POST-EXERCISE DIETARY STRATEGIES FOR REGULATING APPETITE IN INDIVIDUALS WITH OVERWEIGHT

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Bachelor of Science, University of Lethbridge, 2017

A thesis submitted
in partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE

in

KINESIOLOGY

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Date of Defense: August 20th, 2019

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Abstract

Background: Evidence suggests that exercise, despite being recommended for weight management, is not effective for weight loss partially due to increased compensatory energy intake (EI). The impact of post-exercise diet on appetite and EI requires further investigation.

Objective: To determine if specific post-exercise dietary strategies, including prebiotic supplementation or fasting, differentially modulate appetite and EI after an acute bout of exercise.

Methods: In a randomized crossover study, individuals with overweight received one of three recovery beverages: 1) water control (FAST); 2) sweetened-milk (SM/FED); or 3) sweetened-milk + prebiotic (SM+P) after cycling for 45min (65-70% VO_{2peak}). EI, subjective appetite, gastrointestinal feelings, and appetite-regulatory hormones were assessed.

Results: Post-exercise prebiotic supplementation increased measures of satiety and decreased EI the day following exercise. Fasting temporarily increased post-exercise hunger, but did not modify EI.

Conclusions: Both prebiotic supplementation and fasting modify the post-exercise appetite response. Prebiotics may help individuals with overweight reduce post-exercise EI.

Acknowledgements

I would like to express my greatest appreciation to Dr. Marc Bomhof for his valuable and constructive suggestions, his patience, and his willingness to give his time to aid in this journey. The knowledge and insight that has been shared with me is invaluable. I would also like to thank my committee members, Dr. Jennifer Copeland and Dr. Steve Wiseman, for their continued support throughout each step of the thesis.

Finally, I would like to thank all the participants for their time and effort, as well as the University of Lethbridge and CIHR for funding my degree.

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List of Abbreviations

Symbol	Definition
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
CCK	Cholecystokinin
EI	Energy intake
FAST	Water control trial
FED	Post-exercise nutrient-intake trial
FFA	Free fatty-acid receptor
GLP-1	Glucagon-like peptide-1
GLTEQ	Godin's Leisure Time Exercise Questionnaire
GPR	G-protein receptor
HFS	High fat and sugar
IL-6	Interleukin-6
MACs	Microbial accessible carbohydrates
PAR-Q+	Physical Activity Readiness Questionnaire for Everyone
POST-BFST	Post-breakfast
POST-EX	Post-exercise
PP	Post-prandial
PRE-BFST	Pre-breakfast
PRE-EX	Pre-exercise
PYY	Peptide tyrosine-tyrosine
SCFAs	Short-chain fatty acids
SD	Standard error of the mean
SGLT1	Sodium-linked glucose transporter-1
SM	Sweetened-milk trial
SM+P	Sweetened-milk + prebiotic trial
TEI	Total energy intake
VAS	Visual analogue scale
VO_{2peak}	Peak oxygen uptake

Chapter 1: Introduction and Literature Review

Introduction

According to Statistics Canada, obesity rates in Canada have increased by 17.5% since 2003 (1) and have tripled worldwide since 1975 (2). Obesity increases the risk of preventable diseases such as cardiovascular disease (3), non-alcoholic fatty liver disease (4), kidney disease (5), and hypertension (6). While obesity is a complex and multifaceted disease, positive energy balance is central to obesity pathogenesis (7). In attempt to mitigate obesity pathogenesis and the risk of preventable diseases, lifestyle modifications are often recommended for weight loss. Lifestyle changes typically include dietary modifications or increases in physical activity through adoption of an exercise program (8, 9). Physical activity has been shown to improve metabolic health for both lean and overweight individuals (10), as well as decrease the risk of preventable diseases (11). Although 65% of individuals attempting to lose weight report using physical activity (8), Statistics Canada reports that only 32% of Canadians aged 18-39 meet the minimum physical activity guidelines (12). Low physical activity may lead to less than anticipated amounts of weight loss and positive energy balance, as well as changes in appetite-regulating signals leading to overconsumption. Given that only a third of the Canadian adult population meets the minimum recommended physical activity guidelines, two thirds of the population have an increased risk for developing metabolic complications and preventable diseases due to low physical activity.

When exercise is used in attempt to lose weight an energy deficit is created. An energy deficit of approximately 500 calories per day would create an estimated 0.5 kg of weight loss per week (13). If this energy deficit is maintained for 1 year, it would lead to

an anticipated weight loss of 26 kg; however, when long-term exercise interventions are used to create an energy deficit it has been demonstrated that only a moderate 2-6 kg of weight will be lost in 1-2 years through lifestyle modifications (9). Despite the initial weight loss that is generally observed with acute lifestyle interventions, most individuals do not sustain the weight loss past 12 months with weight returning to baseline values (14-17). Ogden et al. (18) showed that the anticipated weight regain 3-years post weight loss is between 2-7 kg depending on the degree of physical activity maintained and energy intake compensation. This amount of weight regain is equal to or more than the weight loss that has been demonstrated by lifestyle modifications over 1-2 years.

When there is a lack of sustained weight loss, it is hypothesized to be due to energy compensation after exercise. Energy compensation occurs when the energy expended from exercise changes behavior patterns, resulting in an increased energy intake (19, 20). A systematic review by Riou et al. (21) showed for short term exercise interventions, participants compensate 18 ± 93% of calories expended. More importantly, participants compensated approximately 84% of the calories expended during long-term (> 80 weeks) exercise interventions. Through a regression analysis, Riou et al. (21) concluded that longer exercise interventions result in higher degrees of energy compensation, which could mean that individuals pursuing a lifestyle of physical activity are more likely to compensate for the energy expended and less likely to lose weight.

An individual's habitual diet is another significant factor in the etiology of obesity in western countries. The habitually consumed high fat and sugar (HFS) diet is energy dense and highly palatable, making it a primary contributor to a positive energy balance, weight gain, and development of increased adiposity levels (22). The 2015 Dietary

Guidelines Advisory Committee Scientific Report by the USDA and Department of Health and Human Services (23) showed processed foods high in added sugar and saturated fat are commonly overconsumed, while consumption of vegetables, fruits, and whole grains tend to be low. These patterns of intake were seen in conjunction with 66% of respondents falling into the overweight or obese body mass index (BMI) classifications (23).

The composition and diversity of the gut microbiota also plays a role in the etiology of obesity, and is affected by both activity level and habitually consumed diet. The microbial community makes up a 'microbial organ' which contributes to regulation of host physiology. A HFS diet decreases the diversity of the microbial community and the levels of beneficial bacteria largely due to low levels of dietary fiber contained within this diet. Specifically, prebiotic fiber, a substrate utilized by the gut microbiota to create health benefits to the host (24), aids in promotion of a diverse gut microbiota (25). Beneficial bacteria in the large intestine ferment prebiotic fiber leading to the generation of short-chain fatty acids (SCFAs) as metabolic by-products. SCFAs have been demonstrated to decrease inflammation and aid in the release of appetite-regulating hormones that decrease hunger. By decreasing hunger, prebiotic fiber reduces energy intake, contributing to weight loss. Exercise also improves the diversity of bacteria (26) and may help attenuate the changes seen from consumption of a HFS diet (27). Individuals with higher BMIs tend to have a less diverse microbiota and less beneficial bacteria (28), contributing to the increased levels of inflammation and disease processes common to overweight or obesity.

Since there is a less than anticipated weight loss seen due to energy compensation associated with chronic exercise interventions, it is important to increase the efficacy of

exercise for weight loss in attempt to allow for sustainable habitual physical activity and associated health benefits. Exercise increases cardiorespiratory fitness, lowers triglycerides, and increases insulin sensitivity (10, 29), thereby increasing metabolic health. Exercise has also been shown to improve cognitive functioning in older adults (30) and increase perception of quality of life (31). These adaptations due to exercise are important in promoting health and well-being, and therefore exercise should continue to be recommended as a part of daily living (32) regardless of if weight loss is observed. In addition to maintaining physical activity, the effects of HFS diets and energy compensation must be mitigated. Decreasing compensatory behaviors and the effects of a HFS diet may be accomplished through strategic manipulation of the post-exercise diet. Specifically, the addition of a post-exercise prebiotic fiber supplement may aid in the release of satiety-stimulating hormones.

Energy Balance and Appetite Regulation

Appetite regulation involves the complex interaction of neurohormonal signaling mechanisms and environmental ques that govern energy intake. This complex system is governed through the interaction of the homeostatic and hedonic energy systems. The homeostatic energy system matches energy intake to energy expenditure in attempt to maintain weight (33). Homeostatic energy regulation is accomplished through neurohormonal signaling mechanisms that are ultimately governed by the hypothalamus. In contrast, the hedonic energy system is associated with feeding for pleasure (34) and increases the intake of highly palatable (high fat, sugar, and salt) foods (35). It is believed that the hedonic system exists to aid in the promotion of behaviors that promote survival (36). Environmental cues and to some extent neurohormonal signaling mechanisms

govern the hedonic energy system. Despite being able to describe the hedonic and homeostatic energy systems separately, there are complex interactions between these two energy systems. When exposed to highly palatable food, the hedonic energy system can override the homeostatic system to increase the feelings of reward from eating, leading to increased energy intake even in the absence of physiological hunger (36). Furthermore, during times of energy deficiency, increased homeostatic hunger serves to enhance the sensitivity of the hedonic system leading to increased food reward.

The common neurohormonal signaling mechanisms involved in appetite regulation are produced in the gastrointestinal tract and exert their effects through endocrine signaling via the gut-brain axis to control eating behavior (37). There are two types of appetite-regulating hormones: anorexigenic and orexigenic. Anorexigenic hormones increase satiety, whereas orexigenic hormones increase feelings of hunger. Anorexigenic hormones include peptide tyrosine-tyrosine (PYY), glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), leptin, and insulin. There is one orexigenic hormone, ghrelin. The hormones PYY and GLP-1 are produced by the enteroendocrine L-cells and CCK is produced by the I-cells in the small intestines in response to macronutrient ingestion (38-41). The hormone leptin is released from adipose tissue in proportion to the amount of adipose tissue within the body (42). Both the hormones insulin and leptin are long-term energy balance regulators, whereas the others are acute (meal-by-meal) satiety hormones (43). The hormone ghrelin is produced by the fundus of the stomach; Levels of ghrelin increase prior to meal-time and decrease immediately after eating (41). Each of these hormones exert their effect and ultimately change eating behavior by activating appetite-regulating structures in the brain. The brain structures associated with appetite regulation include the hypothalamus, corticolimbic system, and the hindbrain (42). A

systematic review by Zanchi et al. (37) showed that ghrelin increases neuronal activity in the reward pathways which includes structures such as the ventral tegmental area, nucleus accumbens, amygdala, and hippocampus. It has also been shown that the peptides PYY, GLP-1, and leptin are associated with activation of brain regions that induce satiety.

In obesity, there are alterations in the sensitivity of appetite-regulating brain regions and satiety hormone levels (37). Horstmann et al. (44) showed that grey matter in areas that code the value and importance of food, such as the nucleus accumbens, orbitofrontal cortex, and the hypothalamus positively correlated with levels of obesity. The changes in the structures are hypothesized to influence decision making between high-reward options despite increased risk and safer, less risky options. Similarly, Kahathuduwa et al. (45) showed that individuals with obesity had decreased activity in brain regions associated with executive control and decision making, as well as increased levels of food cravings. After a 3-week period of caloric restriction, the same brain regions had increased activity and participants reported less cravings. The increase in risk taking behaviors due to changes in brain structure in individuals with obesity may increase the likelihood of consumption of a HFS diet.

The hormones leptin and insulin are also increased with levels of obesity. Despite having satiating effects when released normally, chronically increased levels of leptin and insulin lead to desensitization of the satiating effects as well as a decrease in the sensitivity of the reward pathways to food (34, 46). Since leptin and insulin transporters through the blood brain barrier are saturable, it has been hypothesized that the desensitization during chronic increases is due to saturation of the receptors in the brain. The desensitization and lack of reward leads to a higher drive to seek out highly palatable

foods in attempt to feel rewarded and satiated. The modification of the brain in obesity may reflect behavioral changes linked to excessive energy-intake and obesity.

Compounding these changes in brain neurophysiology, when individuals with obesity or overweight lose weight, levels of anorexigenic hormones (e.g. GLP-1) decrease and levels of the orexigenic hormone (e.g. ghrelin) increase (47, 48). The change in the levels of satiety hormones after weight loss leads to increased hunger and decreased satiety. These changes remain when weight loss has been maintained for greater than or equal to one year (20, 48). The altered appetite signals can pose significant challenges for individuals attempting to maintain or induce weight loss. The changes in appetite-regulating hormones necessitate an intervention that can re-regulate hormonal levels to allow for weight loss to be sustainable in the long term. Given that exercise is commonly recommended for weight loss, it is important to analyze how the adoption of an exercise regime changes appetite-regulating hormones and the sensitivity to their effects.

Exercise recommendations for weight loss

The current recommended dose of aerobic exercise for adults to maintain health and reap metabolic benefits of exercise is 150 minutes of moderate to vigorous physical activity per week and at least two sessions of strength training for muscle fitness and maintenance (49). This also serves as the basis of exercise recommendations for increasing health in individuals with overweight or obesity (50). However, according to the American College of Sports Medicine, 150 – 250 minutes of moderate intensity physical activity per week will produce moderate weight loss, and in order to lose significant amounts of weight and maintain weight loss chronically, greater than 250 minutes of physical activity per week is recommended and must be maintained (50). As

shown by Tate et al. (51) only those sustaining high physical activity levels per week (defined as an expenditure of 2500 calories/week or walking 75 minutes/day) over the course of 30-months maintained significant weight loss of 12 kg, whereas those who had sustained lower levels of physical activity only maintained a weight loss of 0.8 kg.

Despite these physical activity recommendations for weight loss and maintenance in obesity, many individuals who participate in physical activity with the goal of losing weight do not achieve the anticipated amount of weight loss. Pooled analysis of strictly moderate intensity aerobic exercise interventions for weight loss show that only moderate levels of weight loss (2 - 6 kg) is attained by individuals with overweight or obesity (17, 29, 52), with this weight loss becoming insignificant by 30-months post intervention due to an increase in compensatory behaviors (14-16, 21). Similarly, a pre-post intervention by Myers et al. (53) showed that after women completed a 12-week intervention of 5 vigorous exercise sessions per week their daily energy intake and post-prandial hunger ratings were significantly increased. Participants only lost 22% of the expected weight loss from the exercise intervention.

It is largely believed that weight loss is unsustainable because of the dysregulation of the appetite-regulating hormones leading to compensatory eating patterns (19, 54, 55). In a systematic review by Beaulieu et al. (55) the relationship between daily habitual physical activity and energy intake was shown as a J-shaped curve. Low levels (less than 150 minutes per week), high levels (420 - 839 minutes per week), and very high levels (greater than 840 minutes per week) of physical activity were associated with increased energy intakes; whereas, moderate levels of physical activity (150 – 420 minutes per week) were associated with the lowest levels of energy intake (55). In 2012 and 2013 the percentage of adults meeting the Canadian guidelines for moderate to vigorous physical

activity was 32% and 18% for adults aged 18 to 39 and 40 to 59, respectively (12). Most Canadian adults fall into the range of low activity levels, and therefore are likely consuming an increased energy intake without increased energy expenditure, which may increase the likelihood of developing overweight or obesity. The J-shaped curve, however, does not consider the hormonal response to weight loss as well as does not differentiate between normal weight and individuals with overweight or obesity.

Highlighted by Finlayson et al. (19), after an acute bout of 50 minutes of aerobic exercise at 70% of maximum aerobic capacity, half of the study participants were found to be compensators for energy expended. These compensators rated an *ad libitum* meal as significantly less pleasant after no exercise and had a higher drive for highly palatable food post-exercise. The compensators also had a significantly higher BMI and body fat percentage and reported less regular exercise than those who were non-compensators. Similarly, both Finlayson et al. (56) and King et al. (57) found comparable results through a 12-week aerobic exercise intervention which aimed to increase energy expenditure by 500 calories/day for 5 days a week in individuals with overweight and obesity. It was demonstrated that 41% - 51% of participants were compensators and lost significantly less weight relative to non-compensators. King et al. (57) showed that the energy intake of compensators and non-compensators significantly differed. Compensators increased their energy intake by an average of 268 calories per day, whereas non-compensators decreased their caloric intake by 130 calories per day. Furthermore, Finlayson et al. (56) showed that after a chronic exercise intervention compensators had a higher liking and wanting for highly palatable food. Wan et al. (58) also noted that there was an immediate increase in the drive for energy intake in trained male cyclists when given a post-exercise drink that was not calorically dense compared to a higher calorie chocolate milk

beverage; however, both sessions ate the same number of total calories over a 28-hour period. Trained, lean individuals may be able to modify their caloric intake to match energy expenditure unlike individuals with overweight or obesity using physical activity as a method for weight loss. Although, Maraki et al. (59) found that a single 1-hour training session in young, normal weight females led to increased subjective hunger and decreased satiety; however, there were no differences in daily energy intake, resulting in a lower relative energy intake with exercise than in the non-exercise control trial. Taken together, these studies show that both acute and chronic exercise may increase the drive for highly palatable food. The increased drive for palatable food is in part due to the hedonic energy system overriding the homeostatic energy system, increasing total daily energy intake, and thus leading to a less than anticipated weight loss.

