The effect of Methylphenidate on Energy Expenditure in Individuals with Obesity: A Randomized, Double-Blind, Placebo Controlled Pilot Trial

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Thesis Abstract

Objectives: Most weight loss medications target reductions in energy intake while neglecting energy expenditure, a critical predictor of weight loss/regain. This pilot study examined the effect of short-acting methylphenidate (MPH) on resting energy expenditure (REE), thermic effect of food (TEF), physical activity energy expenditure (PAEE), and how changes in energy expenditure relate to changes in body composition in youth and adults living with obesity.

Methods: This study was a randomized, double-blind, placebo-controlled two-parallel arm study. In total, 19 participants were screened, of which 14 participants were randomized into the study, but complete data was only collected for 12, and only analyzed for 10 participants. Those 10 participants aged 28.8 ± 6.9 yrs. (5 Male, 5 Female) were randomized to receive either MPH (0.5 mg/kg) (n = 5) or placebo (n =5) twice daily for 60 days. Participants' REE and TEF (indirect calorimetry), were measured at baseline (no drug/placebo), and day 60 post-treatment (drug/placebo). Participants' PAEE (Actical) was measured between screening and baseline for a 1-week period (no drug/placebo), and on day 53 for a 1-week period (drug/placebo). Participants' anthropometrics were measured using DEXA at baseline, and day 60 post-treatment.

Results: From baseline to day 60, MPH showed a relative difference to placebo in relative REE (Relative REE: $F(1, 8) = 4.235$, $p = 0.074$, $d = 0.83$, $\pi^2 = 0.346$) of 10%, evidenced by a 6% increase in relative REE kcal/kg (18.53 ± 1.97 Kcal/day/kg at baseline, 19.71 ± 2.52 Kcal/day/kg at final) for the MPH group, and a 4% decrease (19.08 ± 2.36 Kcal/day/kg at baseline, 18.26 ± 2.04 Kcal/day/kg at final) in placebo, translating to moderate-effect size (Cohen's d=0.63) favouring MPH. From baseline to day 60, there were no significant differences between groups on changes in TEF (TEF AUC: $F(1, 8) = 0.079$, $p = 0.785$, $d = 0.15$, $\pi^2 = 0.010$) or any PAEE variables such as sedentary behavior (SB: $F(1, 8) = 0.455$, $p = 0.52$, $d = 0.02$, $\pi^2 = 0.054$), light physical activity (LPA: $F(1, 8) = 0.504$, $p = 0.50$, $d = 0.16$, $\pi^2 = 0.059$), moderate physical activity (MPA: $F(1, 8) = 0.281$, $p = 0.61$, $d = 0.19$, $\pi^2 = 0.034$), moderate-to-vigorous physical activity (MVPA: $F(1, 8) = 0.120$, $p = 0.74$, $d = 0.15$, $\pi^2 = 0.015$), or vigorous physical activity (VPA: $F(1, 8) = 3.495$, $p = 0.098$, $d = 0.91$, $\pi^2 = 0.304$) . Mean change in body weight (kg) resulted in a weight loss of roughly -2.66 ± 2.00 kg in the MPH group and -1.64 ± 1.41 kg in the

placebo group, differences that were not statistically significant. Mean change in both groups for body fat% of -0.33 ± 2.08 %, mean change in fat mass of -1.05 ± 2.59 kg, and finally a mean change in fat-free mass of -0.06 ± 1.19 kg was reported. Changes in relative REE were inversely correlated with changes in body weight ($r = -0.599$, $p = 0.067$), body fat ($r = -0.524$, $p = 0.12$) and fat mass ($r = -0.599$, $p = 0.096$). These associations were stronger in the MPH group.

Conclusions: Our data suggests that MPH administration may lead to a meaningful increase in relative REE, and these suggested changes were associated with reductions in adiposity among individuals with obesity. These preliminary findings suggest that MPH should be further examined using a larger sample size and study duration to determine its effectiveness in promoting weight loss and maintenance of weight loss in individuals with obesity, a population at high risk of morbidity and premature mortality.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AT	Adaptive Thermogenesis
AUC	Area Under the Curve
BMI	Body-mass index
CHEO	Children's Hospital of Eastern Ontario
DAT	Dopamine Transporters
DEXA	Dual X-Ray Absorptiometry
ECG	Electrocardiogram
EE	Energy Expenditure
EI	Energy Intake
FFM	Fat-Free Mass
FM	Fat Mass
LPA	Light Physical Activity
MCID	Minimal Clinically Important Difference
MPA	Moderate Physical Activity
MPH	Methylphenidate
MVPA	Moderate-to-Vigorous Physical Activity
NEAT	Non-Exercise Activity Thermogenesis
NICE	National Institutes of Health and Care Excellence
PA	Physical Activity
PAEE	Physical Activity Energy Expenditure
REE	Resting Energy Expenditure
SB	Sedentary Behaviour
TDEE	Total Daily Energy Expenditure
TEE	Total Energy Expenditure
TEF	Thermic Effect of Food
VAS	Visual Analog Scale
VPA	Vigorous Physical Activity

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1.0 CHAPTER 1 - INTRODUCTION

1.1 Background

Obesity is defined as having a body-mass index (BMI) of over 30 kg/m^2 in adults and being at or above the 95th percentile for age and sex in children **(**World Health Organizations growth curves; Cole et al., 2000). The prevalence of obesity in youth (1 in 7) and adults (1 in 4) (Bancej et al., 2015) is reaching epidemic proportions (Stevens et al., 2012; Shields et al., 2011). Obesity is also known to be strongly associated with adverse medical (i.e. diabetes) (Pi-Sunyer, 2009; Melanson et al., 2001), psychosocial (i.e. depression.) (Petry et al., 2008; Wadden et al., 1985) and health economic outcomes (i.e. burden of cost) (Anis et al., 2010; Birmingham et al., 1999).

Research shows that weight loss of 5 % to 10 % of body weight, the minimal clinically important difference (MCID), markedly reduces risk of obesity-related chronic diseases and mortality (Khera et al., 2016). Diet and exercise are the standard components of behavioural interventions for obesity, while pharmacotherapy and bariatric surgery represent treatments that are targeted when diet and exercise alone cannot adequately manage clinical obesity (Soleymani et al., 2016). Bariatric surgery, while effective in the long term, is considered a last resort therapy option due to invasiveness and potential harms (Chang et al., 2014). Thus, behavioural interventions and pharmacotherapy, or their combination, are considered front line therapies.

Obesity is now recognized as a chronic disease needing ongoing management. Given this, combined with meta-analytic data (Franz et al., 2007) providing strong evidence that pharmacotherapy is more effective than diet and/or exercise alone in the long-term management of obesity, drug therapy is appealing. The ideal pharmacotherapy intervention would be one that focuses on both sides of the energy balance equation and yields successful long-term results.

More specifically, a comprehensive intervention would aim to decrease energy intake (EI) and increase energy expenditure (EE).

There are currently seven approved pharmacological agents indicated for obesity treatment (Orlistat, Setmelanotide, Qsymia, Phentermine, Lorcaserin, GLP-1 Liraglutide and Contrave) (Srivastava et al., 2019; Chan et al., 2013; Crane & McGowan, 2015). Three are currently approved in Canada; Orlistat, Liraglutide, and Contrave. All are shown to be effective, however, they are considered sub-optimal due to their own limitations. Orlistat has shown promising weight loss over placebo at 1 year (Padwal et al., 2004), however, due its intolerable levels of gastrointestinal side-effects (Torgerson et al., 2004) it can be considered sub-optimal. Liraglutide administered in parallel to diet and exercise, has demonstrated even greater weight loss over placebo (Mehta et al., 2017) than Orlistat. Although effective, the high cost ($430) per month, along with its need for subcutaneous injection, act as barriers in its widespread use. Lastly, Contrave has demonstrated even greater weight loss over placebo after a 56-weeks intervention involving diet and exercise (Greenway et al., 2010). Although quite effective, participants on the 32 mg dosage of Contrave reported frequent adverse events such as nausea (32.5%), constipation (19.2%), headaches (17.6%) and vomiting (10.7%) (Sherman et al., 2016) among other serious concerns about the safety and tolerability (NICE, 2017).

Taken together, the use of current medications for obesity treatment may be sub-optimal because they either do not achieve the 5% of body weight loss over placebo at 1-year (Orlistat) (Franz et al., 2007) needed for chronic disease reduction, are very expensive (Liraglutide and Contrave) or poorly tolerated (Orlistat and Contrave). Moreover, none of the currently approved drug therapies have demonstrated an impact on REE (Manning et al., 2014); a critical component for inducing and maintaining weight loss (Camps et al., 2013; Rosenbaum et al., 2008).

However, these limitations can potentially be addressed by stimulant medications, such as Methlypnheidate (MPH), due to its demonstrated effect on REE (Lorello et al., 2008). As well, MPH can be administered orally and removes the discomfort of requiring an injection, unlike Liraglutide, and is also inexpensive. Finally, none of the discussed medications are indicated for a pediatric population in Canada. This is problematic, as the vast majority of youth with obesity will become adults with obesity (Simmonds et al., 2016), even those who received behavioural treatment in childhood (Epstein et al., 1994).

