A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity.* Science, 2007. **316**(5826): p. 889-94.
203. Scott, L.J., et al., *A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants.* Science, 2007. **316**(5829): p. 1341-5.
204. Han, Z., et al., *Crystal structure of the FTO protein reveals basis for its substrate specificity.* Nature, 2010. **464**(7292): p. 1205-9.
205. Wu, Q., et al., *The obesity-associated Fto gene is a transcriptional coactivator.* Biochem Biophys Res Commun, 2010. **401**(3): p. 390-5.
206. Cecil, J.E., et al., *An obesity-associated FTO gene variant and increased energy intake in children.* N Engl J Med, 2008. **359**(24): p. 2558-66.

207. Wardle, J., et al., *Obesity associated genetic variation in FTO is associated with diminished satiety.* J Clin Endocrinol Metab, 2008. **93**(9): p. 3640-3.
208. Archer, E., C.J. Lavie, and J.O. Hill, *The Contributions of 'Diet', 'Genes', and Physical Activity to the Etiology of Obesity: Contrary Evidence and Consilience.* Prog Cardiovasc Dis, 2018. **61**(2): p. 89-102.
209. Ayabe, M., et al., *Epoch length and the physical activity bout analysis: an accelerometry research issue.* BMC Res Notes, 2013. **6**: p. 20.
210. Weir, J.B.D., *New Methods for Calculating Metabolic Rate with Special Reference to Protein Metabolism.* Journal of Physiology-London, 1949. **109**(1-2): p. 1-9.
211. Rothney, M.P., et al., *Precision of GE Lunar iDXA for the measurement of total and regional body composition in nonobese adults.* J Clin Densitom, 2012. **15**(4): p. 399-404.
212. Nelson, K.M., et al., *Prediction of resting energy expenditure from fat-free mass and fat mass.* Am J Clin Nutr, 1992. **56**(5): p. 848-56.
213. Cunningham, J.J., *A reanalysis of the factors influencing basal metabolic rate in normal adults.* Am J Clin Nutr, 1980. **33**(11): p. 2372-4.
214. Byrne, N.M., et al., *Does metabolic compensation explain the majority of less-than-expected weight loss in obese adults during a short-term severe diet and exercise intervention?* Int J Obes (Lond), 2012. **36**(11): p. 1472-8.
215. Müller, M.J. and A. Bosy-Westphal, *Adaptive thermogenesis with weight loss in humans.* Obesity, 2013. **21**(2): p. 218-228.
216. Elia, M., R. Stratton, and J. Stubbs, *Techniques for the study of energy balance in man.* Proc Nutr Soc, 2003. **62**(2): p. 529-37.
217. Forbes, G.B., *Do obese individuals gain weight more easily than nonobese individuals?* Am J Clin Nutr, 1990. **52**(2): p. 224-7.
218. Bahr, R., et al., *Effect of duration of exercise on excess postexercise O2 consumption.* J Appl Physiol (1985), 1987. **62**(2): p. 485-90.
219. Biswas, A., et al., *Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis.* Ann Intern Med, 2015. **162**(2): p. 123-32.
220. Ekelund, U., et al., *Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women.* Lancet, 2016. **388**(10051): p. 1302-10.
221. Patel, A.V., et al., *Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults.* Am J Epidemiol, 2010. **172**(4): p. 419-29.
222. van der Ploeg, H.P., et al., *Sitting time and all-cause mortality risk in 222 497 Australian adults.* Arch Intern Med, 2012. **172**(6): p. 494-500.
223. Weigle, D.S., et al., *Weight loss leads to a marked decrease in nonresting energy expenditure in ambulatory human subjects.* Metabolism, 1988. **37**(10): p. 930-6.
224. Herd, S.L., et al., *Moderate exercise, postprandial lipemia, and skeletal muscle lipoprotein lipase activity.* Metabolism, 2001. **50**(7): p. 756-62.

225. Kim, I.Y., et al., *Prolonged sitting negatively affects the postprandial plasma triglyceride-lowering effect of acute exercise.* Am J Physiol Endocrinol Metab, 2016. **311**(5): p. E891-e898.
226. Malkova, D., et al., *Prior exercise and postprandial substrate extraction across the human leg.* Am J Physiol Endocrinol Metab, 2000. **279**(5): p. E1020-8.

VITA

H. Michael Hays, BA BS

EDUCATION:

University of Kentucky, Lexington KY

Masters of Science (Expected)

Human Nutrition and Food systems

Thesis: "Energy Compensation with Exercise is not Dependent on Dose"

University of Kentucky, Lexington KY

Bachelor of Science (Received December 2018)

Major: Dietetics and Human Nutrition

Austin Peay State University, Clarksville TN

Bachelor of Art (Received May 2009)

Major: Business Administration

PUBLICATIONS

Hays HM, Flack KD. Energy Compensation with Exercise and Dietary-Induced Weight Loss. *Current Obesity Report,* Submitted: in review

Flack KD**, Hays HM**, Moreland J. New Insights into Energy Compensation with Exercise. *Medicine & Science in Sports & Exercise,* Submitted: in review

Flack KD**, Hays HM**, Moreland J. Incentive Sensitization for Exercise Reinforcement to Increase Exercise Behaviors. *Health Psychology,* Submitted: in press

Flack KD**, Hays HM**, Moreland J. The Consequences of Exercise-induced Weight loss on Food Reinforcement. *PLOS ONE,* Submitted: in review

PUBLISHED EXTENSION PUBLICATIONS

Flack, KD, **Hays HM**, Moreland J. *Carbohydrates and Athletic Performance*. (2019). University of Kentucky College of Agriculture, Food and Environment Cooperative Extension Service. FCS3-621

Flack, KD, **Hays HM**, Moreland J. *Dietary Fat and Athletic Performance*. (2019). University of Kentucky College of Agriculture, Food and Environment Cooperative Extension Service. FCS3-622

Flack, KD, **Hays HM**, Moreland J. *Hydration and Athletic Performance*. (2019). University of Kentucky College of Agriculture, Food and Environment Cooperative Extension Service. FCS3-623

Flack, KD, **Hays HM**, Moreland J. *Protein and Athletic Performance*. (2019). University of Kentucky College of Agriculture, Food and Environment Cooperative Extension Service. FCS3-624

Flack KD, **Hays HM**, Moreland J. *Supplements and Athletic Performance*. (2019). University of Kentucky College of Agriculture, Food and Environment Cooperative Extension Service. FCS3-625

Flack KD, **Hays, HM**, Moreland J. *Vitamins, Minerals, and Athletic Performance*. (2019). University of Kentucky College of Agriculture, Food and Environment Cooperative Extension Service. FCS3-626

PUBLISHED ABSTRACTS / PRESENTATIONS

Moreland J, **Hays HM**, Flack KD. *Appetite Regulating Hormones Effects on Energy Compensation*. Accepted for oral presentation at The Obesity Society conference, Las Vegas, NV, 2019.

Hays HM, Moreland J, Flack KD. *Energy Compensation with Exercise: Role on Intensity, Duration, Frequency and Energy Expenditure.* Accepted for poster presentation at The Obesity Society conference, Las Vegas, NV, 2019.