The differences in energy intake due to increasing physical activity levels may be due to changes in the appetite-regulating hormones in the acute and chronic periods after exercise. As levels of recreational activity increase, individuals were found to have higher levels of ghrelin in the fasted state, but also higher levels of GLP-1 in both the fasted and post-prandial state (55). In the acute period after aerobic exercise, Panissa et al. (60) found that relative energy intake in healthy males and females was decreased following either high intensity interval exercise or a steady state exercise (maintained at 60% of the maximum perceived intensity). Likely aiding in a lowered energy intake, a significant decrease in the area under the curve (AUC) for ghrelin was associated with high intensity exercise sessions. Less research has been conducted on the chronic impact of exercise on appetite-regulating hormones. Given that energy compensation reaches approximately 84% in long-term exercise interventions (21), it appears that the acute increases in gut-derived satiety hormones after exercise are not maintained long-term.

The response of appetite-regulating hormones in individuals with overweight or obesity differs from lean to normal weight individuals in the postprandial and post-exercise period. This difference in response may be due to the blunted response of ghrelin and anorexigenic hormones in the post-prandial period (61), leading to increased feelings of hunger. Increased perceived hunger and levels of acylated-ghrelin have been shown in individuals with overweight or obesity after an acute bout of exercise in the evening (62). Similarly, another study demonstrated that there were no differences in the fasted levels of PYY in response to 15 days of a 1 hour per day vigorous walking program (63). It has also been shown that energy intake and subjective hunger levels remain consistent despite increases in satiety hormones after acute and chronic aerobic exercise interventions (64, 65). The lack of energy intake adjustment after exercise observed in individuals with overweight or obesity may be due to a decreased sensitivity to the appetite-regulating hormones (66). A reduction in the sensitivity to these satiety signals contribute to increased intake of highly palatable foods. Individuals with overweight or obesity, therefore, may be susceptible to increased energy intake and limited weight loss with exercise. A recent study by Blundell et al. suggested that a post-exercise dietary strategy may be necessary to decrease energy compensation after exercise (53).

Dietary recommendations for recreationally active individuals

Common post-exercise nutrition recommendations are typically geared towards athletes looking to recover muscle and liver glycogen stores quickly to allow for increased performance and recovery for the next bout of exercise (67-69). These recommendations include high amounts of carbohydrates immediately after exercise, as consumption of carbohydrates in the post-exercise period aids in glycogen restoration (70,

71). For optimal recovery, a review by Pritchett et al. (72) suggests consumption of 1.0 - 1.5 g of simple carbohydrates per kilogram of body weight at 2 hour intervals for up to 6 hours. A frequently recommended post-exercise food for restoration of glycogen and muscle repair is chocolate milk. Chocolate milk is recommended because of its essential amino acid content and increased carbohydrate content as compared to normal milk (71, 73). However, these recommendations are specific for athletes. For athletes, it is recommended that daily caloric intake when participating in light exercise includes 3-5 g of carbohydrate per kilogram of body weight per day (74), 1 - 1.2 g/kg of body weight of protein per day, and 20 to 35% of their calories from fat (75). For a 70 kg individual, this would translate to 210 – 350 g (840 – 1400 calories) of carbohydrate to support performance and recovery from light exercise each day, 70 – 84 g (280 – 336 calories) of protein, and therefore a total daily energy intake of 1493 – 2315 calories, assuming 20% of calories are taken in from fat. These recommendations are not aimed at producing weight loss, as weight loss involves the creation of an energy deficit. Instead, post-exercise nutrition recommendations for athletes are primarily aimed towards maintenance of body weight and performance.

The food environment, convenience, and nutritional knowledge also play a role in the choice of the types of food eaten by both athletes and recreational or non-athletes (76). Many food manufactures advertise and promote post-exercise supplements to aid in recovery after exercise. These high carbohydrate/sugar supplements are frequently used by athletes and non-athletes, in part due to the convenience. Furthermore, the post-exercise hedonic drive for carbohydrate-rich foods is also increased after aerobic exercise and may promote the consumption of these foods. Food manufactures have effectively marketed the message that post-exercise recovery requires the consumption of these high

glycemic food. The combination of all these factors may promote post-exercise eating patterns that promote energy compensation. Interestingly, despite all the various factors that influence post-exercise energy consumption, no specific evidence-based guidelines have been published to date detailing specific post-exercise nutritional strategies that promote sustained weight loss.

One potential nutritional strategy after exercise that may be used in attempt to attain a negative energy balance is fasting; however, it has been shown that intermittent fasting does not produce different results from continuous energy restriction (77). This is highlighted by a study on individuals participating in fasting for Ramadan, which includes refraining from eating and drinking (including water) from sun rise to set. These individuals did not experience changes in body mass or subjective ratings of hunger (78), but fasting for 24 hours increased the hedonic reward of food, feelings of appetite, and the wanting and liking of sweet foods (79). It has also been shown in a systematic review and meta-analysis that fasting after exercise decreases future exercise performance by decreasing recovery (80); however, there have been no trials focusing on the potential effects of fasting after exercise on appetite regulation.

The changes in the hedonic reward of food observed with intermittent fasting may indicate that fasting after exercise may not be beneficial for energy intake and may promote compensatory eating patterns. In contrast, the common recommendations for post-exercise recovery, as mentioned above, include high amounts of carbohydrate, typically rich in simple sugars, and are considered high glycemic foods. Consuming carbohydrates in the form of simple sugars also increases the hedonic reward of food, especially when fructose is consumed (81). Therefore, between caloric restriction, either from intermittent fasting or a general decrease in calories, and the commonly

recommended post-exercise recovery foods such as chocolate milk and convenience foods, individuals looking to use exercise to aid in weight loss may already be at a disadvantage due to the physiological changes in hormones causing an increased drive to eat high fat, high sugar foods. Secondly, those participating in exercise recreationally likely do not need to restore muscle and liver glycogen immediately and, therefore, nutritional recommendations should be aimed at the promotion of eating well to aid in overall health and well-being.

The gut microbiota, appetite, and prebiotics

An aspect of the human body that is largely influenced by habitual diet and lifestyle is the gut microbiota. The microbiota is a community of bacteria that resides in the large intestine which relay effects associated with health and disease (82). These bacteria within the gut contribute to health via production of vitamins, essential amino acids, and metabolic byproducts from undigested dietary components, such as fermentable fiber (83). The metabolic byproducts of fermentable fiber include SCFAs, such as butyrate, propionate, and acetate. SCFAs provide energy for the host and have been demonstrated to elicit significant effects on host-metabolism (83).

The composition of the gut microbiota changes depending on the state of health an individual and the diet they habitually consume (84). Interestingly, changes in the composition of the microbiota can be seen within 24 hours of a dietary change (84). The two predominant bacterial groups in the large intestine are Firmicutes and Bacteroidetes, and the ratio of these groups has been observed to change depending on health status of the individual (85). Specific genera of bacteria, including the beneficial bacteria *Lactobacillus* spp. and *Bifidobacterium* spp., are affected by lifestyle and dietary

modification (86). A decrease in *Lactobacillus* spp. and *Bifidobacterium* spp. has been linked to increased rates of obesity, cardiovascular disease, and type II diabetes (87).

To counteract adverse changes in gut microbiota and increase metabolic health, lifestyle changes that impact the composition and diversity of the microbiota are required; specifically, a diet that is high in microbiota-accessible carbohydrates (MACs) is important in the promotion of health. MACs are non-digestible carbohydrates that are primarily derived from dietary fibers (88). MACs are an important source of carbon to the bacteria in the gut and promote the diversity and increase in beneficial bacteria (88). The habitual diet in western countries is a HFS diet, which has also been shown to be low in dietary fiber (89). This decrease in dietary fiber, as compared to traditional diets where fiber consumption ranges between 50 – 150g per day (90), is connected with a decrease in the production of SCFAs (91), and thus is associated with increased low grade inflammation and obesity-associated metabolic disease (92).

A specific MAC of interest is a prebiotic fiber. Prebiotic fiber is a fermentable fiber source that stimulates the growth and diversity of beneficial bacteria in the large intestine (93) and creates health benefits for the host. There are multiple types of prebiotic fiber including inulin, fructo-oligosaccharides, oligofructose, and galacto-oligosaccharides (94). The addition of a prebiotic fiber supplement to a daily diet regiment is a lifestyle modification that increases beneficial bacteria, therein decreasing inflammation, increasing the satiety hormones GLP-1 and PYY, and thus promoting increased feelings of satiety and weight loss. Prebiotic fiber elicits its effects through fermentation in the large intestine increasing levels of SCFAs produced (94). SCFAs have been shown to aid in the control of subjective satiety and appetite through modulation of the appetite-regulating hormones (95). Satiety hormones are modulated through the

binding of SCFAs to Free Fatty Acid Receptor 2 (FFA2) and Free Fatty Acid Receptor 3 (FFA3) causing colonic L-cells to release the anorexigenic hormones GLP-1 and PYY (96-98). Similarly, acetate and propionate bind to G-Protein Receptors (GPR) 41 and 43 expressed in the small intestine, colon, and adipocytes to decrease inflammatory responses. GPR41 activation is also responsible for the release of PYY (99).

A study by Parnell et al. (100) highlights the effects of the addition of 21 grams of a prebiotic supplement per day given over 12 weeks in overweight adults. After receiving the prebiotic supplement the participants in the study had significantly lower body weight and AUC for ghrelin, while the AUC for PYY increased compared to a similar dose of the placebo maltodextrin. Similarly, Dewulf et al. (101) showed in a double-blind, placebo-controlled trial that 3 months of 16 g/day of a 50/50 mixture of inulin and oligofructose in 15 women with obesity led to significant decreases in fat mass and decreased levels of Bacteroidetes, bacteria associated with impaired health status. Hume et al. (102) showed that a 16-week intervention of 8 grams per day of a prebiotic supplement is effective at improving appetite regulation and increasing subjective ratings of fullness in children with overweight or obesity. In another study Cani et al. (103) showed that supplementation with 16g of prebiotics per day for 2 weeks decreased total daily energy intake and subjective hunger, while increasing subjective satiety and levels of GLP-1 and PYY just 10 minutes after receiving the dose. Similar findings have been shown with acute supplementation of a prebiotic. Rahat-Rozenbloom et al. (104) showed in 13 individuals with overweight or obesity and 12 lean individuals that a single dose of 24g of inulin after an overnight fast significantly increased SCFA AUC after 4-6 hours, which was associated with a significant decrease in the AUC of ghrelin. Similarly, Tarini & Wolever (105) showed a significant increase in SCFAs and GLP-1 and decrease in

ghrelin over a 6-hour period after a 24g dose of inulin. Each of these studies highlight the effect of prebiotic supplements on appetite-regulating hormones, specifically the decrease in the levels of ghrelin and the increase in the levels of PYY and GLP-1 in association with the dose given. The changes in the appetite-regulating hormone levels are likely due to the change in the diversity of the microbiota and production of SCFAs, which indirectly modulate levels of energy intake and subjective feelings of hunger (103, 106).

Another factor that has been shown to modulate the diversity of the gut microbiota is exercise. Clarke et al. (26) showed that elite rugby players matched with individuals with similar ages and BMI, or only age-matched had significantly more microbial diversity. Specifically, the levels of the mucin-degrader *Akkermansia muciniphilia* were significantly increased. This species has been shown to inversely correlate with levels of obesity and metabolic disorder due to increasing gut-barrier function in the large intestine (107).

Summary

Since exercise is a prominently used lifestyle modification for weight loss, it is important to understand how exercise affects energy balance and why there is less than anticipated amounts weight loss with chronic exercise interventions. Given that the triad, consisting of the commonly consumed HFS diet, chronic exercise intervention energy compensation, and increasing levels of overweight and obesity, modifies the brain, gut microbiota, and systemic sensitivity to appetite-regulating hormones it is necessary to find novel methods to decrease energy compensation through regulation of the appetite-regulating hormones. Since exercise and nutrition play a large role in maintaining metabolic health regardless of weight loss, it is important to continue to recommend

these; however, the use of these lifestyle modifications is largely in attempt to decrease weight, if weight loss is not seen because of energy compensation individuals are less likely to be motivated to continue with exercise and nutrition interventions chronically. To understand the relationship between exercise and nutrition for post-exercise appetite-regulation, it is necessary to examine the post-exercise response to nutrient intake in comparison to a fasted state. Similarly, a post-exercise modification that may increase subjective and objective measures of satiety is a prebiotic fiber supplement.

Purpose and Hypothesis

The purpose of this thesis was to examine the effect of post-exercise diet on appetite regulation in individuals with overweight. The first study, Chapter Two, examined if post-exercise appetite-regulation is differentially modulated through nutrient-intake as compared to a fasted state. Chapter Three examined if a post-exercise prebiotic supplement increased levels of subjective and objective measures of satiety. This data was collected through a randomized cross-over intervention with three separate arms, and was then split into two analyses to compare a fed versus a fasted state, and a fed versus fed + prebiotic supplement. The fed arm in each chapter is the same data set. It was hypothesized that a fed state will differentially modulate appetite-regulation post-exercise in individuals with overweight. Similarly, it was hypothesized that a prebiotic supplement may offer increased subjective and objective measures of satiety, as well as decrease energy intake over 3-days. Following Chapter Two and Chapter Three will be a chapter providing a general discussion and conclusions.

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Chapter 2: Influence of post-exercise fasting on hunger and satiety in adults with overweight.

Abstract

Evidence suggests that exercise may elicit anorexigenic appetite-regulatory effects. It remains unclear how post-exercise energy intake modifies the appetite response. Given that feeding or fasting post-exercise may differentially modulate post-exercise appetite-regulation, the objective of this study was to examine the appetite response after exercise in a fed versus fasted state. In a randomized crossover intervention, 14 participants (BMI = 26.9 ± 3.5 kg/m^2) received one of two recovery beverages: 1) water control (FAST) or 2) sweetened-milk (FED) after completing a 45min (65-70% VO_{2peak}) exercise session ~2hrs after dinner. Energy intake was assessed through fasted *ad libitum* breakfasts the morning after exercise and 3-day food diaries. Blood samples were taken to assess appetite hormones (GLP-1, PYY, acyl-ghrelin) and visual analogue scales measured subjective appetite. After exercise, FAST demonstrated significantly increased hunger, prospective food consumption, and desire for sweet, salty, savoury, and fatty foods compared to FED. Levels of PYY and GLP-1 after exercise were significantly decreased and levels of ghrelin were increased in FAST with these differences disappearing the day after exercise. Relative to fasting, feeding after exercise increased subjective and objective measures of satiety; however, these changes were not maintained the day after exercise. Energy intake the day after exercise was increased in both sessions. Therefore, fasting post-exercise may temporarily increase appetite, but total 3-day energy intake was lower compared to a fed session.

Introduction

Exercise has well known metabolic benefits including reduced blood pressure, blood sugar, and triglycerides, increased HDL cholesterol, as well as improved cardiovascular fitness (1). Energy expenditure is also increased by physical activity and is therefore believed to be beneficial for weight loss by generating a negative energy balance. It has been observed that ~65% of individuals attempting to lose weight use physical activity (2). While exercise increases energy expenditure, exercise can affect energy intake by modifying appetite through changes in the circulating concentrations of appetite-regulating hormones (3). Macronutrient ingestion can also modify appetite by stimulating the gut to release hormones that promote satiety (4). There is likely a complex relationship between exercise and post-exercise nutrient intake that influences appetite regulation, but to date that interaction has not been thoroughly investigated.