1.2 Rationale and Statement of the Problem

Current pharmacological agents available in Canada for the treatment of Obesity have been shown to have certain drawbacks and limitations making them sub-optimal for treatment (Sherman et al., 2016; Torgerson et al., 2004; Manning et al., 2014). Additionally, and most importantly, many of these agents either do not target EE, or their impact on EE has not been studied. EE is a critical component of energy balance, and should be considered key to any anti-obesity agents success. Evidence suggests that MPH acutely increases EE (Lorello et al., 2008), however, its sustained effect is not known. Furthermore, the effects of sustained MPH administration on REE, have never, to our knowledge, been studied in a non-ADHD population. Therefore, we administered MPH 2x daily over the course of 60 days in order to examine its sustained effect, if any, on 1) Resting energy expenditure (REE) and Thermic Effect of Food (TEF); 2) Physical Activity Energy Expenditure (PAEE) and; 3) the relationship between changes in EE components and changes in anthropometrics (body weight, body fat%, fat mass and fat-free mass).

1.3 Research Objectives

The primary objective of this study was to assess the impact, if any, of sustained MPH administration over 60 days on EE among adolescents and adults with obesity. Specifically, this project aimed to:

1. Examine the effects of short-acting MPH administration on changes in REE and TEF
2. Examine the effects of short-acting MPH administration on changes in free living PAEE
3. Examine the relationship between changes in EE components (REE, TEF, PAEE) and changes in body composition (body weight, body fat%, fat mass and fat-free mass)

2.0 CHAPTER 2 - LITERATURE REVIEW

2.1 Energy Balance & Energy Expenditure

Weight loss occurs when EI is below EE (i.e., negative energy balance) for extended periods of time, a state known as energy deficit. This can be achieved through two methods; 1) Caloric restriction (energy intake reduced) or; 2) Increased energy expenditure (i.e., increased physical activity energy expenditure (PAEE), Resting Energy Expenditure (REE) or Thermic Effect of Food (TEF)) (Müller et al., 2016), or both. Caloric restriction is difficult to achieve for many and contains its own drawbacks such as increasing food reinforcement levels which undermines dietary adherence and long-term weight loss (Fisher & Birch, 1999a; Fisher & Birch, 1999b; Raynor & Epstein, 2003) appetite (Doucet et al., 2000; Hintze et al., 2017) and appetite-related peptides (Sumithran et al., 2011). Although interventions focused solely on reducing EI are shown to be more effective at weight loss than those focused solely on increasing EE through exercise (Foster-Schubert et al., 2012), the negative implications of weight regain are still prevalent because the adaptive metabolic changes underlying weight loss have not been addressed. These adaptive metabolic changes include a disproportionate reduction in REE, relative to the new lowered body weight (Leibel et al., 1995). Moreover, most behavioural and pharmacological interventions have focused on increasing free living physical activity EE rather than non-volitional components (REE), despite REE having shown to be an important predictor of weight re-gain (Buscemi et al., 2005; Ebbeling et al., 2012).

Total energy expenditure (TEE) can be thought of as the total amount of energy the body expends throughout a 24-hour period, encompassing all activity. TEE is the sum of resting energy expenditure (REE), Non-Exercise Activity Thermogenesis (NEAT), thermic effect of food (TEF), and physical activity energy expenditure (PAEE). REE is widely recognized and acknowledged for contributing to approximately 50-70% of TEE (Poehlman, 1989), a proportion that varies as a function of PAEE. TEF contributes approximately 10% and PAEE contributes

the remaining 15-30% of energy expenditure (Poehlman, 1989). NEAT is the energy expended for all activities not including sleeping, eating, or sports-like exercises (Levine, 2003). However, due to the difficulty in measuring NEAT, the cost of valid measurement equipment and the length of time required to accurately measure NEAT (Von Loeffelholz & Birkenfeld, 2018), it was excluded from the present study.

REE accounts for the energy utilized by the body, during non-active periods, in order to maintain homeostasis. This includes metabolic processes essential for body maintenance (i.e. forming cell membranes and structural proteins, shuttling energy, breathing, etc.). REE has previously been studied as a possible intervening point for weight loss and weight regain in humans (Ravussin & Bogardus, 1992). More recently, Buscemi et al. (2005) investigated the relationship between REE and subsequent changes in body size and degree of fatness in a group of Caucasian Italians. In that study, it was found that a low REE (normalizing for fat-free mass) was associated with body weight gain over a long period of time (10-12 years). Furthermore, they also found that the baseline REE was inversely correlated both to change in body weight and change in fat mass (FM). These findings could indicate that perhaps by having individuals increase their REE, or at least attenuate the reduction that follows weight loss, one could decrease the potential for weight re-gain in the future. Evidence suggests that reductions in REE are prevalent following weight loss, with an average weight loss of 8 ± 0.7 kg being associated with an REE reduction of 136 ± 18 kcal per day in adults (Bray et al., 2012). These reductions, following weight loss, act as a strong predictor for weight regain (Ebbeling et al., 2012). Similar findings were shown in other systematic reviews which reported a 15.4 ± 8.7 kcal reduction per kg of weight loss (Schawrtz & Doucet, 2010). This suggests a vicious cycle of obesity prompting weight loss, followed by weight regain and so on. As previously mentioned, there is evidence

that weight loss results in compensatory changes in EE that undermine the maintenance of reduced body weight and that these metabolic changes, known as adaptive thermogenesis, contribute to weight regain (Camps et al., 2013). Adaptive thermogenesis is defined as a disproportional or greater than expected reduction of REE (Camps et al., 2013; Dulloo & Jacquet, 1998). Sustained adaptive thermogenesis favours a positive energy balance, predisposing people to weight regain. and has been identified as a contributing factor to the high recidivism of obesity (Kraschnewski et al., 2010). Interventions targeted at increasing EE could perhaps attenuate this reduction that accompanies weight-loss and help combat the predisposition to weight regain.

A meta-analysis performed by Astrup et al. (1999), aimed to compare the findings of previously published studies that looked at REE in formerly obese subjects (BMI ≤ 27.0) with matched control subjects who had never been obese. Astrup et al. (1999) found that formerly obese subjects had mean relative REE's (1451 ± 180 kcal/day), that were 3-5% lower than the mean relative REE's of the body-weight-matched control subjects (1494 ± 213 kcal/day) who had never been obese, a difference of approximately ~43 kcals/day after adjusting for body composition (FFM and FM). Others have reported comparable findings (Seidell et al., 1992). A study performed by Ravussin et al. (1988), found that a person with a low-adjusted 24-hour TEE (200 kcals per day below the predicted value) had a 59% probability of gaining 7.5 kg or more during a 21-month period, according to their model (accounting for FFM, FM, age, and sex). On the other hand, those with a high-adjusted 24-hour TEE (200 kcals per day above the predicted value) were found to have only a 13% probability of gaining 7.5 kg or more during a 21-month period. In the study, the 15 participants who gained more than 7.5 kg of weight had lower adjusted TEE than the 80 who did not (2262 ± 194 kcal/day as compared with 2349 ±133

kcal/day) despite the two groups being similar in age and initial body composition. The group who gained more than 7.5 kg of weight had a mean age of 25 ± 6 yrs, a mean body weight of 104.4 ± 17.9 kg and a mean body fat of 36 ± 6%, while the group who did not gain had a mean age of 26 ± 5 yrs, a mean body weight of 97.8 ± 19.8 kg and a mean body fat of 36 ± 8%. The significance of these findings is derived from the discovery that a difference of almost 200 kcals per day in TEE can have substantial differences in the prediction of weight gain in individuals. Current behavioural interventions do not address this aspect of EE reduction induced by caloric restriction, resulting in weight regain. This illustrates a need for interventions that can attenuate this reduction in REE in order to achieve better weight loss and maintenance of weight loss.

2.2 Current Pharmacological Agents and Limitations

Quite recently, Franz et al. (2007) examined 80 studies of weight-loss focused clinical trials with a minimum of a ≥1-year follow-up. These studies were categorized according to the type of weight-loss trial, and were placed in either diet al.one; exercise alone; diet with exercise; Meal Replacements; Very-low-energy diet; Orlistat (Pharmacotherapy,); Sibutramine (Pharmacotherapy); or advice alone. Weight-loss was then examined at 6, 12, 24, 36 and 48 months. It was found that at 48 months, Orlistat had the greatest maintained weight loss (over placebo) (5.8 kg), while diet with exercise (3.9 kg) and diet al.one (3.0 kg) followed after. It should be noted that Sibutramine was discontinued due to its adverse psychological effects. In a meta-analysis conducted by Khera et al. (2016), they found that 20-54% (2.6-8.8 kg over placebo) of participants (29,018 total) achieved clinically significant weight loss (≥ 10% total body weight) through Pharmacotherapy at 1 year. In contrast, diet and exercise interventions at 1 year, only provided a weight-loss of 3.0-4.0 kg, with less than 23% of people meeting the clinically significant weight loss threshold of 5%. Recently, the American Medical Association, as well as the Canadian Medical Association, have categorized obesity as a chronic disease that

requires ongoing management (Pollack, 2013; Rich, 2015), similar to diabetes. This has sparked renewed interest towards the treatment of obesity using pharmacotherapy.