Acute bouts of exercise have been observed to produce short-term anorexigenic effects. Anorexigenic hormones, such as peptide tyrosine-tyrosine (PYY) and glucagon-like peptide-1 (GLP-1), produce feelings of satiety, whereas the orexigenic hormone ghrelin produces feelings of hunger as time between meals increase. Anorexigenic hormones PYY and GLP-1 are primarily released from the enteroendocrine L-cells in the small intestine (4), while ghrelin is produced in the fundus of the stomach (5). In a meta-analysis by Schubert et al. (3) it was demonstrated that immediately after an acute bout of aerobic exercise in normal-weight, healthy individuals, concentrations of acylated ghrelin typically decline and PYY and GLP-1 concentrations increase. The myokine interleukin-6 (IL-6) is also believed to mediate the anorexigenic effects of exercise and may increase in proportion to the intensity and duration of an acute bout of exercise (6, 7).

There is evidence that appetite response to exercise may differ as BMI increases. Increased BMI has been shown to attenuate the post-exercise suppression of acylated ghrelin, decrease perceived feelings of post-prandial fullness (8, 9), and diminish the anorexigenic effect of exercise (10). Finlayson et al. (11) highlighted that after an acute bout of 50 minutes of aerobic exercise at 70% of maximum aerobic capacity those who compensated for exercise energy expenditure had a higher BMI and a higher drive for highly palatable food post-exercise in comparison to non-compensators. Several studies have also demonstrated that long-term exercise can increase ghrelin and total daily energy intake (12, 13) which may contribute to lower than expected weight loss commonly observed with exercise interventions (14).

If there is a greater orexigenic drive to consume palatable foods post-exercise in obesity, it is important to understand how post-exercise diet impacts appetite and overall energy intake. Athletes and non-athletes alike are often encouraged to consume protein- and carbohydrate-rich meals to promote post-exercise recovery (15, 16) which will stimulate the release of anorexigenic hormones through via nutrient intake (4). In contrast, fasting would be expected to increase hunger, the hedonic reward of food, and the desire for sweet foods (17). The relationship between exercise and post-exercise energy intake on appetite regulation may therefore be influenced by BMI. Thus, the objective of this study was to examine how fasting versus post-exercise nutrient intake impacts appetite and energy intake after an acute bout of exercise.

Materials and Methods

Participants

14 adults (6 women and 8 men) volunteered and provided written informed consent to participate in the study. To be eligible for the study participants had to be healthy, have a body mass index > 23 $kg \cdot m^{-2}$ and be recreationally active, which was defined as accumulating a minimum of 150 minutes per week of moderate to vigorous physical activity. Exclusion criteria included smoking, taking regular medication that could influence appetite, taking supplemental prebiotics or probiotics, lactose intolerance, or irritable bowel syndrome. Female participants completed all experimental sessions in the early follicular phase of their menstrual cycle (day 1-10) based on self-reported menstruation to control for appetite fluctuations throughout the menstrual cycle (18, 19). All research was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. Ethical approval was obtained from the University of Lethbridge's Human Subject Research Committee, Protocol number #2017-094.

Preliminary Session

During an initial visit to the lab participants were screened for contraindications to the exercise using the Physical Activity Readiness Questionnaire and habitual physical activity was determined using the Godin Leisure Time Exercise Questionnaire (GTLEQ). Participants also completed a modified restrained eating questionnaire (20), as restrained eating has been shown to decrease sensitivity to dietary modifications (21, 22). Height (nearest 0.1cm) and weight (nearest 0.1 kg) were measured using a mechanical beam scale (Heath-o-Meter, Sunbeam Products).

Peak oxygen uptake (VO_{2peak}) was measured directly using an incremental test to exhaustion on an electromagnetically braked cycle ergometer (Velotron, QUARQ, Spearfish, South Dakota, USA). Following a 5-minute warmup at a self-selected pace, participants cycled at 50W for 4-minutes at 80 rpm, after which the test increased by 25

W/min for women and 30 W/min for men until volitional fatigue. Heart rate was measured continuously throughout the test by a Garmin heart rate monitor (HRM-Dual, Garmin, Olathe, Kansas, USA). Oxygen consumption was measured using the Quark CPET (COSMED, Chicago, Illinois, USA) with breath by breath analysis. VO_{2peak} was determined to be the greatest rolling 30-second VO_2 average.

Experimental Sessions

Participants completed two experimental sessions: 1) control (FAST) and 2) sweetened milk (FED), in a randomized crossover trial with a wash-out period of at least one week. Both sessions took place at the same time of day for each participant. Figure 2.1 shows the timeline for each experimental session. Participants kept a 3-day food diary during the day of exercise and subsequent 2-days. All participants were requested to maintain similar eating patterns for each experimental session and they completed the GLTEQ to ensure physical activity was similar for both weeks. Participants were instructed to arrive at the lab in the evening 2 hours after consuming dinner and they provided an appetite rating using a visual analogue scale (VAS) prior to exercising. A pre-exercise (PRE-EX) blood sample was collected from an antecubital vein while participants were in the supine position.

Immediately following the blood draw, participants completed a 45-minute cycling session at 65-70% of their previously determined VO_{2peak}. VO_2 was continuously monitored and wattage was adjusted to maintain intensity throughout each session. A post-exercise drink (10 mL/kg body weight) was provided and participants were instructed to consume it within 10 minutes. In the FAST session the drink was plain water and in the FED session the drink was sweetened milk (Vanilla Vibe, Milk2Go, Quebec, Canada), which amounted to 495 ± 25.3 kcals (63% carbohydrate, 15% fat, 22% protein).

One hour after consuming the drink a second blood sample was drawn and a second appetite rating was provided (POST-EX). Participants left the lab for the remainder of the evening and were asked to refrain from eating or drinking anything with exception of water.

The next morning participants arrived at the lab in a fasted state 12-hours post-exercise. A fasted, pre-breakfast (PRE-BFST) appetite rating was completed and third and final blood sample was drawn. Participants then consumed an *ad libitum* breakfast meal consisting of pre-weighed instant oatmeal (Quaker, PepsiCo, USA), orange juice (President's Choice, Ontario, Canada), and coffee (Starbucks Pike Place instant coffee, Starbucks Corporation, Canada) or black tea (Pure Leaf, Unilever Canada) with cream (18% Dairyland single serve) and/or sugar (Rogers Natural Sugar Packs) to preference served in excess. In both experimental sessions, the same quantity of breakfast food was provided and participants were told to consume as much as they would like until they were satisfied, within 30 minutes. Upon completion of the meal participants provided a final appetite rating (data point denoted as POST-BFST for post-breakfast). The remaining food was weighed to determine (to within 1g) how much energy was consumed based on nutritional information provided on the manufacturer's label.

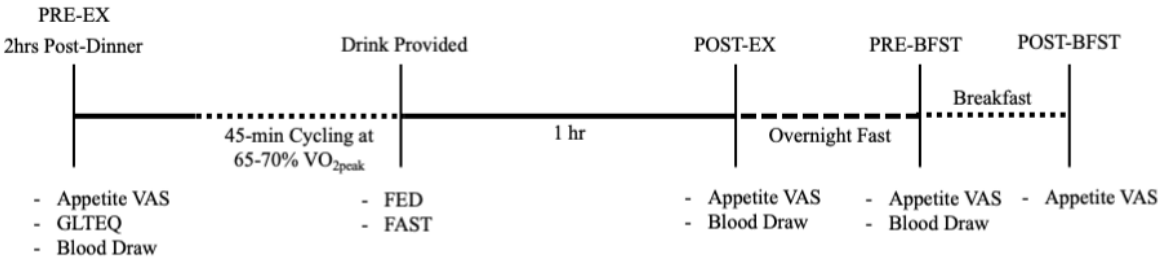

Figure 2.1: Timeline of experimental sessions. VAS: Visual analogue scale; POST-EX: Post-exercise; PRE-BFST: fasted, pre-breakfast; POST-BFST: Post-breakfast.

Appetite Perceptions

Appetite perceptions were assessed using validated 100 mm VAS (23). Each aspect of appetite perceptions is anchored at 0 mm and 100 mm with opposing statements answering the posed question. Participants were asked to place a mark through the horizontal line to indicate their answer for all appetite perceptions. There were eight aspects of appetite assessed: Hunger (anchored by "I am not hungry at all" and "I have never been more hungry"), Satisfaction (anchored by "I am completely empty" and "I cannot eat another bite"), Fullness (anchored by "Not at all full" and "Totally full"), Prospective Food Consumption (PFC) (anchored by "Nothing at all" and "A lot"), and types of food participants would like to eat (Sweet, Salty, Savoury, or Fatty; All anchored by "Yes, very much" and "No, not at all").

3-Day Food Diaries

3-day food diaries began on the day of the experimental session. Participants were given the option to track intake with an online resource (MyFitnessPal™) or through written diaries. Email and verbal reminders were used to ensure compliance with tracking food each day of the trial. To assist with accuracy, each participant was provided with a digital food scale and instruction on how to accurately complete a food diary. The 3-day food records were analyzed using FoodWorks 14 Software (The Nutritional Company, Long Valley, NJ).

Blood Collection and Analysis

All blood samples were collected into pre-cooled 6 mL EDTA vacutainers. Immediately after collection, a protease inhibitor cocktail containing DPP IV inhibitor (10ul/ml blood; MilliporeSigma Corporation, Ontario Canada), Sigma protease inhibitor (1mg/ml blood; SigmaFast, MilliporeSigma Corporation, Ontario Canada) and Pefabloc (1mg/ml blood; MilliporeSigma Corporation, Ontario Canada) was added to the sample to

prevent degradation of satiety hormones. Samples were centrifuged at 2000 rpm for 10-minutes at 4°C. Plasma aliquots were stored at -80°C for later analysis.

The concentration of PYY was determined using the Human PYY (Total) ELISA kits (MilliporeSigma Corporation, Ontario, Canada). Intra-assay and inter-assay variation was 2.39 ± 1.14% and 3.09 ± 3.29%, respectively. GLP-1 concentration was assessed using the High Sensitivity GLP-1 Active Chemiluminescent ELISA kits (MilliporeSigma Corporation, Ontario, Canada), which had inter- and intra-assay variations of 6.20 ± 6.71% and 6.75 ± 5.46%, respectively. Ghrelin concentration was assessed by the Human Ghrelin (Active) kits (MilliporeSigma Corporation, Ontario, Canada) and the inter- and intra-assay variations were 2.73 ± 3.11% and 2.11 ± 1.50%, respectively. IL-6 concentrations were analyzed with the Human IL-6 ELISA kits (MilliporeSigma Corporation, Ontario Canada) which had an intra-assay variation of 23.34 ± 7.46%. All samples were assayed in duplicate.

Statistical Analysis

Data were analyzed using the SPSS software v25.0 for Windows. POST-EX blood sample hormone (GLP-1, PYY, ghrelin, and IL-6) concentrations were normalized to PRE-EX values and analyzed as absolute change in concentration. Data from POST-EX blood draw is missing from one participant due to a missed venipuncture. To account for the missing data point we assessed the average change in concentrations of hormones and interpolated the change for this data point. IL-6 concentrations were transformed logarithmically due to skew. Differences were examined using one-way or two-way repeated measures analysis of variance (ANOVA). When there was a main effect, a post-hoc LSD pairwise comparison was used to examine significant differences. Cohen's d

(24) was calculated for all pairwise comparisons to examine the effect size. A small effect sized is defined as <0.2; moderate effect size 0.20 ≥ 0.80; and large effect size > 0.80. Area under the curve (AUC) analysis was completed for hormonal analysis and appetite perceptions. AUC estimations were calculated using trapezoidal sums. Statistical significance was set at $P < 0.05$. All results are presented as mean ± standard deviation (SD).

Results

Participants

14 participants (8 male and 6 female) completed the study. Participants had an average age of 26.8 ± 6.7 years, height of 174.5 ± 11.1 cm, weight of 82.5 ± 15.8 kg, and VO_{2peak} of 37.3 ± 7.5 $mL \cdot kg^{-1} \cdot min^{-1}$. Participants had an average BMI of 26.9 ± 3.5 kg/m^2 (range: 23.0 – 33.7 kg/m^2), with nine participants falling in the overweight category (≥ 25.0 kg/m^2 and < 30.0 kg/m^2) and three in the obese category (≥ 30.0 kg/m^2). Participants had a restrained eating score of 12.2 ± 3.9. Female participants were testing on day 6.6 ± 6.7 of the menstrual cycle. The exercise intensity for FAST (67.5 ± 6.4% VO_2) and FED (68.0 ± 4.9% VO_2) did not differ between sessions.

Appetite Perceptions

All appetite AUC comparisons (Table 2.1) revealed that during FAST participants had significantly higher overall hunger ($P = 0.02$; d=0.75), PFC ($P = 0.012$; d = 1.17), and desires for something sweet ($P = 0.001$; d = 0.76), salty ($P = 0.001$; d = 0.81), savoury ($P < 0.005$; d = 1.05), and fatty ($P < 0.005$; d = 1.07), and lower overall satisfaction ($P = 0.001$; d = 1.43) and fullness ($P = 0.002$; d = 1.04) than FED.

There were significant main effects of session for satisfaction ($P = 0.02$), fullness ($P = 0.01$), and desire for something sweet ($P = 0.006$), salty ($P = 0.01$), savoury ($P = 0.04$), and fatty ($P = 0.001$). There were significant main effects of time for all appetite ratings ($P < 0.05$). There were also significant interaction effects for time*session for satisfaction ($P = 0.001$), fullness ($P = 0.005$), PFC ($P = 0.007$), and desires for sweet ($P = 0.009$), salty ($P = 0.004$), and savoury foods ($P = 0.002$). The interaction effect was approaching significance for hunger ($P = 0.07$) and desire for something fatty ($P = 0.06$). Post-hoc pairwise comparison analyses revealed that during FAST at POST-EX participants reported significantly higher levels of hunger ($P = 0.029$; $d = 0.89$), PFC ($P = 0.019$; $d = 1.21$), and desire for sweet ($P < 0.005$, $d = 1.24$), salty ($P = 0.001$, $d = 1.25$), and savoury ($P < 0.005$, $d = 1.49$) foods, and significantly lower levels of satisfaction ($P = 0.001$; $d = 1.18$) and fullness ($P = 0.008$; $d = 1.21$). During FAST at PRE-BFST participants reported significantly lower satisfaction ($P = 0.001$; $d = 1.21$), and a significantly larger desire for savoury foods ($P = 0.023$; $d = 0.51$). There was a trend at PRE-BFST during FAST for participants to report increased hunger ($P = 0.064$; $d = 0.46$) and PFC (($P = 0.057$; $d = 0.64$) (Figure 2.2). There were no significant pairwise comparisons at PRE-EX or POST-BFST ($P > 0.05$).

Table 2.1: Appetite perceptions AUC[1].