As previously mentioned, there are currently 3 approved anti-obesity (Srivastava et al., 2019; Chan et al., 2013; Crane & McGowan, 2015) agents available in Canada; Orlistat, Liraglutide, and Contrave. Orlistat has been shown to demonstrate results of approximately 3 kg of weight loss over placebo at 1 year (Padwal et al., 2004), however its mechanism of action sometimes leads to intolerable levels of gastrointestinal side-effects (Torgerson et al., 2004). Liraglutide, as an adjunct to diet and exercise, has shown greater weight loss (4-6 kg) than Orlistat, at 1-year relative to placebo based on a meta-analysis (Mehta et al., 2017). Liraglutide's high cost ($430 per month), coupled with its only form of administration being through subcutaneous injection, have been identified as barriers to its widespread clinical use. Finally, Naltraxone/Bupropion (Contrave) was shown to exhibit approximately 3.5 kg (16 mg dosage) and 5.7 kg (32 mg dosage) weight loss over placebo after a 56-week intervention in adjunct to diet and exercise, respectively (Greenway et al., 2010). However, participants on the 32 mg dosage of Contrave, reported frequent adverse events. These adverse events consisted of nausea (32.5%), constipation (19.2%), headache (17.6%) and vomiting (10.7%), among others (Sherman et al., 2016). As well, serious concerns about the safety and tolerability of Contrave have been expressed by the National Institutes of Health and Care Excellence in the UK (NICE, 2017), who caution its clinical use. Additionally, Contrave and Liraglutide were shown to be associated with the highest odds of adverse event-related treatment discontinuation (Khera et al., 2016), further supporting the concerns for safety and tolerability.

2.3 Methylphenidate (MPH), & Dopamine

MPH is a front-line medication used to treat children and adults with Attention Deficit Hyperactivity Disorder (ADHD) (Wilens et al., 1995), and is a dopamine reuptake inhibitor

(Seeman & Madras, 1998; Gottlieb, 2001). Evidence suggests that dopamine plays a role in mediating the reinforcing value of food (Berridge, 1996; Berridge & Robinson, 1998), which has been shown to be a strong determinant of excessive food intake and obesity (Epstein et al., 2007). Dopamine is both a hormone and neurotransmitter, and is the primary neurotransmitter in the mammalian brain. Dopamine is central in governing cognition, emotion, locomotor activity, food intake and endocrine regulation (Missale et al., 1998). There are three major dopaminergic pathways; the nigrostriatal pathway, the motor control related circuit; the mesocortical pathway, the motivation and emotion related circuit; and finally, the mesolimbic pathway, the reward related circuit (Berthoud, 2007). Dopamine is synthesized from the amino acid tyrosine, mainly by nervous tissue and the medulla of the adrenal glands. The biosynthesis of dopamine begins with the hydration of the amino acid L-tyrosine to L-DOPA. This step is limited by the enzyme tyrosine hydroxylase. Following this, the rate limiting enzyme DOPA decarboxylase converts L-DOPA to dopamine (Marieb, 1998). In a study performed by Wang et al. (2001), it was seen that low levels of circulating brain dopamine are related to the development of obesity. It is theorizied that the mechanism underlying this reduction in dopamine release could be related to a rapid dopamine transport and/or reduced brain dopamine signaling. As mentioned previously, MPH is a dopamine reuptake inhibitor (Seeman & Madras, 1998; Gottlieb, 2001), and by administering MPH, which reaches peak concentrations 1-hour after ingestion (Volkow et al., 2002), it inhibits the activity of dopamine transporters (DAT) by roughly 50-75% (Volkow et al., 2001). MPH partially blocks dopamine reuptake by binding and blocking DAT or carrier proteins. DAT removes dopamine once it has been released into the brain. Blocking these transporters leads to increased levels of available dopamine in the brain. Essentially, the underlying hypothesis behind this mechanism is that DAT acts as one of the main regulators for

dopamine in the extracellular space, and by blocking them with MPH it would result in greater dopamine signaling (Giros et al., 1996), leading to higher levels of synaptic dopamine. Volkow et al. (2001) have shown that therapeutic doses of orally administered MPH (0.25-1.0 mg/kg) caused significant dopamine transporter blockades (50-75%) in 11 healthy male subjects (mean age 30 ± 7 years, mean body weight 172 ± 23lbs). This study used positron emission tomography and [(11)C] aclopride, a D2 receptor radioligand that competes with endogenous dopamine for binding to the receptor, in order to evaluate whether MPH changed extracellular dopamine in the human brain (Volkow et al., 2001). Dopamine infusion has also been shown to provide a dose-dependent thermogenic effect on REE (Ruttimann et al., 1991). For example, dopamine infusion (5 and 10 micrograms/kg·min) was shown to cause a 6% (2-9 kcal/min) and 15% (12-21 kcal/min) increase in REE, respectively in 8 healthy young males with a normal body weight (51-89 kg), demonstrating the potential role of dopamine to affect metabolism.

2.4 MPH and Energy Expenditure in those with ADHD

Although MPH has been widely shown to reduce energy intake (Goldfield et al., 2017), it has also been shown to affect EE. MPH has been shown to reduce TEE via its effect on PAEE in an ADHD population (Butte et al., 1999). Butte et al. (1999), administered MPH (average dose of 24±10 mg/d) to 31 children with ADHD and monitored their REE and PAEE using room respiration calorimetry as well as microwave motion detectors. This study found a significant reduction in PAEE and REE in the sample of ADHD children, showcasing the impact MPH has on two of the three EE components. Perhaps, if the population were not children with ADHD, MPH would demonstrate its typical excitatory effects (Kratz et al., 2009) much like other stimulants such as caffeine. Given there is little research on the effects of MPH, a stimulant, on REE or PAEE, a brief review of the most commonly used stimulant (caffeine) follows.

Graham (2001) conducted a meta-analysis on caffeine and found that it can act as an ergogenic aid and allow athletes to train at greater power outputs and/or for a longer period of time, leading to an increase in PAEE. It was also shown to increase speed and power output (Graham, 2001). As well, Astrup et al. (1990) conducted a double-blind placebo controlled study and found that caffeine produces a thermogenic dose-dependent response on REE, similar to what has been seen in dopamine infusion (Ruttimann et al., 1991). They administered either a placebo, or 3 different doses of caffeine (100 mg, 200 mg, and 400 mg) to 6 healthy, normal weight (mean weight 70.1 ± 13.1 kg) adults (3 male and 3 female) between the ages of 20-32 yrs (mean age 25 ± 1 yrs), who were habitual coffee drinkers (< 100-200 mg/day of caffeine). REE was measured 30 min before caffeine/placebo ingestion, and was measured at 30 min intervals for a period of 3-hours. Astrup et al. found that REE increased by 9.2 ± 5.7, 7.2 ± 6.0, 32.4 ± 8.2 kcal/hr over the placebo for the 100 mg, 200 mg and 400 mg dose, respectively. The thermogenic effects of the 100 mg and 400 mg dose was found to be a significant increase in REE over the placebo. Ideally, since MPH is a central nervous system stimulant like caffeine, the theory is that MPH would provide a similar dose-dependent increase in REE. This field of research has not been well studied, in fact, to our knowledge, there has been only one study examining the effect of MPH on REE in a population without ADHD.

2.5 MPH & Energy Expenditure in Animals and Humans without ADHD

In a study performed by Lorello et al. (2008) with the objective of examining the effect of fast-release MPH on REE and TEF, they found that orally administered MPH significantly increases REE and TEF (at 90 minutes). The participants consisted of 14 healthy adults (7 men and 7 women) between the ages of 18 and 40, all of which were normal weight (20. 0 $kg/m^2 \leq$ BMI $\geq$ 24.9 kg/m^2). The researchers administered either a placebo, or MPH at a 0.5 mg/kg dosage, both 1-hr prior to data collection. Following the 1-hr after administration, the REE

measurement of the participants was taken for 30 minutes. After the REE was measured, the participants were given a standardized breakfast, and then TEF was evaluated every 30 min for 3-hours. They reported an increase of approximately 7% in REE and 5% in TEF (at 90 minutes) when compared to the placebo (Lorello et al., 2008).

As mentioned previously, studies have shown that the infusion of dopamine produces a thermogenic effect, dependent on the dose (Nakagawa et al., 1994; Ruttimann et al., 1991). Perhaps indicating that dose size of MPH (a known dopamine reuptake inhibitor) in the study may affect increases in REE and TEF. Additionally, the increased REE and TEF that was observed during Lorello et al. (2008) study occurred in the absence of concomitant increases in heart rate or blood pressure, which are sometimes reported as side-effects of MPH. The measurable acute increase in EE over the entire sampling period was 10.0 ± 13.5 kcal. However, when extrapolating these findings over the course of an entire day, TEE can potentially increase non-volitional EE up to 188 kcal a day. In alignment with previously highlighted findings by Ravussin et al. (1988), a 200 kcal difference in TEE can have significant attenuating effects on weight gain. These findings (Lorello et al., 2008) clearly demonstrate the effect of fast-release MPH on EE. These effects should be further evaluated outside of a laboratory setting in order to test feasibility to better assess the potential of MPH as an anti-obesity agent.