	FAST	**FED**
Hunger	39,201 ± 14,409	28,197 ± 14,936*
Satisfaction	27,798 ± 10,747	41,311 ± 7957*
Full	29,892 ± 14,289	44,827 ± 14,454*
Prospective Consumption	48,287 ± 13,802	32,651 ± 12,947*
Sweet	33,206 ± 21,115	48,706 ± 19,692*
Salty	43,393 ± 21,338	59,214 ± 17,284*
Savoury	31,534 ± 18,257	50,161 ± 17,358*
Fatty	43,266 ± 16,960	61,226 ± 16,459*

[1]Values are means ± SD, n = 14. * $P < 0.05$

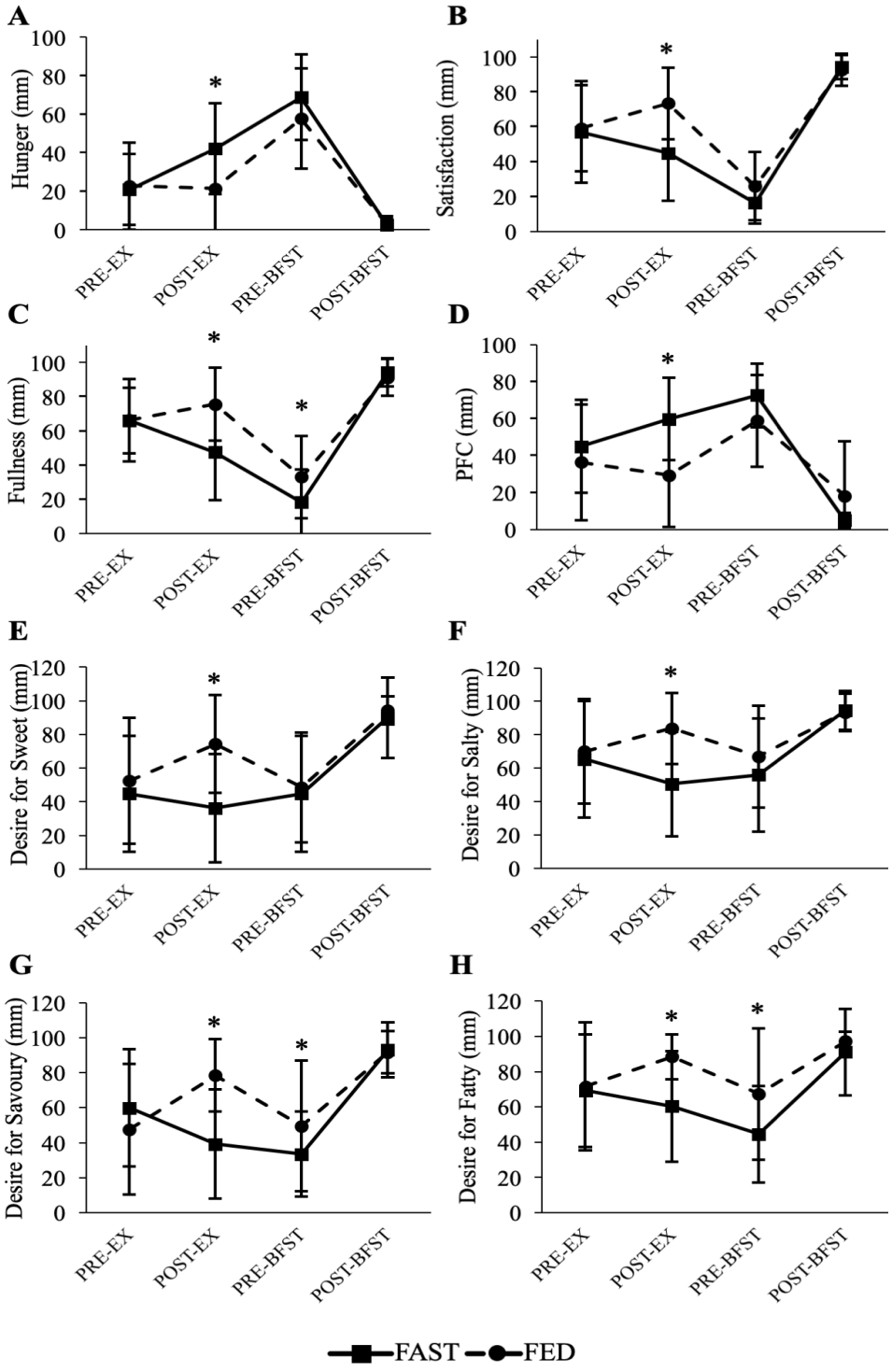

Figure 2.2: Change of appetite perception as assessed through VAS over both experimental sessions for A) hunger, B) satisfaction, C) fullness, D) PFC, E) desire for something sweet, F) desire for something salty, G) desire for something savoury, and H) desire for something fatty. Values are means ± SD, n = 14. (FAST: Water Control; FED: Sweetened Milk; PRE-EX: Pre-exercise baseline measurement; POST-EX: Post-exercise; PRE-BFST: Pre-breakfast, fasted measurement; POST-BFST: Post-breakfast). *: significant difference between sessions where $P < 0.05$.

Energy Intake

Energy intake assessed through food diaries had a significant main effect of time ($P < 0.005$), but no significant main effect of session ($P = 0.33$). Within session comparisons revealed that during both FAST and FED sessions, participants consumed significantly more calories the day after exercise (Day 2) than on Day 1 (FAST: $P = 0.001$, $d = 1.09$; FED: $P = 0.002$, $d = 0.96$) and Day 3 (FAST: $P = 0.009$, $d = 0.68$; FED: $P = 0.007$, $d = 0.85$) (Figure 2.3). There were no significant differences between Day 1 and Day 3 for either trial ($P = 0.19$ and $P = 0.64$ for FAST and FED, respectively). Total energy intake (TEI) analyses revealed that over the course of the 3-days, FAST consumed significantly less total calories than FED ($P = 0.033$; $d = 0.42$).

There were no significant differences between FAST and FED in *ad libitum* breakfast energy intake, where FAST consumed 734 ± 252 kcals and FED consumed 673 ± 227 ($P = 0.24$).

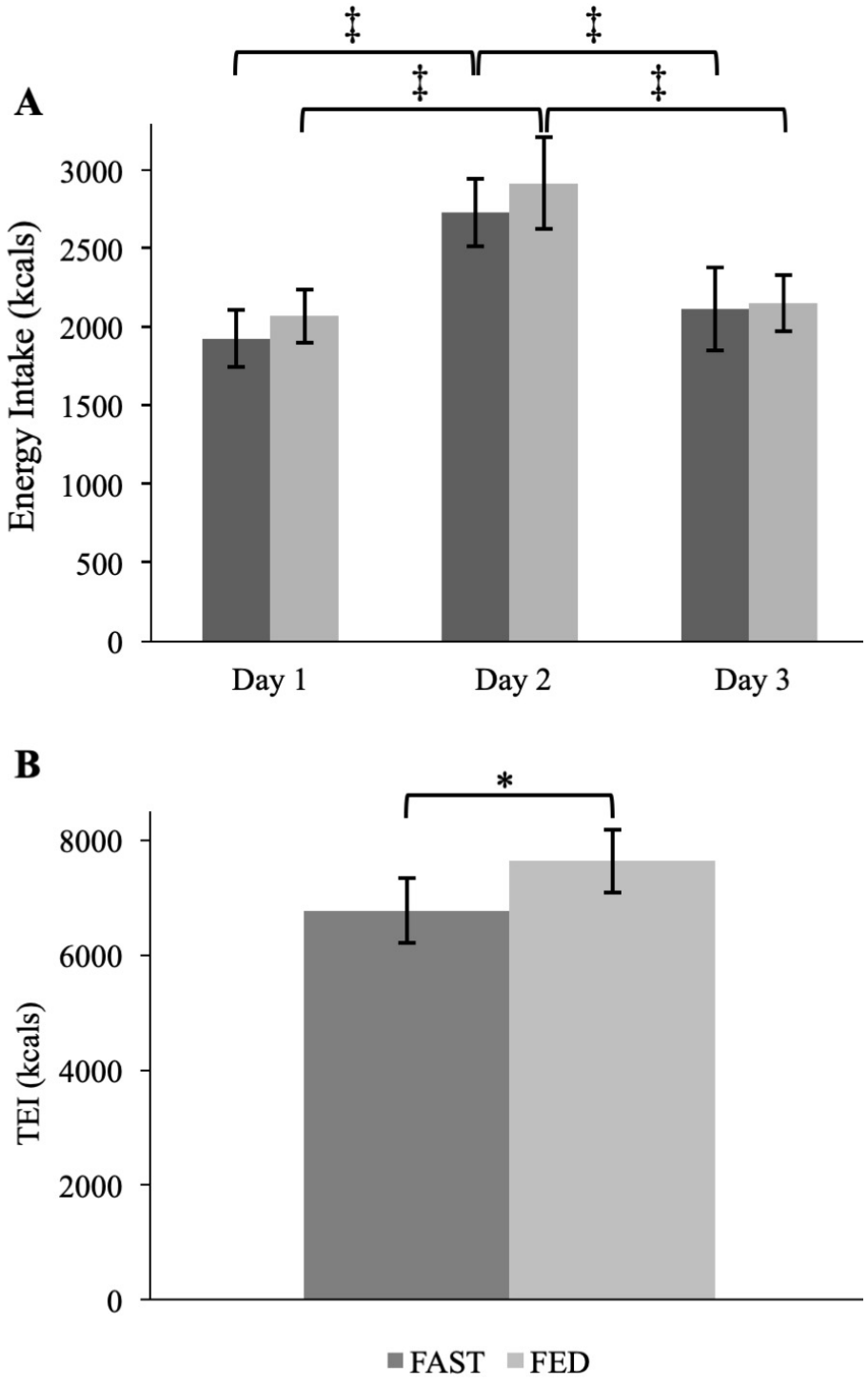

Figure 2.3: A) Daily energy intake over 3 days where Day 1 is the day of exercise, Day 2 including the *ad libitum* breakfast, and Day 3 being the 2nd day after exercise. B) Total energy intake over the 3-day food diaries. Values are means ± SD, n = 14. (FAST: Water control and FED: Sweetened Milk). ‡: significant main effect of time relative to day 1 and day 3, $P < 0.05$; *: Significant difference between sessions, $P < 0.05$.

Appetite Regulatory Signals

Plasma GLP-1

During FED, participants had a significantly larger change in GLP-1 concentrations from PRE-EX to POST-EX in comparison to FAST ($P = 0.025$; $d = 0.90$) (Figure 2.4A). Within session during FAST participants had significantly higher concentrations of GLP-1 at PRE-EX compared to POST-EX ($P = 0.028$; $d = 0.63$), whereas there was no significant difference between PRE-EX and POST-EX during FED ($P = 0.13$). There was also no significant difference in fasted concentrations of GLP-1 ($P = 0.99$).

Plasma Total PYY

During FED participants had a significantly larger change from PRE-EX compared to FAST at POST-EX ($P = 0.002$; $d = 1.12$) (Figure 2.4B). During FAST participants, had significantly higher PYY levels at PRE-EX in comparison to POST-EX ($P = 0.013$; $d = 0.66$), whereas PRE-EX levels during FED tended to be lower than POST-EX ($P = 0.08$; $d = 0.27$). There were no significant differences in fasted PYY concentrations ($P = 0.37$).

Plasma Active Ghrelin

There were no significant differences between FAST and FED in the change in levels of active ghrelin from PRE-EX to POST-EX ($P = 0.104$) or between levels of active ghrelin at PRE-BFST ($P = 0.69$) (Figure 2.4C). FED had significantly higher levels of active ghrelin at PRE-EX in comparison to POST-EX ($P = 0.02$; $d = 0.65$), whereas FAST had no difference between PRE-EX and POST-EX ($P = 0.67$).

IL-6

There were no significant differences in the relative concentrations of IL-6 at POST-EX ($P = 0.84$), or between PRE-BFST concentrations of IL-6 ($P = 0.87$) (Figure 2.4D). Throughout both FAST and FED participants had significantly increased concentrations of IL-6 at POST-EX in comparison to PRE-EX (FAST: $P = 0.024$, $d = 0.27$; FED: $P = 0.051$, $d = 0.27$).

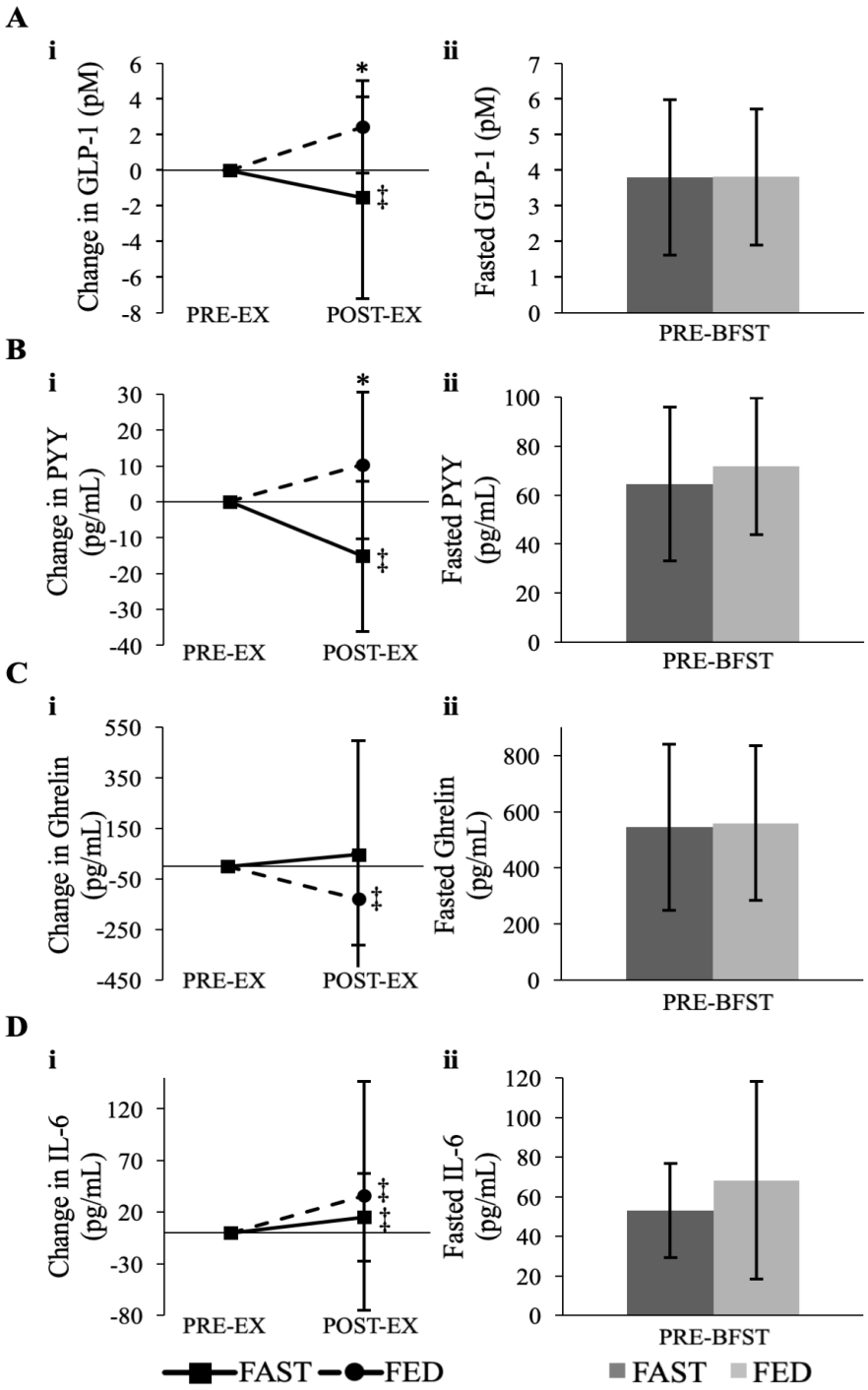

Figure 2.4: Hormone levels throughout each trial. i) represents the relative change in levels from PRE-EX to POST-EX, and ii) displays fasted levels the morning after exercise, as well as A) displays GLP-1, B) PYY, C) active ghrelin, and D) IL-6. Values are means ± SD, n = 14 for PRE-EX and PRE-BFST, n = 13 for POST-EX. (FAST: Water control and FED: Sweetened Milk). *: significant difference between sessions, $P < 0.05$. ‡: significant within session difference, $P < 0.05$.

Discussion and Conclusion

In this study we compared the effects of a fasted or fed state on post-exercise appetite and energy intake in individuals with overweight. We found that POST-EX concentrations of GLP-1 and PYY relative to PRE-EX concentrations had a significantly larger decrease during FAST compared to FED. Along with decreased anorexigenic hormones, during FAST participants reported significantly more hunger, prospective food consumption, and desire for sweet, salty, savoury, and fatty foods, while reporting significantly decreased satisfaction. Despite the lack of differences in energy intake with the *ad libitum* breakfast, participants in both trials significantly increased their energy intake the day after exercise (Day 2), demonstrating that there may be an increase in compensatory eating patterns after an acute bout of exercise in both the FED and FAST sessions. Overall, despite the increased orexigenic response immediately following exercise in the fasted state, 3-day food record analysis suggests that total energy intake remained greater during FED compared to FAST.

Exercise has generally been shown to elicit anorexigenic effects after a single acute bout of vigorous exercise (3, 25, 26). Unlike our findings, an abundance of research has demonstrated that ghrelin is suppressed while levels of PYY and GLP-1 increase (3). Panissa et al. (26) found that 20 adults subjected to 3 different bouts of acute aerobic exercise and a no-exercise control session had lower AUC for acylated ghrelin as exercise intensity increased as compared to the control, and that relative energy intake including a pre-exercise standardized breakfast and an *ad libitum* lunch was significantly lower for all exercise sessions compared to the control. Similarly, Hazell et al. (27) found that in 10 active men subjected to moderate intensity continuous exercise, high intensity continuous exercise, or sprint interval training, PYY concentrations were significantly increased after

high intensity exercise in comparison to control. In our study, we found that concentrations of PYY and GLP-1 increased 1-hour post-exercise when participants were fed immediately after exercise; whereas, when they fasted PYY and GLP-1 concentrations decreased. In the two previously mentioned studies, the post-exercise blood draws were completed immediately after exercise, exercise was initiated in the morning after a standardized breakfast, and the exercise trials were compared to a no-exercise control session. In our study, our post-exercise blood draw was 1-hour after exercise and participants began exercise in the evening 2-hours after a full-day of free-living food intake. Our participants also had a higher average (26.9 ± 3.5 kg/m^2) and a larger range ($23.0 – 33.7$ kg/m^2) of BMI in comparison to these studies.

The hormone response to vigorous aerobic exercise has been observed to differ between those who are lean and those with overweight or obesity (8-11, 28, 29). A study by Adam and Westerterp-Plantenga (30) found that 27 previously sedentary individuals with obesity had no difference between GLP-1 AUC levels after 1-hour of exercise at 25% of their maximum power output in a fasted state, compared to a non-exercise, rest session. Similarly, in a study comparing runners to walkers working at 70% of their VO_{2max} for 1-hour, it was found that the walkers, who had a significantly higher fat-mass than the runners, appeared to have a blunted acyl-ghrelin response, and no significant change in AUC compared to a rest session (9). Interestingly, we observed an increase in post-exercise concentrations of ghrelin and reduction in PYY and GLP-1 in the FAST session. The changes in these hormones post-exercise opposes what would be anticipated based on previously published post-exercise appetite-regulation research. Although our

study did not contain a non-exercise comparison session, the post-exercise hormonal changes suggested an acute orexigenic effect with exercise.

Long-term exercise interventions have demonstrated that there is generally a high level of energy compensation (13, 31). Riou et al. (31) showed in a systematic review that energy compensation reaches 84% as the length of exercise intervention increases, regardless of fat mass or age. Wan et al. (32) also observed that previously trained, lean and healthy cyclists, when given either reduced-fat chocolate milk or a low-calorie sports drink post-exercise, modified their energy intake based on the post-exercise energy intake. Regardless of whether athletes consumed a low calorie or high calorie, post-exercise beverage, total caloric intake did not differ after 28hrs. This highlights that recreationally active individuals may modulate energy intake to maintain energy balance. The post-exercise increase in appetite observed in our study would suggest a similar response in energy compensation. However, while we found that FAST consumed more *ad libitum* breakfast compared to FED (734 vs. 673 kcals, respectively), the difference was not significant. Similar *ad libitum* energy intake between these two sessions may be explained by concentrations of GLP-1, PYY, and active ghrelin in the FAST group returning to levels matching those of FED the morning after exercise. In keeping with the observation that *ad libitum* intake was the same, energy intake calculations from Day 2 and Day 3 food records suggests that energy intake was the same between the two trials. When accounting for post-exercise recovery beverage with the feeding trial, overall 3-day EI with FAST was significantly lower than FED. So, despite post-exercise energy consumption increasing post-exercise satiety in the FED trial, our participants still consumed significantly more calories over 3-days (3-day TEI FAST = 6771 ± 2098, and FED = 7138 ± 2021 kcals). However, these 3-day energy intake assessments relied on

food records, which are prone to error (33). More research is required to accurately examine long-term energy compensation with exercise.

It has been proposed that IL-6 concentrations may mediate anorexigenic effects of acute exercise through its effects as a myokine (7). As anticipated, we observed that IL-6 concentrations were significantly increased from PRE-EX to POST-EX, however IL-6 concentrations were not significantly different between sessions. The similar IL-6 pattern and differential satiety hormone secretion between sessions and reduction in GLP-1 and PYY in the FAST group suggests that IL-6 may not have played a prominent role in the secretion of satiety hormones in our study. The differential patterns between FED and FAST are likely the result of nutrient intake rather than exercise mediated mechanisms (34-36). Interestingly, previous research has observed that in individuals with obesity, the typical appetite hormone response may be blunted compared to lean individuals. Heden et al. (8) showed that 14 individuals with obesity had no change in acylated ghrelin after exercise compared to a rest session, as well as the post-prandial satiety response to a meal the morning after exercise was decreased in comparison to normal weight individuals. Given this differential response, it may be possible that total energy compensation in a lean group of individuals may be reduced with post-exercise nutrient intake compared to individuals with overweight or obesity.

It will be important to address further dietary interventions for appetite-regulation after exercise in attempt to decrease chronic energy compensation the day after an acute bout of exercise rather than only immediately post-exercise in individuals with overweight or obesity. The extent to which various macronutrients impact the post-exercise satiety response also requires further investigation. For example, research in recreational athletes shows increased satiety with skim milk relative to an isocaloric post-

exercise orange juice beverage (37). There is also a large cultural interest in the principle of fasting for weight loss, which may mediate appetite-regulation differentially from continuous energy restriction. We observed similar concentrations of GLP-1, PYY, and active ghrelin the morning following exercise, despite the differences in post-exercise energy consumption. While intermittent fasting has not been found to produce different weight loss from a continuous energy restricted diets (38), there is growing interest in time-restricted feeding as an effective tool to manage weight (39). While fasting after exercise may be challenging for individuals given the acute increase in hunger, with evidence that appetite-regulating hormones are normalized the morning following exercise regardless of energy intake, a post-exercise fast may be a viable option to help manage appetite and weight. Thus, more research is necessary to clarify the effects of fasting, or other possible dietary strategies, on appetite regulation after exercise for weight maintenance or loss.

This study has several limitations. Firstly, our study did not include a rest session and therefore it is unknown how the objective and subjective measures of satiety with exercise in a fed or fasted state would compare to rest. Similarly, we utilized 3-day food diaries which have been demonstrated to have high levels of bias due to self-report and are prone to error (33). Furthermore, our assessment of appetite-regulating hormone concentrations was 1-hour post-exercise, whereas most assessments occur immediately after exercise which may account for some differences between our observations and previously published literature. Similarly, we had a wide range of BMI measurements which may change post-exercise appetite responses.

In conclusion, fasting after exercise may increase subjective measures of hunger and temporarily increase orexigenic hormones 1-hour post-exercise. However, these

changes do not remain the day after exercise. Further research is needed to determine the effects of post-exercise energy intake and nutrient modification on energy compensation for individuals with overweight or obesity. Strategies to mitigate energy compensation may be necessary for exercise to be efficacious for weight loss and maintenance, allowing for individuals to maintain exercise and attain the associated metabolic benefits.

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Chapter 3: Post-exercise prebiotics help to reduce appetite and energy intake in adults with overweight

Abstract

Evidence suggests that exercise, despite being recommended for weight management, is not effective for weight loss in part due to compensatory energy intake (EI). Enhancing the effectiveness of exercise for weight loss may be accomplished through dietary strategies that help to suppress appetite and EI post-exercise. Prebiotics have been shown to increase hormones that induce satiety, decrease energy intake, and therefore induce weight loss. Thus, a prebiotic may be beneficial in decreasing compensatory energy intake post-exercise. Our aim was to determine if the consumption of a prebiotic fiber post-exercise increases satiety and decreases EI after an acute bout of exercise in individuals with overweight. In a randomized crossover study, participants (BMI: 26.9 ± 3.5 $kg \cdot m^{-2}$, 18-50yrs) received one of two recovery beverages: 1) sweetened-milk (SM) or 2) sweetened-milk + 20g prebiotic (SM+P) after completing a 45min (65-70% VO_{2peak}) exercise session ~2hrs after dinner. Fasted *ad libitum* breakfasts the morning after exercise and 3-day food diaries assessed energy intake. Blood samples were collected to assess satiety hormones (GLP-1, PYY, and acyl-ghrelin) and visual analogue scales measured subjective appetite. During SM+P, participants reported significantly increased satisfaction in the fasted state the morning after exercise and had decreased AUC for hunger. There was a larger relative increase in GLP-1 during SM+P from baseline to post-drink, although this did not reach statistical significance (P=0.053). Participants also consumed fewer calories during the *ad libitum* breakfast during SM+P

compared to SM. Therefore, the addition of a prebiotic fiber to a post-exercise meal may increase satiety, thereby decreasing EI after an acute bout of exercise.

Introduction

Chronic exercise interventions, despite increasing overall energy expenditure, have been shown to yield weight loss results that are less than anticipated (1, 2). This is problematic given that 65% of individuals attempting to lose weight use exercise (3). Furthermore, evidence suggests that the weight loss that is achieved via exercise is not commonly maintained past 1 year (4-7). Myers et al. (2) observed that after a 12-week pre-post exercise intervention in 24 women with overweight, total energy intake and pre-meal hunger were significantly increased and fullness was decreased. Participants only lost 22% of the predicted weight loss based on the increased energy expenditure with the exercise intervention. Unsuccessful weight loss with exercise can serve to reduce the satisfaction with exercise outcomes as well as the motivation to continue and maintain exercise patterns (8). This is particularly concerning given that the cessation of exercise negates many of the weight-independent benefits of exercise such as increased insulin sensitivity, decreased blood pressure and triglycerides, and increased cardiorespiratory fitness (9). Since body weight is a large motivating factor for many individuals, it is important to understand both the mechanisms of energy compensation and how the efficacy of exercise for weight loss can be improved using strategies that help to limit energy compensation. As recently noted in a study by Blundell and colleagues (2), specific dietary strategies may be necessary to aid in appetite regulation and decrease compensatory energy intake for chronic exercise interventions.

Appetite regulation governs energy intake through the complex interaction of neurohormonal signaling mechanisms and environmental cues. Anorexigenic and orexigenic appetite-regulating hormones aid in creating feelings of satiety and hunger, respectively. Anorexigenic hormones include peptide tyrosine-tyrosine (PYY), glucagon-

like peptide-1 (GLP-1), leptin, and insulin. Ghrelin, released from the stomach, is the only known orexigenic hormone. GLP-1, PYY, and ghrelin are acute (meal-by-meal) satiety regulators, whereas insulin and leptin are long-term energy balance regulators (10). Exercise, diet, and to some extent the presence of overweight and obesity have all been shown to modify appetite regulation through alterations in the secretion of appetite-regulating hormones (11-13).

Acute bouts of cardiovascular exercise have been shown to create anorectic effects in lean and normal weight individuals (14, 15); however, the appetite-regulating hormone response to exercise differs between normal weight and individuals with overweight and obesity (16-18). While levels of PYY and GLP-1 increase and ghrelin decreases in normal weight individuals, these changes are blunted or not seen in individuals with overweight or obesity. Similarly, postprandial appetite-regulating hormone responses may be blunted in individuals with overweight or obesity (15). These differences in hormone response may contribute to increased compensatory energy intake after exercise and lower than anticipated amounts of weight loss with exercise (2). Based on measures of fat free and fat mass after long-term exercise interventions it is estimated that energy compensation reaches ~84% (19). Given this degree of energy compensation, strategies that modulate post-exercise appetite response to decrease energy compensation are warranted to support weight loss and sustained recreational activity in those using exercise for weight loss.

A method of modulating appetite regulation is through dietary strategies. One dietary strategy is the implementation of a prebiotic supplement. A prebiotic is a substrate that is selectively utilized by the host microorganisms that promotes health benefits (20). Oligofructose is a type of fermentable prebiotic fiber that has been shown to increase

beneficial bacteria and their metabolic byproducts, short-chain fatty acids (SCFAs) which elicit increased secretion of the satiety hormones GLP-1 and PYY (21-26). Some chronic prebiotic supplementation studies have found significant reductions in body weight in both adults (27) and children (28). To date, no studies have examined the impact of prebiotics on satiety hormone secretion after exercise in attempt to decrease energy compensation. Therefore, the objective of this study was to examine if a post-exercise prebiotic supplement modulates appetite regulation and energy intake after an acute bout of vigorous aerobic exercise in individuals with overweight or obesity.

Materials and Methods

Participants

14 adults (6 women and 8 men; BMI: 26.9 ± 3.5 $kg \cdot m^{-2}$) volunteered and provided written informed consent to participate in this study. To be eligible for the study, participants had to be healthy, have a BMI > 23 $kg \cdot m^{-2}$, and be recreationally active, defined as accumulating a minimum of 150 minutes per week of moderate to vigorous physical activity. Smoking, taking regular medication that could influence appetite, consumption of prebiotics or probiotics, lactose intolerance, or irritable bowel syndrome were exclusion criteria. To control for appetite fluctuations throughout the menstrual cycle (29, 30) female participants were tested in the early follicular phase (day 1-10) based on self-reported menstruation. All research was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. Ethical approval was obtained from the University of Lethbridge's Human Subject Research Committee, Protocol number #2017-094.

Preliminary Session

First, participants were screened for contraindications to the exercise through the Physical Activity Readiness Questionnaire (PAR-Q+), and Godin's Leisure Time Exercise Questionnaire (GLTEQ) determined habitual physical activity. A Restrained Eating Questionnaire, modified from de Lauzon et al (31) was also completed since restrained eating has been shown to decrease sensitivity to dietary modifications (32, 33) and may confound possible changes in energy intake. The questionnaire had a maximum possible score of 24 through 6 questions. A score of 24 would show total restraint. Height (nearest 0.1cm) and weight (nearest 0.1 kg) were measured using a mechanical beam scale (Heath-o-Meter, Sunbeam Products).

An incremental test to exhaustion on an electromagnetically braked cycle ergometer (Velotron, QUARQ, Spearfish, South Dakota, USA) was used to assess peak oxygen uptake (VO_{2peak}) using breath-by-breath analysis with a metabolic cart (Quark CPET, COSMED, Chicago, Illinois, USA). Following a 5-minute warm-up at a self-selected pace, participants cycled at 50W for 4-minutes at 80 rpm. After the 4-minutes the test increased by 25 W/min for women or 30 W/min for men until volitional failure or 80 rpm could no longer be maintained. Heart rate was measured continuously throughout the test by a Garmin heart rate monitor (HRM-Dual, Garmin, Olathe, Kansas, USA). At the end of the VO_{2peak} test, VO_{2peak} was determined to be the greatest 30-second average, which allowed for calculation of 65-70% VO_{2peak} for the target exercise intensity during the experimental trials.

Experimental Sessions

Participants completed two experimental arms, 1) sweetened milk (SM) (Vanilla Vibe, Milk2Go, Quebec, Canada), and 2) sweetened milk with 20 grams of a 50/50 mixture of inulin and oligofructose (SM+P) (Prebiotin, Jackson GI Medical,

Pennsylvania, USA). Sessions were completed in a randomized order with a wash-out period of at least one week for males and approximately one month for females. Each session took place at the same time of day. For each trial, participants completed a 3-day food diary starting the morning of the experimental session to measure energy intake. Participants were asked to maintain similar eating patterns for each experimental session. Upon arrival to the lab ~2-hours after consuming their dinner, participants were given an appetite and gastrointestinal perceptions visual analogue scale (VAS) for pre-exercise (PRE-EX) ratings. Once surveys were completed, PRE-EX venous blood samples were collected from the antecubital vein into precooled EDTA vacutainers while participants laid in the supine position. Following the blood draw participants completed a 45-minute cycling session at 65-70% of VO_{2peak}. Oxygen consumption was monitored continuously throughout each exercise session. A post-exercise drink of SM or SM+P (10 mL/kg body weight, average post-exercise energy intake = 495 ± 25 kcals) was given to the participants to finish within 10 minutes. Participants remained in the lab for 1 hour after consumption of the drink and were asked to refrain from consuming any liquids other than what was provided. One hour after consuming the drink, a post-exercise (POST-EX) blood sample was taken and another appetite VAS was completed. Participants were asked to refrain from eating or drinking anything with exception of water until arriving back at the lab the next morning. The time between when participants left the lab and came back in the morning was the same for each session completed.

The morning after exercise participants reported to the lab in a fasted state around the time they would typically consume breakfast. Pre-breakfast (PRE-BFST) appetite and gastrointestinal VASs were completed and a venous blood sample was taken. An *ad*

libitum breakfast meal was then provided to participants, consisting of pre-weighed instant oatmeal (Quaker, PepsiCo, USA), orange juice (President's Choice, Ontario, Canada), and coffee (Starbucks Pike Place instant coffee, Starbucks Corporation, Canada) or black tea (Pure Leaf, Unilever Canada) with cream (18% Dairyland single serve) and/or sugar (Rogers Natural Sugar Packs) to preference, all served in excess. In both sessions, the same quantity of breakfast food was provided. Participants were told to consume as much or as little as they would like until they were satisfied and had 30 minutes to do so. Once finished eating, participants filled out a final appetite perceptions VAS (data point denoted as POST-BFST). After participants finished the experimental session, the food was weighed again to determine (to within 1g) how much food was consumed. These weights were used to calculate energy intake based on manufacturers' nutrition labels. An overview of the timeline for each experimental session is shown in Figure 3.1.