To the best of our knowledge no data exists on the effects of MPH on free-living PAEE among humans without ADHD, but laboratory studies with animals are informative. When looking at locomotor activity in animal models, Thanos et al. (2015) found that rats treated with two different doses of MPH (30 mg/kg and 60 mg/kg) were significantly more active ($p < 0.05$) than their placebo counterparts at certain time points (2/4/6 hour post injection). Overall, however, they found that at the 10-hour post injection time point the rats were significantly less

physically active than their placebo counterparts ($p < 0.05$). This pattern of increased PAEE at 4-hours followed by a compensation of reduced locomotor activity at 10-hours is consistent with the pharmacokinetics of MPH which reaches peak concentration at 1-hour post-ingestion and tends to have a 4-hour half-life (Wargin et al., 1983).

The effects of sustained administration of MPH on PAEE in humans without ADHD has not been well investigated. However, Roelands et al. (2008) examined the effect of MPH on cyclist performance on 8 healthy, well-trained male cyclists (mean age 26 ± 5 yrs; weight 77.9 ± 6.4 kg; maximal workload 361 ± 18 Watts). The subjects either ingested a placebo (20 mg) or MPH (20 mg) 1-hour before the start of exercise and were then asked to complete cycling tasks for 60 min at 55% of maximal workload followed by a time trial in two different temperature conditions. Roelands et al. (2008) found that the MPH group were able to complete the time trial task in the heat significantly quicker (16% faster) than the placebo group. These findings showcase the similarity between excitatory effects of MPH and caffeine, as discussed previously. Caffeine was also found to help increase speed (Graham, 2001), similar to these demonstrated effects of MPH. Although EE was not measured for this study (Roelands et al. 2008), findings suggest MPH may promote exercise intensity and tolerance, possibly through increased central nervous system tone.

2.6 Summary and Research Gap

In summary, MPH has been shown to acutely increase TEE through increases in REE and TEF, with data indicating increases in TEE potentially up to 188 kcal/day (Lorello et al., 2008). When examining the literature, it is shown that current obesity medications (Orlistat, Liraglutide, and Contrave) have many drawbacks that make them sub-optimal for weight loss treatment. The shortcomings of these obesity medications include: 1) induce insufficient weight loss over placebo at 1-year (Orlistat) (Franz et al., 2007); 2) have a limited effect on REE, which is an

important predictor for weight-loss and maintenance (Camps et al., 2013; Rosenbaum et al., 2008); 3) they are poorly tolerated (Orlistat and Contrave), expensive (Liraglutide and Contrave) or administered via injection (Liraglutide); and 4) they are not recommended for children and youth. These limitations can potentially be addressed by MPH as discussed previously. As well, no other studies testing this effect of MPH on EE has been performed outside of the laboratory, and as such, clinical studies are needed to further identify its potential effect on EE and weight management strategies. Furthermore, it is important to note that all the studies testing MPH and its effect on EE in non-ADHD populations presented were performed only on adults (Lorello et al., 2008). As such, the effects of MPH on EE in youth with obesity remain uninvestigated. This is important given that roughly 80% of youth with obesity remain obese in adulthood (Simmonds et al., 2016), and early intervention in childhood has been shown to be more effective than in adulthood (Pandita et al., 2016).

2.7 Purpose

The current study was designed to fill the aforementioned research gaps by evaluating the effects of MPH on all components of EE over a 60-day period in a population of youth and adults with obesity, without ADHD. While the effects of EI were examined in a larger study, this thesis will focus solely on how EE was impacted by MPH over 2-months. Specifically, the current thesis will focus on discussing the changes, if any, surrounding our findings on;

1. The effects of short-acting MPH administration on changes in REE and TEF
2. The effects of short-acting MPH administration on changes in free living PAEE
3. The relationship between changes in EE components (REE, TEF, PAEE) and changes in body composition (body weight, body fat%, fat mass and fat-free mass)

3.0 CHAPTER 3 -METHODOLOGY

3.1 Study Population and Inclusion/Exclusion Criteria

3.1.1 Study Population

The study recruitment, flow and attrition are depicted in the CONSORT figure (Figure 1). More specifically, 19 participants were screened, of which 14 participants were randomized in, with 12 participants data being collected, and only 10 of those participants data was analyzed. The study sample had a mean age of 28.8 ± 6.9 years of age, a mean baseline body weight of 107.3 ± 2.3 kg and a mean BMI of 36.8 ± 4.4 kg/m^2, that met the criteria for obesity. For youth, obesity was defined as having a BMI equal or greater than 95th percentile for age and sex according to the World Health Organizations growth curves (Cole et al., 2000). For adults, obesity is defined as having a BMI of 30 kg/m^2 or higher. The randomization was performed by the Children's Hospital of Eastern Ontario (CHEO) pharmacy to ensure anonymity, using a 1:1 ratio in blocks of 2, stratified by sex. Two randomization lists were used, one for each gender, and participants were randomized into the study upon consent and completion of the clinical screening visit. Numbers for randomization were assigned in a sequential order. Recruitment of the participants was achieved through a variety of sources:

1. Dr. Stasia Hadjiyannakis's Centre for Healthy Active Living clinic at CHEO
2. Fliers posted across local universities, work buildings, hospitals and community centers.
3. Newspaper advertisements run in local Ottawa papers and city buses.

After initial contact of potential participants (through phone or e-mail), they were screened through the inclusion criteria to ensure they were eligible.

3.1.2 Inclusion Criteria

- Males and females 16 to 40 years old;
- BMI in the obese category (above 29.9 kg/m^2); or in the 95th percentile or higher for children
- Willing to comply with procedures, and sign informed consent forms;
- Able to swallow a placebo pill that will be used in the study (same size as study drug)
- Pass the tests performed on the screening visit (Electrocardiogram (ECG), resting vitals for heart rate and blood pressure) after ingestion of MPH (0.5 mg/kg) as a test dose

3.1.3 Exclusion Criteria

- smoker (the main outcome is energy intake and smoking is known to impact appetite);
- known serious (anaphylactic) food allergies, including lactose;
- history of previous MPH use or allergy to MPH;
- not a restrained eater based on cut-score (11 or higher) on Three Factor Eating Questionnaire (Stunkard & Messick, 1985) (See Appendix A);
- history of ADHD or current diagnosis of an axis 1 psychiatric disorder (e.g., depression, panic disorder, schizophrenia) as measured by clinical interview, self-report, the Wender-Utah Rating Scale (McCann et al., 2000; Rossini & O'Connor, 1995; Stein et al., 1995) (See Appendix B) and the Beck Depression Inventory (See Appendix C);
- current use of antidepressants, thyroid medication, or any medication that could affect appetite;
- high blood pressure defined as blood pressure ≥ 160/100 mmHg

- pre-existing cardiovascular disorders including uncontrolled hypertension, angina pectoris, arterial occlusive disease, heart failure, cardiomyopathies, myocardial infarction, and cardiac arrhythmia;
- diabetes (Type 1 and Type 2);
- excessive use of alcohol or alcoholism, or current addictions to opiates, cocaine or stimulants as measured by the Drug Abuse Screening Test (See Appendix D);
- glaucoma;
- personal or family history of seizure disorders;
- currently taking MAO inhibitors, pressor agents, coumarin, anticonvulsants, phenylbutazone, or tricyclic antidepressants;
- history of thyroid disease;
- personal or family history of motor tics or Tourettes's Syndrome;
- not pregnant, as determined by commercially available pregnancy test taken by female participants prior to test dose of MPH.
- after the test dose of MPH; systolic blood pressure exceeding baseline reading by 20 mmHg; diastolic blood pressure exceeding the baseline reading by 10 mmHg; BP > 160/100; or resting pulse increased by 20 beats/minute from the baseline (as measured by the study nurse on site) will be excluded from the study

3.2 Study Design

The study was a randomized, double-blind, placebo-controlled 2 parallel arm study. This study was designed in compliance to Consort guidelines for drug trials (Schultz et al., 2010). This study recruited participants between the ages of 16-40 years old, with a BMI > 29.9 kg/m^2. In total, 12 adults (6 male and 6 female) completed the study. Data collection was performed at the

Behavioural and Metabolic Research Unit located at the Lee's campus of the University of Ottawa. From the 12 adults, data was analyzed for 10 (5 male and 5 female) (Figure 1)

Participants were randomly assigned to either the placebo or the drug (MPH) group. This procedure was done completely blind to both the participants and the researchers involved, and was implemented by the CHEO pharmacy. The MPH group received the study drug, whereby the dose was based on body weight. Both groups followed a 7-day titration protocol ranging from 0.25 mg/kg up to 0.50 mg/kg (Figure 2). Participants took either MPH or placebo, two times daily 1-hour before meals (lunch and dinner) over a period of 60 days (consecutively). Prior to being placed into one of the two groups, participants first underwent two phases of screening. The first point of contact was a telephone pre-screen (see Appendix E), and if the participant met the criteria, they were then invited to the lab for a clinical screening visit. The clinical screening visit involved further determining eligibility criteria, obtaining informed consent as well as the participant taking a test dose of MPH under the supervision of the study nurse to closely monitor the participant for any potential adverse reactions prior to beginning the study.