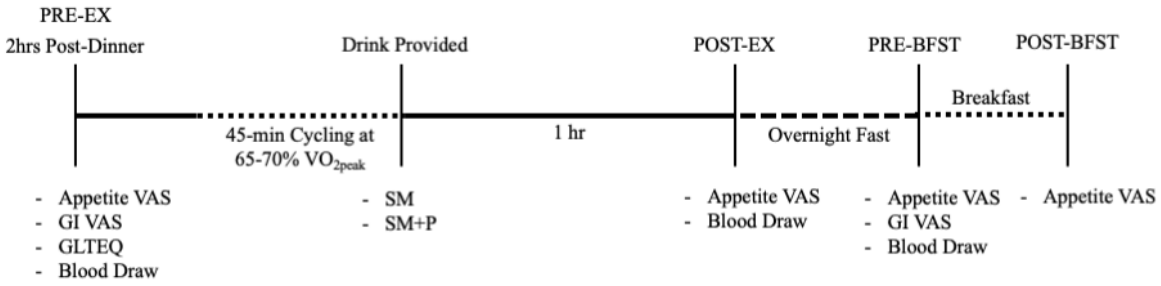

Figure 3.1: Timeline of experimental sessions. GI: Gastrointestinal; PRE-EX: Pre-exercise; POST-EX: Post-exercise; PRE-BFST: Pre-breakfast; POST-BFST: Post-breakfast; GLTEQ: Godin's Leisure Time Exercise Questionnaire.

Appetite Perceptions

Appetite perceptions were assessed using a validated 100 mm VAS (34). Each category of appetite perceptions was anchored at 0 mm and 100 mm with opposing statements that answered each question. There were eight aspects of appetite assessed:

hunger (anchored by “I am not hungry at all” and “I have never been more hungry”), satisfaction (anchored by “I am completely empty” and “I cannot eat another bite”), fullness (anchored by “Not at all full” and “Totally full”), prospective food consumption (PFC) (anchored by “Nothing at all” and “A lot”), and types of food participants desired to eat (Sweet, Salty, Savoury, or Fatty; All anchored by “Yes, very much” and “No, not at all”).

Gastrointestinal Perceptions

Gastrointestinal perceptions were assessed by 100 mm VAS. This questionnaire assessed how gastrointestinal feelings surrounding 5 separate categories have, on average, felt over the past 12 hours. Each category was anchored by opposing statements at 0 mm and 100mm. Abdominal comfort was anchored by “Greatly improved” and “Greatly decreased.” Abdominal Distention and Bloating, Flatulence or Passage of Gas, and Rumbling of your Stomach were all anchored by “No problem” and “Very Strong.” Number of Stools (bowel movements) was anchored by “0” and “4 or more.”

3-day Food Diaries

3-day food diaries included the day of exercise and 2 days afterwards. Participants could track intake with an online resource (MyFitnessPal™) or by written food diaries. To ensure compliance, email and verbal reminders were implemented. Participants were given a digital food scale and instruction on how to complete a food diary to increase the accuracy of the diet records. Once finished participants brought their food diaries to the lab. Diaries were inputted into FoodWorks 14 Software (The Nutritional Company, Long Valley, NJ). Calories from all three days for each session were added together to examine the total energy intake (TEI).

Blood Collection and Analysis

All blood samples were collected into 6 mL EDTA vacutainers. To prevent degradation of satiety hormones, DPP IV inhibitor (10ul/ml blood; MillporeSigma Corporation, Ontario Canada), sigma protease inhibitor (1mg/ml of blood; SigmaFast, MillporeSigma Corporation, Ontario Canada), and Pefabloc (1mg/ml of blood; MillporeSigma Corporation, Ontario Canada) was added to the blood samples. Samples were centrifuged at 2000 rpm for 10-minutes at 4°C. Plasma aliquots were stored at -80°C for later analysis.

The concentration of plasma hormones was determined using the Human PYY (Total) kits, High Sensitivity GLP-1 Active Chemiluminescent kits, and Human Ghrelin (Active) ELISA kits (MilliporeSigma Corporation, Ontario, Canada). Inter- and intra-assay variations were 3.09 ± 3.29% and 2.39 ± 1.14% for PYY, 6.20 ± 6.71% and 6.75 ± 5.46% for GLP-1, and 2.73 ± 3.11% and 2.11 ± 1.50% for acyl-ghrelin. All samples were assayed in duplicate and samples from one participant session were analyzed in the same assay to minimize the effects of inter-assay variation.

Statistical Analysis

Data were analyzed using the SPSS software v25.0 for Windows. POST-EX blood sample concentrations were normalized to PRE-EX values and analyzed as absolute change in concentration. Differences were examined using one-way or two-way repeated measures analysis of variance (ANOVA). When there was a main effect, a post-hoc LSD pairwise comparison was used to examine significant differences. Cohen's d (35) was calculated for all pairwise comparisons to examine the effect size. A small effect sized is defined as <0.2; moderate effect size 0.20 ≥ 0.80; and large effect size > 0.80. Area under the curve (AUC) analysis was completed for hormonal analysis and appetite perceptions.

AUC estimations were calculated using trapezoidal sums. Statistical significance was set at $P < 0.05$. All results are presented as mean ± standard deviation (SD).

Results

Subjects

Participants were 26.8 ± 6.7 years old with a BMI of 26.9 ± 3.5 $kg \cdot m^{-2}$, height of 174.5 ± 11.1 cm, and weight of 82.5 ± 15.8 kg. Female participants were tested on day 6.6 ± 6.7 of the menstrual cycle. The average VO_{2peak} was 37.3 ± 7.5 $mL \cdot kg^{-1} \cdot min^{-1}$, with the average exercise intensities being 68.0 ± 4.9% and 69.1 ± 3.7% for SM and SM+P, respectively. Average restrained eating scores were 12.2 ± 3.9.

Gastrointestinal and Appetite Perceptions

Flatulence ratings were slightly elevated between sessions at PRE-BFST, where participants reported reported increased levels of flatulence during SM+P compared to SM ($P = 0.052$; $d = 0.57$). There were significant within session changes during SM+P, including a significant decrease in abdominal comfort ($P = 0.005$) and increase in flatulence ($P < 0.005$) and rumbling ($P = 0.001$) from PRE-EX to PRE-BFST. There were no other differences found within the gastrointestinal perception categories (Figure 3.2).

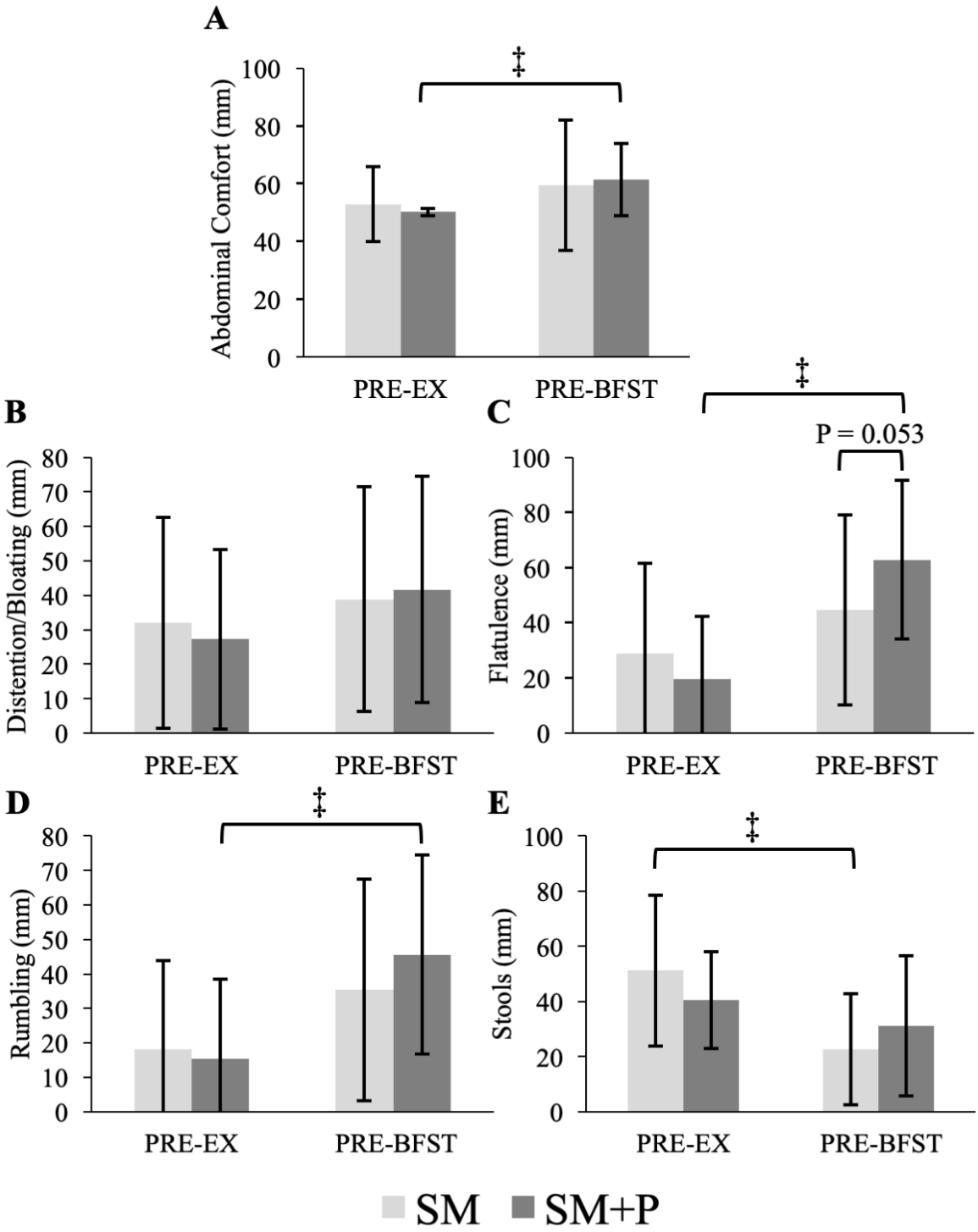

Figure 3.2: Change of gastrointestinal perceptions over 12 hours as assessed through VAS over both experimental sessions for: A) abdominal comfort, B) distention and bloating, C) flatulence, D) rumbling, and E) number of stools. Values are means ± SD, n = 14. (SM: Sweetened milk; SM+P: Sweetened milk + prebiotic; PRE-EX: Pre-exercise; PRE-BFST: Pre-breakfast). ‡: significant within session difference, where $P < 0.05$.

For appetite perceptions, participants reported increased satisfaction at PRE-BFST during SM+P compared to SM ($P = 0.046$; $d = 0.61$) (Figure 3.3B). Similarly, the AUC for satisfaction was numerically larger, but did not reach statistical significance ($P = 0.092$; $d = 0.49$) (Figure 3.4B). Hunger AUC was significantly lower during SM+P compared to SM ($P = 0.009$; $d = 0.29$) (Figure 3.4A). There were no other significant differences found for appetite perceptions.

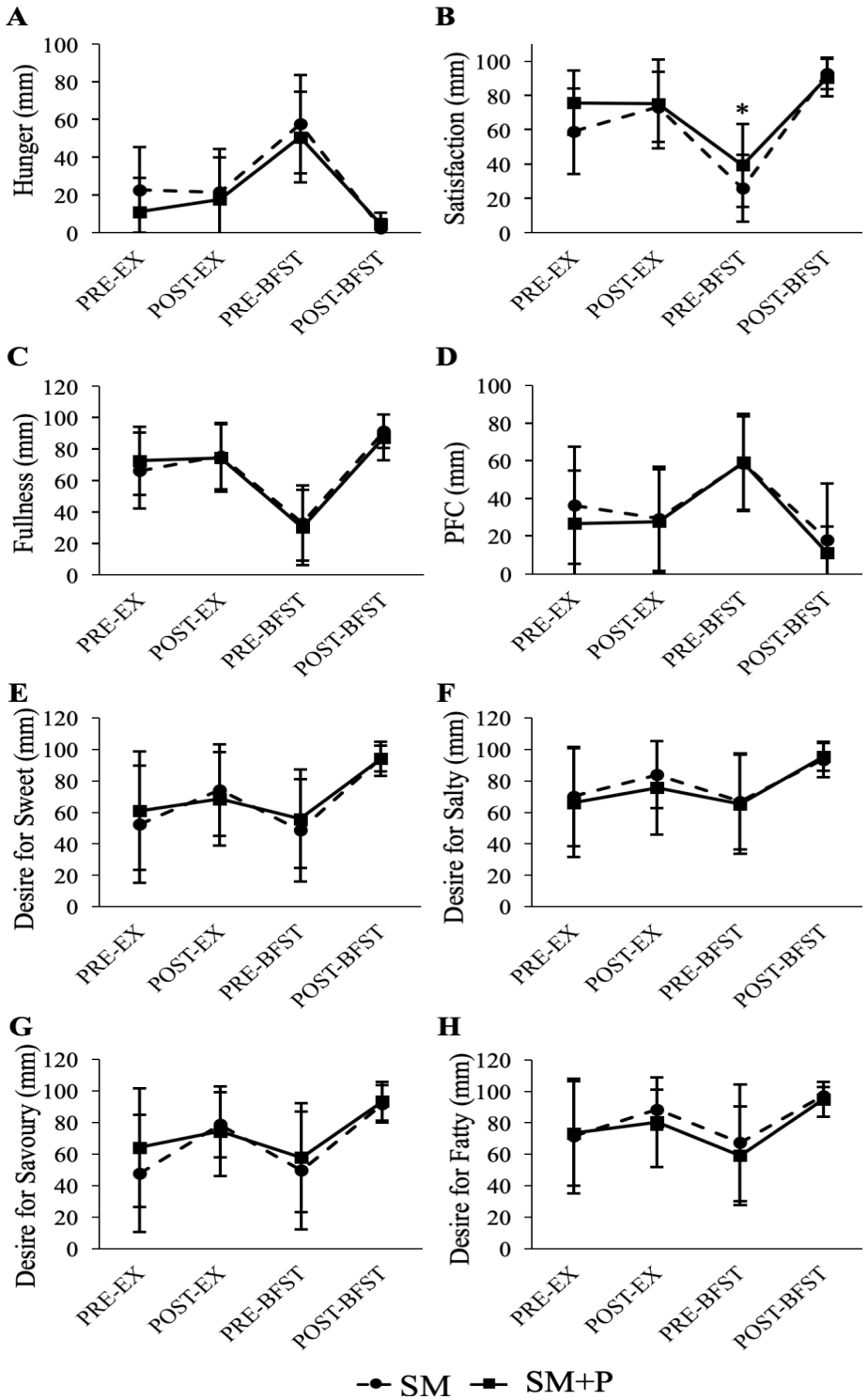

Figure 3.3: Change of appetite perception as assessed through VAS over both experimental sessions for A) hunger, B) satisfaction, C) fullness, D) PFC, and desires for E) something sweet, F) something salty, G) something savoury, and H) something fatty. Values are means ± SD, n = 14. (SM: Sweetened milk; SM+P: sweetened milk + prebiotic; PRE-EX: Pre-exercise; POST-EX: Post-exercise; PRE-BFST: Pre-breakfast; POST-BFST: Post-breakfast). *: significant difference between sessions, where $P < 0.05$.