3.3 Study Procedure

The study procedures, which are also outlined in the study map (Figure 3), consisted of five visits to the laboratory, totaling 24-hours in lab based on the following protocol timeline: An initial clinical screening visit (4-hours), two repeated measures test days (6-hours each; baseline, and final at 60 days), a mid-point visit (1-hour), and a lunch box visit (10 minutes to obtain out of laboratory food). Testing was performed throughout the week and weekend. After the initial laboratory visit and clinical screening visit, participants were randomized prior to the Baseline visit into one of the two groups (MPH or placebo) for the remainder of the study period. The participants underwent a dose titration for 7 days following Baseline. Physical activity (PA) was

tracked using Actical accelerometers (Philips Respironics) over a 1-week period for participants in either group. The first 1-week period of PA tracking was between the clinical screening visit and the Baseline visit, and measured PA behaviour without the influence of drug or placebo. The second 1-week period of PA tracking was during the week of the final repeated measures test day, and measured PA behaviour while under the influence of drug or placebo. Participants also underwent REE and TEF testing through indirect calorimetry during the two repeated measures days (Baseline, and Final visit). As well, there was a mid-point visit that took place on day 30 in which participants returned to the laboratory in order to refill their pill container of either placebo or MPH. Finally, participants returned for the final repeated measures test day on day 60 of the study. Data collection began in October 2017, and ended in August 2018.

3.4 Clinical Screening and Consent (Duration: 4 hours)

Prior to the beginning of the study, the participants were required to undergo a clinical screening visit (~4-hours in duration) in order to ensure they met all inclusion/exclusion criteria. Upon arrival, weight and height were measured in order to determine the participants BMI and ensure they had a BMI greater than 29.9 kg/m^2. The participant was then given a variety of questionnaires;

- Wender-Utah Rating scale (to assess traits compatible with ADHD);
- Beck Depression Inventory (to assess depressive symptoms);
- Three Factor eating questionnaire (to assess eating style);
- And the Drug Abuse screening test (to ensure no underlying drug problem).

As well, if the participant was female, a pregnancy test was administered (upon consent). If the participant was pregnant, they were excluded from the study. This did not occur during this study. The participant was then presented with the consent form and asked to read and sign the

form. Eligible participants underwent all the measures as outlined in the Case Report Form (see Appendix F) under the supervision of the study nurse. The nurse practitioner then administered a test dose of 0.5 mg/kg of MPH, and observed the participants vital signs over a period of 3-hours, after the ingestion of MPH, in order to monitor any potential side effects (see Appendix G). Should the participant have rated the side effects as "Moderate" then they were excluded from the study. As previously listed in the exclusion criteria, if at any point during the observation the participant experienced an abnormal ECG, or any significant changes in systolic/diastolic blood pressure or pulse, then they were excluded. Multiple ECGs were taken through the observation, and were assessed by the Cardiologist (Dr. Ron Vexler for adults, and Dr. Jane Lougheed for children) for a normal sinus rhythm. Participants that met all criteria were then sent home with an omni-directional accelerometer, as well as instructions on how to use and fill out a log sheet, used to track wear time.

3.5 Dose Rationale and Titration

In a laboratory study performed by Leddy et al. (2004), it was discovered that the minimal effective dose of MPH in adults (mean age of 26.3 ± 6.9 yrs, mean BMI of 36.5 ± 4.6 kg/m^2) that reduced food intake was 0.5 mg/kg, as such this was determined to be the test dose for the clinical screening visit. The maximum daily dose of MPH is 100 mg, according to the National Institutes of Health and Clinical excellence (NICE) 2008 guidelines for treatment of adult ADHD (NICE, 2018). Therefore, the weight restriction for this study is 200 kg (approximately 445 lbs) to accommodate our dosing based on 0.5 mg/kg, consistent with the guidelines developed by the Canadian ADHD Resource Alliance (CADDRA, 2011) which adjusts dose depending on body weight. Our dosing protocol is also consistent with the NICE (NICE, 2018) guidelines for stimulant use. As well, there are two types of MPH; fast-release (6-hour duration, peak 2-4-hour)

and slow-release (12-hour duration, peak 3-8-hours). For the purpose of this study, fast-release MPH was chosen. It has been shown that there is no difference in adult compliance between fast-release and slow-release MPH (Cascade et al., 2008). Furthermore, in vivo evidence in humans has indicated that average peak-drug concentrations were similar between fast-release and slow-release MPH (Spencer et al., 2006), and that fast-release MPH achieved this peak concentration several hours earlier than slow-release MPH. Based on these findings, we believed that using multiple fast-release MPH medication allowed for a higher sustained peak concentration throughout the day and therefore have a stronger and longer acting effect than a single dosage of slow-release MPH.

Participants underwent a titration (Figure 2), 3 days after Baseline, commencing immediately after the participant had completed their three days of eating exclusively from the lunch boxes. The participants were titrated to their best tolerated dose of MPH over the course of 7 days. The doses ranged from 0.25 mg/kg to 1.00 mg/kg for participants. The dose titration began at 0.25 mg/kg and increased each day by the following: day two 15% increase, day three 30% increase, day four 45% increase, day five 60% increase, day six 75% increase, and finally day seven 100% increase. Participants were asked to rate their side effects from home using a secure online server at CHEO (see Appendix H), this helped to ensure compliance as the participant was prompted (through email) to complete this task daily during titration. Should the participant have rated any side effects as greater than moderate severity, the study coordinator (Dr. Jameason Cameron) was informed, as well as the study psychiatrist (Dr. Phillipe Robaey) and the titration would have been lowered to a more tolerable dose. However, there were no instances where this occurred in the current study.

3.6 Repeated Measures Test Days (Duration: 6 hours each, 2 test days)

All participants were instructed to arrive early in the morning and have maintained a 12-hour overnight fast, as well as restraining from any vigorous physical activities for at least 48-hours. Participants underwent the following measurements:

7:30 Arrive at the laboratory after an overnight fast. Visual Analog scales administered in order to measure appetite. Participants answered questions in relation to their physical activity during the last three days to ensure no vigorous physical activity occurred.

7:40 Vital signs and assessment of body composition were taken (blood pressure, heart rate, waist circumference, height, weight, fat mass, fat free mass and percent body fat using the DEXA). Participants rate their appetite sensations throughout the morning at 60-minute intervals.

8:00-8:30: Participant rested quietly in a supne position.

8:30-9:00: Measurement of REE using indirect calorimetry.

9:05-9:20: A standardized breakfast was served (White bread, butter, strawberry jam, cheddar cheese and orange juice).

9:30-12:30: Measurement of TEF was taken using indirect calorimetry for 3-hours. In between measurements, the participant performed two 10-minute computer tasks measuring impulsivity and food reinforcement. The participant also underwent a 15-minute smell test.

12:30-13:00: The participant was provided with an ad-libitum lunch buffet, after which appetite and palatability were assessed with VAS.

End of the experimental session.

The same measurements were repeated for Final visit as well. At Baseline, participants were not given any placebo or MPH prior to eating the standardized breakfast nor the ad libitum lunch. On the Final repeated measure test day the participant did ingest the placebo or MPH,

depending on the group they were placed in, prior to the standardized breakfast. Participants were also tasked with returning their lunch boxes on the Final repeated measures test day.

3.7 Mid-point and Lunch visit

3.7.1 Mid-point visit

On day 30 of the study, participants were required to visit the laboratory for 1-hour for the Mid-point visit. During the mid-point visit the following were assessed; perceived side-effects, body weight, impulsivity, food reinforcement, and smell function. Additionally, participants were given the last month of placebo or MPH.

3.7.2 Lunch Visit

Participants returned on day 56 (4 days before final measures test day) in order to obtain their 3 days food supply lunch box, from which they were asked to exclusively eat from.

3.8 Measurements

For the scope of this thesis (examining solely EE) only the relevant measurements were included (EE, and anthropometrics). However, there are many components that are being measured such as energy intake, body composition, relative reinforcing value of food, eating behavior etc., but they are not the focus of this particular thesis.

3.8.1 Anthropometrics

Weight was assessed using a SECA scale (Seca GmBH & Co. Hamburg Germany) calibrated to 0.1 kg. Height was assessed using a SECA standiometer (Seca GmBH & Co. Hamburg Germany). BMI (kg/m^2) was calculated using these two measurements. Waist circumference was also measured using an anthropometric tape by placing the tape horizontally midway between the bottom of the rib cage and the iliac crest, and recording the measurement at the end of a normal expiration as defined by the Canadian society of Exercise Physiology (CSEP, 2004).

Body composition (%Body fat, fat mass and fat-free mass) was assessed using Dual-energy X-ray Absorptiometry (Lunar Prodigy, General Electric, Madison, WI, USA).

3.8.2 Measures of Energy Expenditure

Energy expenditure was measured in two different ways in order to assess REE, TEF and PAEE.

3.8.2.1 Energy Expenditure through physical activity (Actical accelerometer)

The first method of measurement was done through the use of an Actical (Philips Respironics). The Actical is a small sensor that measures any and all motion, noting down the occurrence and intensity when motion occurs. The device was fastened to a belt which was worn around the waist of the participant. The Actical measured PAEE, as well as the time spent in sedentary, light, moderate and/or vigorous physical activity (See **Table 1** and **Table 2** for cut-offs) (Romanzini et al., 2012). The Actical was chosen as it has been shown to have good reliability and validity in the populations studied (Puyau et al., 2004; Esliger et al., 2007; Wang et al., 2011; Colley & Tremblay, 2011). Valid wear-time per day is considered 10-hours per day, consisting of 4 valid days in a 7-day period (Katapally & Muhajarine, 2014).

3.8.2.2 Resting Energy Expenditure (Indirect calorimetry)

The second method for measuring EE was through indirect calorimetry and examined REE. As discussed previously, REE was assessed during repeated measures test days (Baseline, and Final). Prior to data collection, the participant was asked to rest in the supine position for 30 minutes in order to ensure an accurate measurement of REE. After the 30-minute resting period, O_2 consumption and CO_2 production was measured continuously over 30 minutes with samples being collected every minute through the use of the ventilated hood technique and a Vmax Encore 29N metabolic cart (SensorMedics, Yorba Linda, CA).

3.8.2.3 The Thermic effect of food (Indirect calorimetry)

The same method, indirect calorimetry through the use of the ventilated hood technique, was used to measure TEF. TEF was measured after the participant were given a standardized breakfast (~450 kcals). The measurements were taken for 30 minutes, every 30 minutes for a period of 4-hours, resulting in 4 measures of TEF being collected. The samples were collected every minute over the 30-minute sampling period, with the use of the Vmax Encore 29N metabolic cart.

3.9 Safety Protocol

The present study's safety protocol excluded those with adverse reactions, including those presenting with cardiac abnormalities (e.g. flutter, block, junctional, and pacemaker abnormalities), systolic blood pressure exceeding pre-MPH test dose reading by 20 mmHg, diastolic blood pressure exceeding baseline by 10 mmHg, BP of 160/100 or higher, or resting heart rate increases of 20 beats/minute from baseline (pre-test dose). For the current study, no participant was excluded based on their responses to test dose (0.5 mg/kg) or reported any symptom greater than mild-moderate severity. We also monitored with daily reporting of side effects/adverse events using CHEO's REDCAP web-based system during the first two-weeks after administration, and twice monthly thereafter. Participants who rated symptoms greater than moderate severity activated a multi-phase screening and safety protocol. Briefly, participants were first called by the research coordinator (Dr. Jameason Cameron) who reported severe side-effects. Dr. Cameron would immediately page the on-call study psychiatrist (Dr. Phillippe Robaey) at CHEO to relay this information. Dr. Robaey, who is also licensed to treat adults, would contact the participant by phone to further evaluate, and if clinically warranted, he would perform a more thorough examination at CHEO. This psychiatrist, who is not affiliated with the

trial to preserve blinding and reduce biased clinical decision making, will then provide appropriate clinical care, which may involve discontinuing participation in case of severe adverse drug reactions. For the current study, we did not have to activate that plan due to no participants reporting severe side-effects.

Information provided to all participants in the present study, including our data safety and monitoring protocol, is consistent with CONSORT guidelines for conducting pharmacological trials (Moher et al., 2010) and reporting harms (Ioannadis et al., 2004), Good Clinical Practice guidelines and Health Canada's Division 5 regulations (ICH guidelines, 2016; Health Canada, 2001)

3.10 Data Analysis

The data was analyzed through the use of independent t-tests at baseline, repeated measures analysis of variance (ANOVA), analysis of covariance (ANCOVA, where applicable), and Pearson correlations of change (delta) scores. A total of 12 participants completed the trial (5 MPH, 7 Placebo). Two participants' EE data were removed from statistical analyses. One participant's data was removed, as the data indicated violation of study guidelines (non-fasted REE sampling). Another participant's data was deemed to be an outlier (approximately 1000 kcals above baseline readings for REE), and as such was excluded from data analyses. Furthermore, one participant's data (placebo group) for TEF measures was incomplete, and as such the participants missing data was imputed using SPSS imputing protocols. The data was imputed 5 times, and the average of those 5 imputations were taken and used for analyses. In total, data on 10 participants were analyzed, 5 in placebo group, and 5 in the MPH group.

3.10.1 Independent T-tests

Baseline characteristics (age, sex, SES, anthropometrics) of each group were summarized and examined through independent t-tests to determine whether group differences existed and if the randomization of participants was successful. If groups differed on a variable that was also related to the primary outcomes of EE, they were statistically controlled in analyses.

3.10.2 Repeated Measures ANOVA

The main objectives of whether MPH leads to any changes in REE or TEF (objective 1) were tested through the use of a group (mph VS Placebo) x time (baseline, 60-days) repeated measures ANOVA. Objective 2, which examined changes in PAEE between the groups over time were also evaluated using a group (MPH vs Placebo) by time (baseline, 60-days) repeated measures ANOVA. In the case where the groups differed at baseline on demographic, anthropometrics, or other potentially cofounding variables, they were statistically controlled using an ANCOVA, although this was not needed. Effect sizes were calculated based on Cohen's d (Cohen, 1980) using Carlson and Schmidt's (1999) method for calculating effect size, and ETA squared to aid interpretation of results.

3.10.3 Change Scores and Pearson Correlation

Pre-post (baseline- 60 days) change scores were calculated for REE, TEF and PAEE, as well as many other variables such as adiposity, fat-free mass and other body composition indicators. Once the pre-post change scores were calculated, a Pearson correlation was run to help determine if changes in REE, TEF or PAEE were correlated with any change in body composition (Objective 3).

4.0 CHAPTER 4 - RESULTS

As shown in the consort flow chart in **Figure 1**, a total of 19 participants were screened. From the 19 participants, 5 were not randomized due to decision to not participate (4) or not meeting inclusion criteria (1). From these remaining 14 participants, complete data were collected on 12 participants. Two participants' data were incomplete as they were not able to complete the study, due to their own time constraints (1) or failing to attend a repeated measures test day (1). From these 12 participants, there was a total of 7 (4 male, 3 female) in the placebo group, and 5 (2 male, 3 female) in the MPH group. From these 12 participants, only 10 participants data was used for analysis, due to outliers in the data (1) or failure to adhere to pre-testing requirements (1) (i.e. not fasted).

4.1 Baseline Characteristics & Anthropometrics

As illustrated in **Table 3**, the sample population had a mean age of 28.8 ± 6.9 years of age, a mean baseline body weight of 107.3± 2.3 kg and a mean BMI of 36.8 ± 4.4 kg/m^2. An independent sample T-test revealed no significant differences ($p < 0.05$) between groups (MPH and placebo) for baseline sociodemographic, anthropometric characteristics, REE, TEF, or free-living PAEE.

As shown in **Table 4**, an independent samples T-test revealed no significant differences ($p < 0.05$) between groups (MPH and placebo) for body composition measures (FFM, FM, %BF) and energy expenditure measures (REE, and TEF), although some of the effect sizes obtained were large.

Change scores in the MPH group revealed reductions in body weight (2.66 ± 2.00 kg), body fat% (1.08 ± 1.71 %), fat mass (2.23 ± 2.37 kg), and fat-free mass (0.54 ± 0.99 kg),

Change scores in the placebo group revealed reductions in body weight (1.64 ± 1.41 kg), and increases in body fat% (0.42 ± 2.32 %), fat mass (0.132 ± 2.81 kg) and fat-free mass (0.41 ± 1.28 kg). These groups differences for weight loss, favouring MPH, trended towards significance ($p > 0.05$), while group differences for body fat%, fat mass, and fat-free mass were not significant (See **Table 4**).

4.2 Effects of MPH on Resting Energy Expenditure and Thermic Effect of Food

The repeated measures ANOVA on Relative REE Relative REE: F(1, 8) = 4.235, p = 0.074, d = 0.83, $\pi^2 = 0.346$) a trend toward greater increases in MPH compared to placebo with a large effect size, as demonstrated by Cohen's *d* As can be seen in **Table 5** (and **Figure 4)**, a repeated measures ANOVA yielded a trend toward greater increases in the MPH group (18.53 ± 1.97 kcal/day/kg at baseline, to 19.71 ± 2.52 kcal/day/kg at final) of approximately 6% over the study, compared to placebo (19.08 ± 2.36 kcal/day/kg at baseline, to 18.26 ± 2.04 kcal/day/kg at final) which decreased approximately 4%, for a relative difference of 10% between groups.