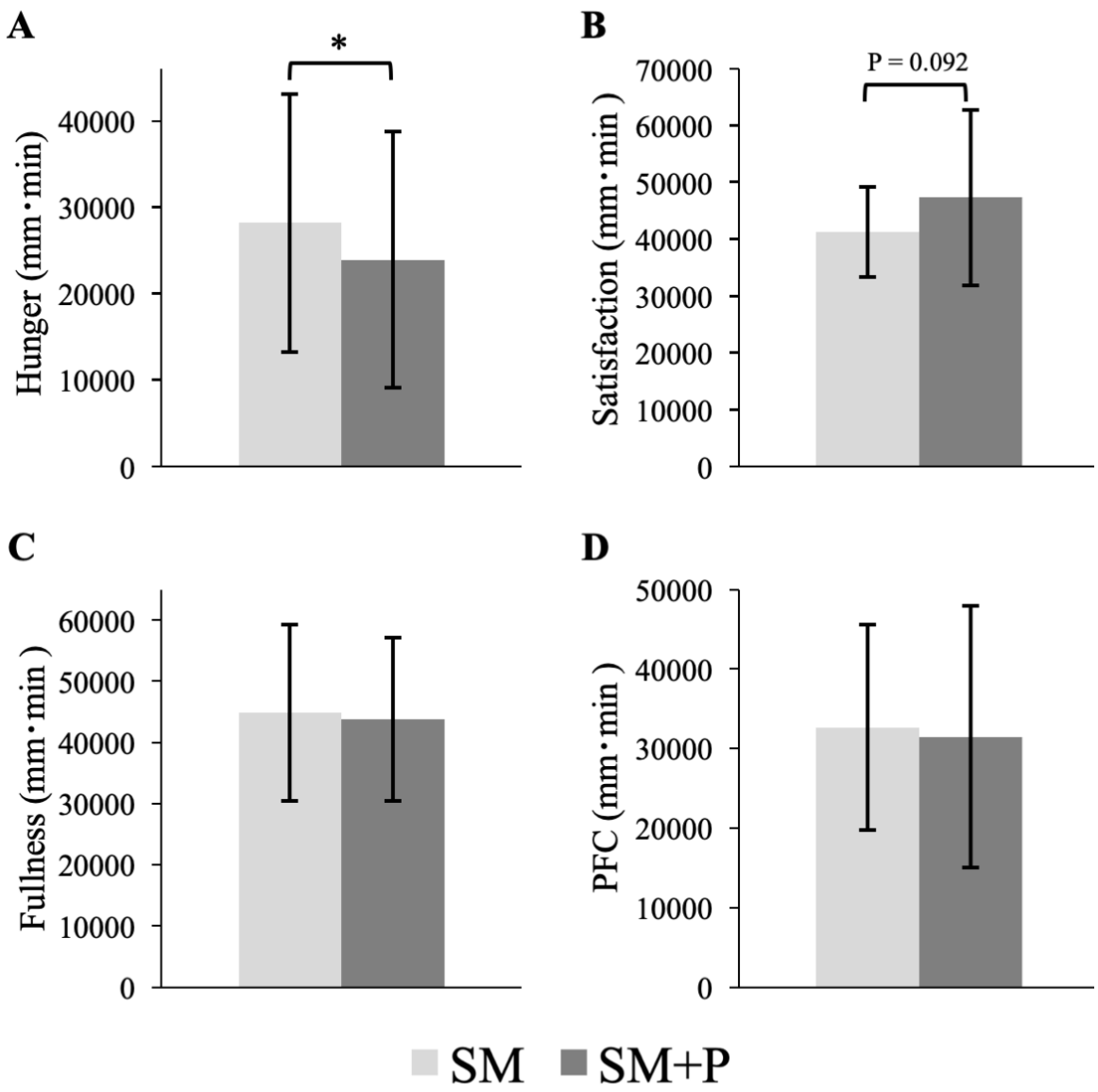

Figure 3.4: AUC for appetite perceptions as assessed through VAS over both experimental sessions for A) hunger, B) satisfaction, C) fullness, and D) PFC (SM: Sweetened milk; SM+P: sweetened milk + prebiotic; PFC: Prospective food consumption). Values are means ± SD, n = 14. *: significant difference between sessions, where $P < 0.05$.

Energy Intake

During SM there was a main effect of time for 3-day energy intake ($P = 0.001$). On Day 2 (the day after exercise) in the SM session participants consumed significantly more calories than on Day 1 ($P = 0.002$; $d = 0.96$) and Day 3 ($P = 0.007$; $d = 0.85$). In contrast, there was no significant effect of time during SM+P ($P = 0.072$) (Figure 3.5). Total EI remained the same between sessions ($P = 0.62$). During the *ad libitum* breakfast meal, participants consumed fewer calories during SM+P than SM, however this did not reach statistical significance (SM+P: 606 ± 55 kcal; SM: 673 ± 61 kcal; $P = 0.087$; $d = 0.31$) (Figure 3.5).

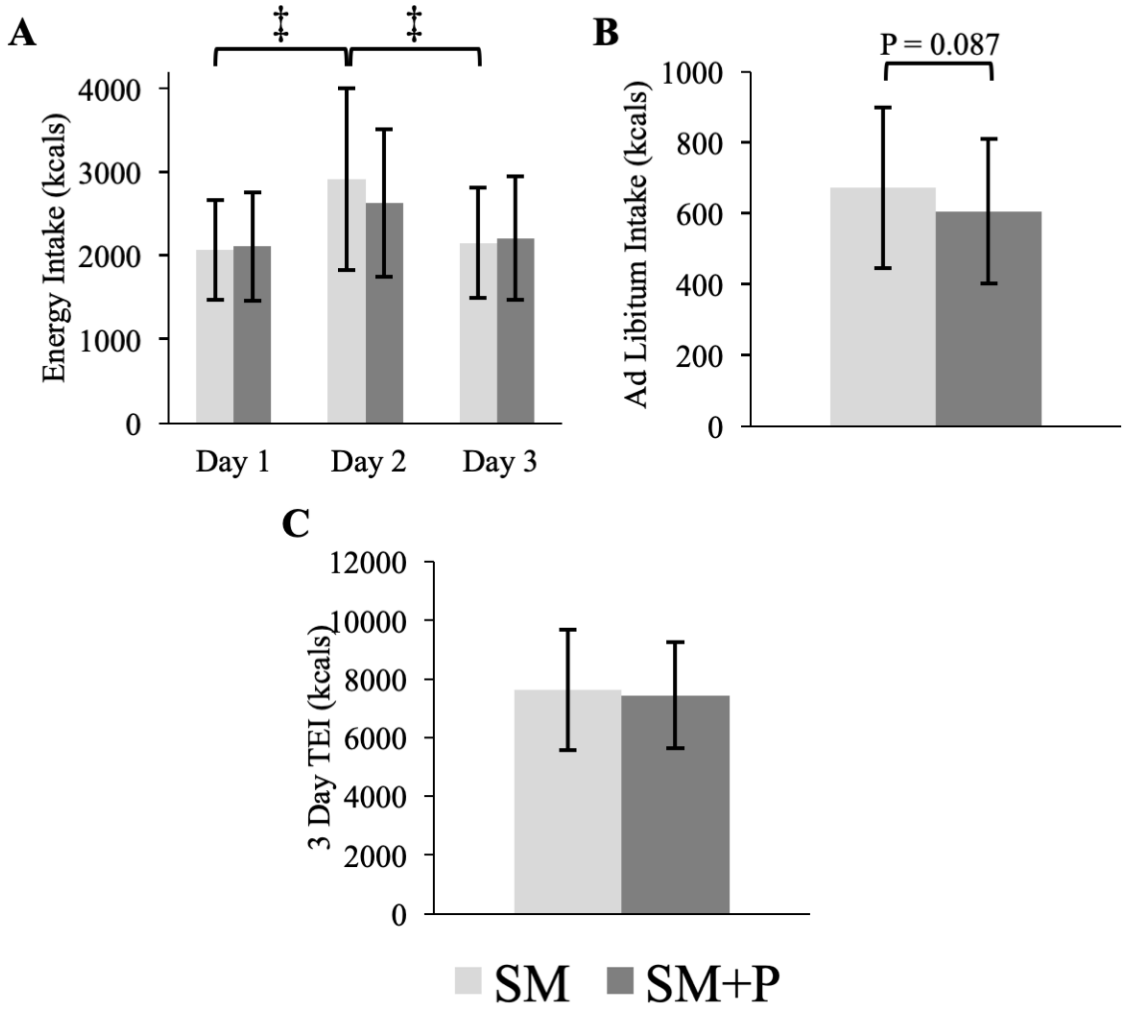

Figure 3.5: A) Daily energy intake over 3 days: Day 1 being the day of exercise; Day 2 including the *ad libitum* breakfast; Day 3 being the 2nd day after exercise, B) *ad libitum* breakfast energy intake, and C) 3-day TEI. Values are means ± SD, n = 14. (SM: Sweetened milk, and SM+P: sweetened milk + prebiotic; TEI: Total energy intake). ‡: significant main effect of time, where $P < 0.05$.

Appetite Regulatory Signals

Plasma GLP-1

Participants had a larger change in GLP-1 from PRE-EX to POST-EX during SM+P compared to SM, which was approaching significance ($P = 0.053$; $d = 0.55$) (Figure 3.6A). Within session during SM+P, participants had significantly increased GLP-1 concentrations at POST-EX compared to PRE-EX ($P = 0.001$; $d = 0.88$), whereas

the increase from PRE-EX during SM was not significant. There were no significant differences between sessions in the PRE-BFST concentrations of GLP-1 (P = 0.99).

Plasma Total PYY

Within session during SM+P, participants had significantly increased concentrations of PYY at POST-EX compared to PRE-EX (P = 0.02; d = 0.34). There was a tendency for PYY to increase during SM at POST-EX relative to PRE-EX (P = 0.08; d = 0.27) (Figure 3.6B). There was no significant difference between sessions at PRE-BFST (P = 0.363) or between sessions for the relative changes from PRE-EX to POST-EX (P = 0.31).

Plasma Acyl-Ghrelin

During both SM and SM+P participants had significant within session differences between PRE-EX and POST-EX, where PRE-EX concentrations of acyl-ghrelin were increased compared to POST-EX (SM: P = 0.02, d = 0.65; SM+P: P = 0.001, d = 0.97) (Figure 3.6C). The relative change in acyl-ghrelin from PRE-EX to POST-EX did not differ between sessions (P = 0.20) and levels did not differ between session at PRE-BFST (P = 0.69).

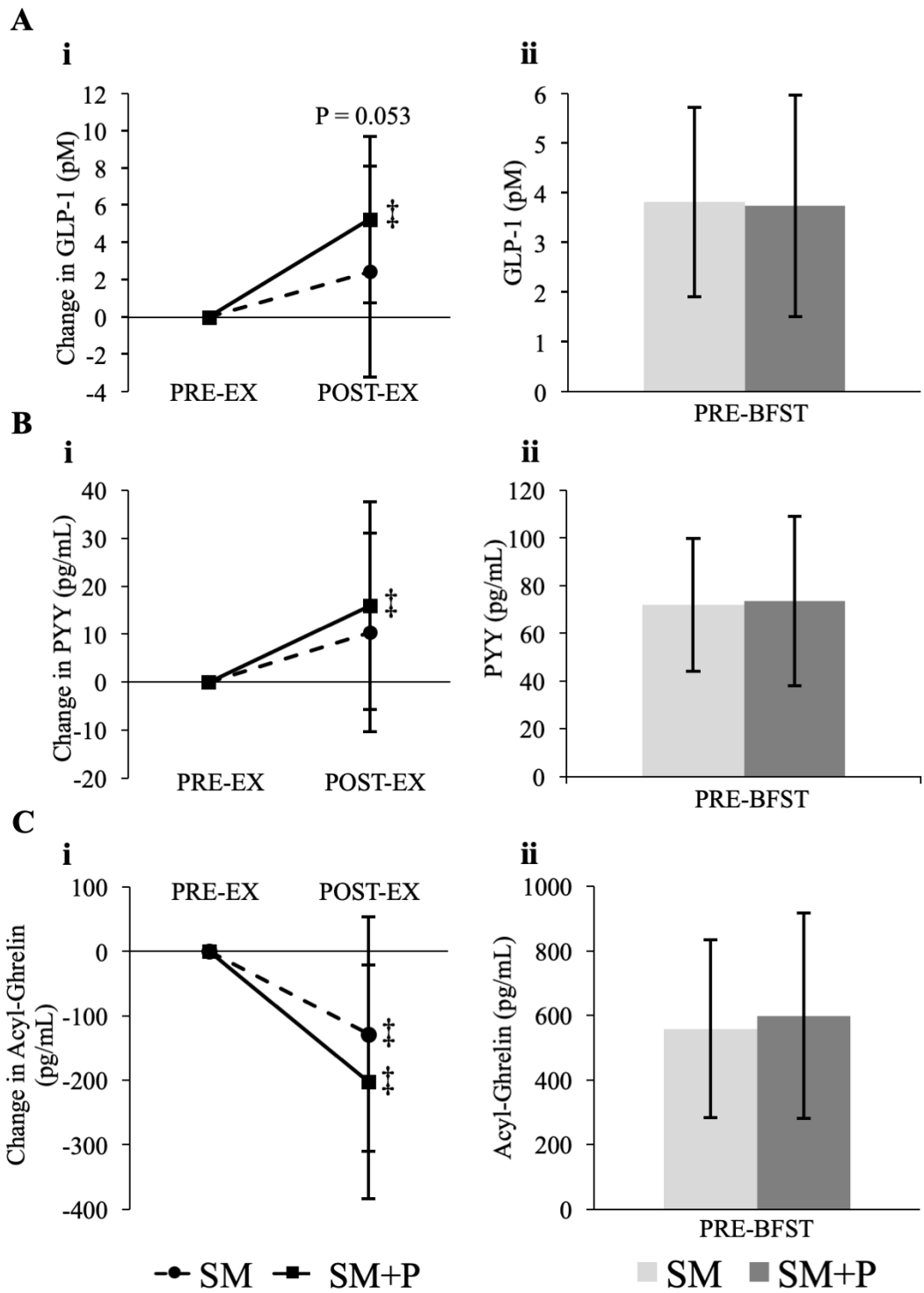

Figure 3.6: Hormone levels throughout each session. i) represents the relative change in levels from PRE-EX to POST-EX, and ii) displays fasted, PRE-BFST levels the morning after exercise, as well as A) displays GLP-1, B) PYY, and C) active acyl-ghrelin. Values are means ± SD, n = 14 for SM and n = 13 for SM+P. (SM: Sweetened milk and SM+P: Sweetened milk + prebiotic; PRE-EX: Pre-exercise; POST-EX: Post-exercise; PRE-BFST: Pre-breakfast). ‡: significant within session difference where $P < 0.05$.

Discussion and Conclusion

Given the evidence that exercise is associated with increased hunger and energy compensation, there is growing interest in the use of dietary strategies to control hunger during the post-exercise period. This study was the first to utilize a prebiotic fiber supplement after exercise in attempt to increase satiety and decrease post-exercise energy intake in individuals with overweight. We found that participants reported increased feelings of satisfaction the morning after exercise in the SM+P trial compared to SM. There was also a decreased AUC for hunger and a trend towards increased AUC for satisfaction during SM+P. These increased feelings of satiety may have aided in decreasing energy intake the day after exercise during SM+P, since when participants consumed SM their EI on Day 2 was significantly increased compared to day 1 and 3, which was not observed during SM+P. Participants also had increased relative levels of GLP-1 from PRE-EX to POST-EX during SM+P, as well as significantly increased levels of both GLP-1 and PYY at POST-EX compared to PRE-EX.

After an acute dose of 20g of a prebiotic supplement post-exercise, we found that participants had significantly increased satisfaction and a decreased AUC for hunger. We also observed that participants did not significantly increase their energy intake the day after exercise in comparison to the day of and the second day after exercise. In contrast, some previously published studies examining an acute period after a single exposure to a prebiotic have failed to find modification in subjective appetite ratings (36-39). However, evidence is still unclear since other studies have reported changes in energy intake. For example, a study of 20 healthy individuals who took two doses of 0g, 5g, or 8g of short-chain fructooligosaccharides over one day showed that the highest dose reduced energy intake in women, but not men, despite no change in subjective appetite ratings of hunger

and satiety (40). Potential explanations for the null findings with acute prebiotic doses include studies that utilized too small of a dose of prebiotic (9g) (39), pairing prebiotics with high fat beverages (37) or other high fibers foods (38), or utilizing too short of an observation and dosage period to allow for adequate fermentation of the prebiotic. The changes in hunger, satisfaction, and satiety hormones observed in our study may have been, in part, due to the increased observation period of approximately 12-hours which included an overnight fast. Furthermore, we examined the impact of inulin and oligofructose after exercise. Previous research has demonstrated that individuals with obesity can experience increased hunger and appetite after an acute bout of exercise. Providing a prebiotic during this increased hunger period may elicit a greater acute satiety response compared to a period when hunger levels might not be as elevated.

The mechanism for the increased feelings of satiety with the prebiotic may have been due to the increased concentrations of anorexigenic hormones GLP-1 and PYY 1-hour after the post-exercise drink. While the mechanisms by which prebiotics elicit their satiety-inducing effects is not completely elucidated, the fermentation of prebiotic fiber generates SCFAs (21) which have been demonstrated to induce the secretion of anorexigenic hormones GLP-1 and PYY in the gastrointestinal tract (22). Fermentation is commonly measured through increases in breath hydrogen. Studies have shown that levels of breath hydrogen increase in a dose-dependent manner within 2 hours of prebiotic supplementation (25, 36-38, 41). While exercise (15) and nutrient intake (42) have also been observed to increase the secretion of the anorectic hormones, the increases observed in GLP-1 and PYY in our study with SM+P relative to SM are likely due to prebiotic fermentation since both sessions included the same exercise intensity and post-exercise recovery beverage. The changes in satiety hormones observed during SM can

likely be attributed to the combined impact of the exercise and post-exercise nutrient-intake.