The repeated measures ANOVA also revealed that for Absolute REE: (F(1, 8) = 3.96, p = 0.082, d = 0.49, $\pi^2 = 0.331$) a trend emerged toward greater increases in MPH compared to placebo, with a moderate effect size as demonstrated by Cohen's *d*. Table 5 also shows that absolute REE (kcal/day) also yielded a non-significant trend showing increases over time for MPH (1866.4 ± 344.5 kcal/day at baseline, to 1918.8 ± 306.5 kcal/day at final) and decreases over time for placebo (2122.6 ± 301.5 kcal/day at baseline, to 2000.8 ± 262.8 kcal/day at final), with a small effect size as shown by Cohen's d.

The repeated measures ANOVA revealed no differences between groups on changes in TEF for area under the curve (AUC)(TEF AUC: F(1, 8) = 0.079, p = 0.785, d = 0.15, $\pi^2 = 0.010$) with a small effect size, as demonstrated by Cohen's *d*. As seen in **Table 5** (**Figure 5**), a repeated

measures ANOVA analyzing changes in TEF AUC (kcal/min) showed a non-significant decrease in TEF for MPH (0.38 ± 0.19 kcal/min at baseline, to 0.25 ± 0.09 kcal/min at final), and placebo (0.46 ± 0.16 kcal/min at baseline, to 0.30 ± 0.08 kcal/min at final), with the placebo group showing a greater trend toward decreasing in TEF than the MPH group.

Individual data for relative REE, as illustrated in Table 6, revealed a closer examination of the change witnessed in both the MPH and placebo group (Figure 6 & Figure 7). It can be seen that 3 out of 5 participants in the MPH group exhibited an increase in relative REE. In contrast, the placebo group noted a drop in relative REE for 4 out of 5 participants.

4.3 Effects of MPH on Physical Activity Energy Expenditure

As shown in **Table 7**, the repeated measures ANOVAs revealed no differences between groups on changes in all PAEE variables. MPH did not produce greater changes in sedentary behavior (mins/day) compared to placebo (SB: F (1, 8) = 0.455, p = 0.52, d = 0.02, π^2 = 0.054) with a very small effect size. MPH did not produce greater changes than placebo on Light physical activity (mins/day) (LPA: F (1, 8) = 0.504, p = 0.50, d = 0.16, π^2 = 0.059), Moderate intensity physical (mins/day) activity (MPA: F (1, 8) = 0.281, p = 0.61, d = 0.19, π^2 = 0.034), Moderate-to-Vigorous physical (mins/day) (MVPA: F (1, 8) = 0.120, p = 0.74, d = 0.15, π^2 = 0.015), or vigorous physical activity (mins/day) (VPA: F (1, 8) = 3.495, p = 0.098, d = 0.91, π^2 = 0.304) although there was a large effect size favouring MPH on vigorous PA, as demonstrated by Cohen's *d*.

4.4 Correlations between changes in Energy Expenditure and Body Composition

Table 5 shows the change scores for the different components of body composition within groups. When both groups are collapsed into one sample, Pearson correlations of change scores (as seen in **Table 8**) indicated that changes in relative REE were moderately inversely correlated

with changes in body weight *(r* = -0.599, *p* = 0.067), changes in body fat% *(r* = -0.522, *p* = 0.121), and changes in fat-mass *(r* = -0.555, *p* = 0.096). Changes in absolute REE were found to be small-to-moderately inversely correlated with changes in body weight *(r* = -0.353, *p* = 0.317), changes in body fat% *(r* = -0.397, *p* = 0.56), and moderately inversely correlated with changes in fat-mass *(r* = -0.401, *p* = 0.251). Additionally, changes in TEF AUC were not found to be significantly correlated with any changes in body weight, body fat%, or fat mass, as demonstrated by Pearson's correlation. However, changes in TEF AUC were found to be moderately inversely correlated with changes in fat-free mass *(r* = -0.594, *p* = 0.070). Finally, changes in light physical activity were also found to be moderately inversely correlated with changes in body weight *(r* = -0.502, *p* = 0.140). As well, changes in MPA and MVPA were found to be moderately positively correlated with changes in body fat% *(r* = 0.418, *p* = 0.229) *(r* = 0.424, *p* = 0.222), respectively. Finally, changes in VPA were found to be weak-to-moderately inversely correlated with changes in fat-free mass *(r* = -0.319, *p* = 0.368). The remaining PAEE variables were shown to have weak correlations *(r* < 0.3).

Change scores within the MPH group, as shown in **Table 9**, show stronger (than placebo) inverse correlations between changes in body composition and changes in relative REE and TEF AUC. Changes in relative REE were moderately inversely correlated with changes in body weight *(r* = -0.653, *p* = 0.232), changes in body fat% *(r* = -0.643, *p* = 0.42), changes in fat mass *(r* = -0.586, *p* = 0.299). Changes in TEF AUC were moderately inversely correlated with changes in fat-free mass *(r* = -0.617, *p* = 0.267). Changes in light physical activity were small-to-moderately inversely correlated with changes in body weight *(r* = -0.356, *p* = 0.557).

Change scores within the placebo group, as shown in **Table 9**, show changes in relative REE were mildly inversely correlated with changes in body weight *(r* = -0.388, *p* = 0.518), body

fat% (*r* = -0.223, *p* = 0.719) and fat mass (*r* = -0.241, *p* = 0.696). Changes in relative TEF AUC were also not correlated with changes in body fat% (*r* = -0.216, *p* = 0.727) and changes in fat-free mass (*r* = -0.640, *p* = 0.244). Changes in sedentary behavior were strongly inversely correlated with changes in body fat% (*r* = -0.860, *p* = 0.061) and fat mass (*r* = -0.806, *p* = 0.099). Additionally, light physical activity was found to be strongly inversely correlated with changes in body weight (*r* = -0.842, *p* = 0.074). Changes in MPA were also shown to be strongly correlated with changes in body weight (*r* = 0.762, *p* = 0.134), body fat% (*r* = 0.669, *p* = 0.217), and fat mass (*r* = 0.768, *p* = 0.13). Changes in MVPA were also found to be strongly correlated with changes in body weight (*r* = 0.788, *p* = 0.114), body fat% (*r* = 0.668, *p* = 0.218), and fat mass (*r* = 0.771, *p* = 0.127). Finally, changes in VPA were also found to be strongly correlated with body weight (*r* = 0.794, *p* = 0.108), body fat% (*r* = 0.425, *p* = 0.476), fat mass (*r* = 0.541, *p* = 0.346) and moderately inversely correlated with changes in fat-free mass (*r* = -0.415, *p* = 0.487).

5.0 CHAPTER 5 - DISCUSSION

This thesis evaluated the effect of Methylphenidate on the three different components of EE (REE, TEF, and PAEE) in individuals with obesity using a randomized, double-blind, placebo-controlled design as a pilot test of MPHs potential as an anti-obesity agent. More specifically, the objective of this study was to examine changes in REE, TEF and PAEE after 60-day administration of either placebo or MPH. This study also examined how changes in these EE variables correlated with changes in anthropometrics such as body weight (kg), body fat%, fat mass (kg) and fat-free mass (kg), to evaluate the impact that changes in EE have on body composition. Although none of the findings in the present study were statistically significant, the trends found, in relation to relative REE, are meaningful and warrant future research.

It is suggested that the increases in relative REE recorded in the MPH group, may have contributed to the reductions seen in body weight, body fat% and fat mass. These findings suggest a rather potent effect of MPH on REE. Furthermore, there were no significant findings in relation to TEF and PAEE variables, suggesting that either MPH does not have an effect on these variables, or we simply did not witness any. Finally, strong inverse correlations were found between changes seen in relative REE and changes in body weight, body fat% and fat mass, suggesting that as relative REE increased, there were decreases in body weight, body fat% and fat mass.

5.1 Resting Energy Expenditure

In this field trial, we aimed to see whether MPH administration had an effect on REE, as was seen in previous laboratory research (Lorello et al., 2008). The hypotheses were; that MPH could attenuate the reduction seen in REE following weight-loss; and actually, increase REE after 60-days (compared to placebo). REE was expressed as two different variables, absolute REE and relative REE. Absolute REE (kcal/day) was the value sampled during the repeated

measures test day. Relative REE is the same measured absolute REE variable, however, it is normalized for the weight of the participant (kcal/day/kg). An important difference between the two variables would be that absolute REE does not factor in the change in body weight of the participants, and as such relative REE represents a more accurate depiction of the isolated effect of MPH on REE as the change in body weight, seen in this study, is considered.

Objective 1 was to examine the effects of short-acting MPH administration on changes in Relative or absolute REE over 60-days (before and after). Indeed, it was found that the mean relative REE of the MPH group increased by approximately 6.4%, while the mean relative REE of the placebo group decreased by approximately 4.3%, for a relative difference of 10.7% favouring MPH. Similarly, the mean absolute REE of the MPH group increased by approximately 2.8%, and the placebo groups mean absolute REE decreased (by approximately 5.7%, for a relative difference of 8.5%. These findings mirror previous literature findings obtained in the laboratory and extend them to the natural environment (Lorello et al., 2008), suggesting that MPH leads to an increase in REE. The relative increase in REE in the MPH group, despite reductions in body weight, suggest a potent effect of MPH on REE.