While short term, acute studies have yielded mixed findings in regards to the satiety-inducing effects of prebiotics, longer-term interventions highlight the effectiveness of a prebiotic supplement for inducing satiety. In a systematic review by Kellow et al. (13), prebiotic supplementation in healthy individuals was shown to significantly increase feelings of satiety. Similarly, Cani et al. (41) showed that 2 weeks of 16g/day in healthy adults given a mixture of inulin and oligofructose increased subjective satiety, beginning 10 minutes after receiving a dose. It has also been shown that after 8-weeks of 30g/day of prebiotic supplementation in healthy individuals with overweight or obesity, hunger and motivation to eat were decreased (25). A study of 55 individuals with overweight or obesity and whom consumed 16g of oligofructose in granola bars or a control bar daily for 12 weeks found that hunger and prospective food consumption were significantly decreased at 12-weeks (43). Furthermore, in a 5-week dose escalation study, where dosage began at 15g/day and finished at 55g/day at the fifth week, participants' hunger decreased significantly at levels greater than or equal to 25g/day in a linear fashion with dosage (44). Although, in another long-term study in healthy individuals with overweight or obesity, 21g/day of oligofructose was not shown to increase satiety, but did significantly increase weight loss while decreasing energy intake (45). The impact of a long-term study using post-exercise prebiotics has yet to be examined. With evidence that prebiotics elicit a satiety-inducing effect with an acute dose after exercise, it is possible that consistent consumption of prebiotics after the completion of an exercise session may help to overcome the orexigenic effects of long-term exercise interventions for individuals with obesity.

In our study, we found that taking a post-exercise prebiotic increased flatulence and resulted in within-session decreases in abdominal comfort and increased rumbling from PRE-EX to PRE-BFST. Other studies assessing supplementation with a prebiotic have reported similar gastrointestinal side effects. Karalus et al. (36) found that 22 healthy women who were given 4 different types of fermentable fibers all experienced significantly increased bloating and flatulence, with oligofructose causing the largest change. Similarly, Bonnema et al. (46) found that both 5g and 10g doses of native inulin or oligofructose produced mild gastrointestinal bloating and flatulence, with the symptoms increasing in a dose-dependent manner. Other studies note that, when given a prebiotic supplement, most participants experience gastrointestinal side effects with ranging severity (44, 47); however, severe symptoms are typically only found in ~1% of individuals (48) and dosages of up to 20g daily for 2-weeks are well tolerated (47). Thus, it is necessary to further examine the effects of chronic prebiotic supplementation with exercise to determine the sustainability of interventions.

This study has several limitations. The 3-day food diaries that we utilized to assess energy intake have been demonstrated to have high levels of misreporting and recall bias (49). Inaccurate self-reported food consumption and error associated with diet analysis may have potentially affected energy intake calculations between sessions. Furthermore, our study also did not include a rest session which would have allowed comparison of subjective and objective measure of satiety between rest and activity, as well as how the effect of a prebiotic supplement may compare between rest and activity. The changes in appetite within the study may also be confounded by the large range in BMI within our participants (23.0 – 33.7 $kg \cdot m^{-2}$), as well as there were no direct measures of adiposity. Thus, since appetite regulation responses may vary with BMI and adiposity levels (15,16)

the changes observed may not truly reflect changes individuals with overweight may experience. Lastly, we do not include any direct measurements of prebiotic fermentation, gut microbiota changes, or levels of SCFAs.

In conclusion, a prebiotic supplement may increase measures of subjective and objective satiety and aid in mitigating increased energy intake the day after exercise. Further research is necessary to determine if chronic prebiotic supplementation after exercise limits overall energy compensation and aids in supporting sustainable weight loss with exercise interventions.

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Chapter 4: General Discussion

Introduction

It is well known that obesity increases the risk of many preventable chronic diseases (1-4). As obesity rates continue to rise it has become increasingly more important to find methods to mitigate obesity pathogenesis. Despite obesity being a multifaceted and highly complex disease, positive energy balance is a central contributor to the development of obesity (5). Lifestyle changes are commonly recommended to decrease energy intake or increase energy expenditure in attempt to lose weight and create an energy deficit (6, 7). Although, many individuals with overweight or obesity who take part in exercise regiments to lose weight typically lose less weight than what would be anticipated due to the increased energy expenditure.

The less than anticipated amounts of weight lost may be due to biological compensatory mechanisms that increase energy intake or decrease energy expenditure to maintain one's weight. It has been shown through a meta-analysis of long-term exercise interventions (8), as well as in a 12-week pre-post exercise intervention for weight loss with women with overweight (9), that caloric energy compensation increases as time spent in an exercise regime increases. Since energy compensation occurs post-exercise in individuals with overweight or obesity it is necessary to understand appetite-regulatory mechanisms governing energy intake after exercise to allow for exercise efficacy for weight loss.

Two factors that are known to modulate appetite are exercise and diet. It has been found that acute bouts of exercise in lean and healthy individuals decrease subjective satiety (10), and suppresses acylated-ghrelin while concomitantly increasing PYY and

GLP-1 (11). Although, individuals with overweight or obesity may have differential appetite-regulating responses to exercise (10, 12). Similarly, it is well known that nutrient intake increases the release of satiety hormones (13). The composition of the intestinal microbiota has also been shown to modify appetite; however, the composition of the gut microbiota can be modulated by both physical activity and diet. To highlight this, it has been observed that men who were extremely active rugby players, in comparison to less active men, had a gut microbiota composition that was associated with decreased BMI and increased health (14). Despite exercise being able to modulate the microbial composition of the gut, it has been shown that diet has a larger impact and more rapidly modifies the gut microbiota (15). Since both diet and exercise modulate the microbial composition of the gut, it is important to analyze the interaction between these lifestyle factors; however, for individuals attempting to lose weight through long-term exercise interventions, diet may be of more importance when attempting to mitigate compensatory energy intake and increase satiety. Thus, specific dietary strategies may be able to aid in modulation of appetite post-exercise in individuals with overweight or obesity.

The objectives of this thesis were:

1. To examine how fasting versus post-exercise nutrient intake impacts appetite and energy intake during the post-exercise period in individuals with overweight and obesity.
2. To examine if a post-exercise prebiotic supplement modulates appetite regulation and energy intake after an acute bout of vigorous aerobic exercise in individuals with overweight or obesity.

In our study comparing fasting versus feeding post-exercise, we found that fasting significantly increased levels of self-reported appetite ~1-hour after exercise, but also

significantly decreased total energy intake over 3-days. Similarly, fasting caused levels of GLP-1 and PYY to significantly decrease from baseline to ~1-hour post-exercise and to have a significantly lower change than compared to feeding. However, all absolute hormone levels did not differ the morning after exercise after an ~12-hour fast. The highlight of this study was the differential modulation of appetite-regulating hormones through post-exercise nutrient intake as compared to a fasted post-exercise state.

The study examining the addition of a prebiotic supplement post-exercise found that the addition of a prebiotic significantly increased satisfaction in the fasted state the morning after exercise, while significantly decreasing the AUC for hunger. There was an increased change in GLP-1 and PYY from PRE-EX to POST-EX during the prebiotic session compared to a fed state. The addition of a prebiotic supplement also increased reported levels of flatulence and rumbling, while decreasing abdominal comfort. The highlight of this study was that a prebiotic may aid in decreasing energy intake the day after exercise in comparison to nutrient intake.

These results warrant further discussion surrounding the consumption of supplements as opposed to a diet rich in whole foods, the applicability of fasting for weight loss and appetite management, and the limitations of food diaries and other tools that may be of interest instead.

"Real" Food versus Supplements

In today's food climate, there is a large reliance on convenient, highly processed foods, which is typically not beneficial for individual health. As it has been pointed out, many active ingredients within foods, when highly processed, are removed (16). In a cross-sectional study examining the association between ultra-processed foods and

obesity within the adult Canadian population it was found that 45% of energy intake per day consists of ultra-processed food (17). Furthermore, the consumption of ultra-processed foods was found to be positively associated with the development of obesity. Similarly, another study compared the effects of consuming ultra-processed foods to unprocessed foods for two weeks in a randomized controlled trial with weight stable, inpatient adults. The researchers found that ultra-processed foods led to a significantly larger energy intake of 500 calories per day, with an associated weight gain, whereas the unprocessed diet lost weight throughout the two weeks (18). These studies highlight the importance of consuming a diet rich in whole foods, despite the hedonic drive to consume the highly convenient, ultra-processed food. For example, an analysis of epidemiological studies looking at whole grain intake and healthy aging points out that the increased markers of health (such as lower rates of hypertension and diabetes) as one ages is associated with an increased intake of whole grains (16). In another study the effects of added beans versus added fiber (matched to the beans) to a meal and no fiber controls in 12 individuals with overweight or obesity with metabolic syndrome was assessed. It was found that there was a significantly greater PYY and cholecystokinin response and a smaller insulin response 5-hours postprandially with added beans compared to added fiber and no fiber trials (19). Thus, outside of the effects of exercise, consuming a diet of whole foods in comparison to highly processed nutrients can decrease hunger and energy intake, but also increase satiety in the short-term, like the decrease in appetite observed with prebiotics in our study. Despite fiber itself being known to increase satiety and decrease appetite (20), similar effects may be attained from non-processed food. Unfortunately, whole foods cannot be considered a ‘prebiotic’ due to the current definition of a prebiotic specifying that a prebiotic must be ‘selectively utilized by host

micro-organisms' to relay specific health effects to the host (21). However, although whole foods may not be selectively utilized by host micro-organisms, whole food may be able to elicit prebiotic-like effects. Further research is needed to elucidate if whole foods are comparable to prebiotic supplements and whether the consumption of whole foods post-exercise may modulate appetite comparably to supplementation with a prebiotic.

Although there are notable issues surrounding the consumption of ultra-processed foods, taking a prebiotic fiber chronically is likely not harmful. A prebiotic may create gastrointestinal side-effects, such as bloating, rumbling, diarrhea, and flatulence (22) as was seen within our acute study, but further issues are unlikely and have not been reported. Prebiotics are also typically well tolerated in doses up to 20g/day, but there is a range in the severity of symptoms experienced by each individual participant (23, 24). In our study, the prebiotic supplement was used to assess the possible effects of fiber as a functional food without possible confounding factors, such as interactions with other macronutrients. Inter-individual variability and sensitivity to certain macro- and micronutrients may be important to consider when providing dietary recommendations for health, wellness, and possibly weight loss. Knowing the inter-individual variation of individuals may provide a method of individualizing nutritional intake recommendations.

Personalized Nutrition

Personalized nutrition is the idea that individualized nutritional recommendations based on individual characteristics, such as behavior, genotype, and phenotype, will be more effective at inducing behavior change than other approaches (25). Although this concept seems promising, there are currently few randomized control trials examining the effectiveness of this strategy long-term. The largest randomized control trial to date is the

Food4Me Study. In one of the studies, 1269 adults from European countries completed the intervention with follow ups at 3-months and 6-months (26). They were randomized to groups receiving conventional dietary advice or personalized nutrition categorized into different levels. Personalized nutrition was determined by either the individual baseline diet, diet and phenotype, or the combination of diet, phenotype, and genotype. This study found that the personalized nutrition groups had higher healthy eating scores and decreased their intake of red meat, salt, and saturated fat; however, there were no significant differences between the differing levels of personalized nutrition. A follow-up study was conducted to analyze the characteristics of the 21% of enrolled participants that dropped out of the study and it was found that there was an increased likelihood of dropout if participants had too frequent feedback, were less than 45 years old, and had obesity. Participants were more likely to remain within the study if they claimed to eat healthy frequently (27). Thus, interventions looking to create behavior change through individualized advice may not target the subset of the population that may need it the most due to increased BMI and increased health risk. This study may have also been limited given dietary advice was being given based on self-reported food frequency questionnaires. Although there may be current downfalls with personalized nutrition, it may be beneficial for future recommendations for post-exercise dietary strategies for controlling appetite. For example, taking in consideration the inter-individual responses to a prebiotic fiber may cater to if the prebiotic will elicit appetite-regulating effects, or whether finding other dietary strategies (such as specific macronutrient intake) would be pertinent.

Food Diaries

It is well known that food diaries and food frequency questionnaires have high levels of misreporting and bias (28). Similarly, Kirkpatrick et al. (29) points out in a systematic review of dietary assessments that shorter assessment tools have a higher likelihood of producing results that support the hypotheses of the studies. In our studies, calculation of total energy intake based on self-reported 3-day diet records may have skewed results towards under-reporting of ultra-processed foods and over-reporting of non-processed foods. This may decrease the accuracy of assessment of energy intake due to exercise and the post-exercise dietary strategies. Self-reported dietary recalls are commonly used to decrease expense and time for analysis. Other methods may increase the accuracy and limit bias, but would involve more intensive work within the study. For example, a systematic review on image-assisted dietary assessment (30) concluded that images decrease the amounts of unreported or misreported foods and provide valid estimates of energy intake if the images are of satisfactory quality. Including image-assisted dietary assessment alongside the food diaries utilized within our studies would increase the accuracy of assessment of energy intake through the dietary strategies imposed by each of our studies. Like our trials, the largest randomized control trial examining personalized nutrition is still possibly subject to bias and misreport due to dietary recall. Further research examining effects of personalized nutrition and general dietary advice are necessary to determine their effectiveness for behavior change chronically and if the assessment of energy intake can be more accurate using multiple dietary assessment tools.

Fasting

There is currently a large cultural interest in the principle of fasting for weight loss and maintenance, which may mediate appetite regulation differentially from continuous energy restriction. Our results suggest that there may be resetting of satiety hormones following a short-term fast. There are multiple definitions of fasting. There are multiday fasts where energy intake is negligible for 2 or more days (commonly known as periodic or prolonged fasting), fasts where an individual goes an extended period of time of 16-48 hours with little to no energy intake (commonly referred to as intermittent fasting), and there are also eating patterns where feeding is restricted to a certain number of hours per day (typically 8 hours) (referred to as time-restricted feeding) (31, 32). Our study including post-exercise fasting would be most like a time-restricted feeding protocol, where if one exercises outside of their window for energy consumption they would not take in any energy until the following day. Despite fasting consistently being found to not produce different weight loss from a continuous energy restricted diet (33), randomized control trials have found that there is less drop-out rates with intermittent fasting even though reported hunger is increased at the beginning of the interventions (34). It has been observed that fasting does not lead to compensatory overconsumption and when periodic or intermittent fasting was utilized, was found to have a carry-over effect in decreasing caloric intake by 23-32% on non-fasting days (31). Similarly, in a study of 34 resistance trained males that were randomized to an 8-hour time-restricted feeding or a normal diet for 8-weeks, with both trials consuming 100% of their energy needs and completing a standardized resistance training program, it was found that those who fasted significantly decreased their fat mass and maintained their fat free mass as compared to those who did not fast on an isocaloric diet (35). In our study, we observed that our participants had

significantly more hunger and less satiation prior to leaving the lab after exercise, but satiety and appetite hormone concentrations the morning after, in the fasted state, were comparable to the post-exercise fed trial. Similarly, the fasting trial ate significantly less calories over 3-days in comparison to the fed trial. This may suggest a resetting of appetite-regulating hormones the morning after fasting if individuals can abstain from energy consumption despite increased hunger. Thus, more research is necessary to clarify the effects of fasting as a possible dietary strategy for appetite regulation after, or in conjunction with, exercise for weight maintenance or loss.

Conclusion

Despite the need for further research examining dietary strategies for appetite regulation and weight management, our study with prebiotic supplementation post-exercise demonstrates the functional ability of a prebiotic fiber to decrease appetite and energy intake in individuals with overweight post-exercise. Similarly, fasting may increase appetite immediately post-exercise, but appears to decrease total energy intake over 3-days compared to feeding post-exercise. Both prebiotic supplementation and fasting post-exercise may modulate appetite-regulation post-exercise, but further research is needed. Furthermore, this work provides insight into possible mechanisms that will aid in decreasing energy compensation post-exercise for individuals with overweight or obesity. This may lead to increased efficacy of long-term exercise interventions for weight loss, and therefore an increased motivation to habitually exercise, allowing individuals to attain the important cardiometabolic benefits of exercise.

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