. This exploratory finding, established in the natural environment, extends previous findings showcasing that MPH led to an acute increase in REE in the laboratory (Lorello et al., 2008). Although not statistically significant the effects of MPH on relative REE were large (d = 0.83), suggesting that the effect may have reached statistical significance with a larger sample size.

When comparing the current study with the study completed by Lorello et al. (2008), which found a significant increase of 7% in absolute REE and TEF, there are a few differences. Firstly, the current study looked at prolonged administration of MPH (60-days), whereas Lorello et al. (2008) looked at a single bout of MPH administration. Furthermore, Lorello et al. (2008) found a

significant increase in absolute REE, and not relative REE. As their study was conducted on a single test-basis, they did not require normalizing for weight change in their participants. As well, the current study population was individuals with obesity, whereas Lorello et al. (2008) used healthy normal weight adults. Additionally, it has been shown that individuals who are losing weight have lower REE levels than normal weight individuals (Astrup et al., 1999), further supporting our use of relative REE. Participants in the current study demonstrated weight loss, whereas Lorello et al. (2008) did not. As well, the current study looked at between subjects comparisons, whereas Lorello et al. (2008) compared changes in EE within participants, using a cross-over design. Despite methodological differences listed, MPH still produced similar findings (increases in REE) using experimental designs, indicating that this increase is most likely due to the influence of the drug.

When further examining the changes seen in relative REE in each individual (Figure 6 & Figure 7) in both the MPH and placebo group, it is apparent that not all individuals responded to the medication in similar forms. From the 5 participants in the MPH group, there were notable increases in relative REE for 3 participants. From the remaining 2 participants, they showed very minor decreases in relative REE -0.51 kcal/day/kg, and -0.25 kcal/day/kg, (Table 6). This could be due to the individuals having shown no response to the drug, as it has previously been discovered that some individuals are non-responders to MPH (Arnold, 2000). Additionally, if the participant was a non-responder and they experienced the measured weight-loss (-1.7 kg), then their drop in REE (-0.51 kcal/day/kg) is to be expected. This drop is comparable with the weight-loss and relative REE reduction seen in the placebo group (-1.66 kg, -0.821 kcal/day/kg). Assuming that these two participants were non-responders to the medication, and isolating for only the mean relative REE increase seen in the remaining 3 participants, we calculate a mean

increase of 2.23 kcal/day/kg in relative REE, while experience a mean weight loss of 3.43 kg. Taken together, a response rate of 60% (3 of 5 participants) showing increases in REE, and the remaining 40% showing stable or minor decreases in REE in the presence of weight loss, is encouraging from a clinical perspective.

This change in relative REE supports our proposed theory that an increase in extracellular dopamine, caused by MPH administration, leads to an increase in REE. These results are consistent with research showing that intravenous dopamine infusion results in a thermogenic effect causing an increase in REE (Nakagawa et al., 1994; Ruttinman et al., 1991). This thermogenic effect caused by the infusion of dopamine was linked to increased glucagon levels in the blood (Nakagawa et al., 1994). It has previously been demonstrated that dopamine does indeed stimulate an increase in glucagon secretion (Leblanc et al., 1977). As well, glucagon has previously been shown to increase EE in humans (Figure 8) (Cegla et al., 2014; Salem et al., 2016). Glucagon, often linked to regulating glucose and lipid metabolism, has also been shown to participate in the control of thermogenesis and energy expenditure (Nair, 1987), and may propose one explanation to this increase in REE.

Objective 3, which aimed to examine the relationship between changes in TEE, REE, TEF, PAEE and changes in body composition in drug and placebo groups. The aim was to test for increases in relative REE, but not TEF and PAEE, were associated with reductions in body weight and percent body fat. Differences in anthropometrics (body weight (kg), body fat%, fat mass (kg), and fat-free mass (kg)) were looked at to determine if there were any correlations with change scores of REE, TEF and PAEE. No anthropometric changes were statistically significant. When examining the correlations between relative REE and various anthropometric variables in the MPH group, we found that changes in relative REE were moderately inversely correlated

with body weight *(r* = -0.653), body fat% *(r* = -0.643), and FM *(r* = -0.586) (see **Table 9**). These inverse correlations indicate that as relative REE increases, body weight, body fat% and FM all decrease. These correlations were much weaker in the placebo group. Given weight loss is typically associated with reductions in REE, this finding illustrates that this increase in relative REE in the MPH group likely led to the improvements in body composition, highlighting that changes in REE might represent a potent mechanism of action in the therapeutic use of MPH in obesity management, although future research is needed to verify these findings.

When isolating for only the Placebo group, the findings are in line with the literature in relation to expected metabolic changes in REE following weight loss. The placebo group had a mean change in body weight of -1.64 ± 1.41 kg (see **Table 4**) over the 60-days. As previously discussed, there is evidence illustrating that reductions in REE are prevalent following weight loss (Bray et al., 2012), suggesting an average reduction of 15.4 kcal per kg of weight loss (Schwartz & Doucet, 2010). This process is indicative of adaptive thermogenesis, and our findings mirror this change. This further supports the impact that MPH has on REE, as the MPH group exhibited a mean weight loss of -2.66 ± 2.00 kg, and still experienced the increases in REE as noted above.

. Our findings indicate that when extrapolated over a 24-hour period (realistic time spent on MPH), REE increases by approximately 200 kcals, which although not statistically significant, could be clinically meaningful. An increase of approximately 200 kcals per 24-hour period above rest, with no other form of intervention results in approximately 1 lb. of weight loss every 17 days, independent of the drug's effect on appetite suppression and food intake, which is noted to be substantive (Goldfield et al., 2007; Schachter et al., 2001; Davis et al., 2012). This increase in REE may also help attenuate weight regain given research shows that a lower

adjusted TEE of approximately 200 kcals predisposed subjects to a 59% probability of gaining 7.5 kg or more over a 21-month period (Ravussin et al., 1988). As well, these findings are also mirror the findings that Lorello et al. (2008) found, specifically in the case of the measureable impact of MPH on REE, as it was extrapolated over the course of the day to be approximately 188 kcals/day. It is evident that the trends revealed in the current study are promising, and that further investigation is warranted with more participants and a longer study period in order to more definitively evaluate the effects of MPH on changes in REE, and how this impacts weight loss and maintenance of weight loss.

5.2 Thermic Effect of Food

TEF encompasses approximately 10% of TEE (Poehlman, 1989), and as such can be thought of as a relatively small but meaningful measure of EE. The objective of the current study in regards to TEF was; 1) determine if MPH could lead to an increase TEF after 60-days. TEF is defined as the increase in EE above REE, following the ingestion of a meal. TEF AUC (kcal/min) was found to decrease in both groups, non-significantly. Surprisingly both placebo (-35%) and MPH (-34%) exhibited a similar decrease in TEF, despite the MPH group showing slightly greater weight (an absolute mean difference of 1.7 kg) and fat loss (an absolute mean difference of 6.57%), and increased REE. It is important to note that these findings are in contrast with previous literature, which indicated an increase in TEF when administering MPH (Lorello at al., 2008). This discrepancy could be due to the differences between studies in protocol and methodology. The primary difference is that the Lorello (2008) study employed an acute laboratory test of MPH on TEF, while the current study employed a field trial design in the natural environment over 60-days. It is possible that MPH may produce acute effects on TEF, but these are not maintained over time. Additional differences between studies involve the

analysis of TEF. The current study aimed to compare two different TEF AUC values, encompassing 4 separate TEF measurements during a three-hour time period. In contrast, Lorello et al. (2008) only examined the change in TEF after administration of MPH during one time point.

In a systematic review performed by D'alessio et al. (1988), they reported 15 papers citing that subjects with obesity had a reduced TEF, when compared to lean subjects. However, they also reported 12 more papers citing that there was no difference in TEF between obese and lean subjects. This suggests that TEF is not a reliable correlate of obesity, and that methodological differences between studies may play a factor in these discrepant results. Some studies suggest sampling TEF for 5-hours or more in order to get an accurate measure of TEF (Reed & Hill, 1996), while other studies have shown varied lengths of measurement, such as 3-hours (Westrate, 1993), are accurate for a standard 600 kcal meal. In contrast, some studies have also shown that TEF did not return to baseline after 4-hours (D'alessio et al., 1998), even for a >600 kcal meal, suggesting once again that the measurement of TEF can be highly variable. This variability is proposed as the primary explanation for why we did not see the expected increase in TEF that corresponded with our increase in REE induced by MPH administration.

Some other studies have suggested that the body weight of a subject may affect TEF, stating that there are differences between individuals who are lean and individuals who are obese (Reed & Hill, 1996). The present study found no significant or meaningful correlations *(*$r < \pm 0.2$, $p > 0.05$) between changes in anthropometrics and changes in TEF values (see **Table 8**), suggesting that the change in body weight did not influence the reduction illustrated in TEF. Furthermore, in relation to Objective 3, changes in TEF AUC were also moderately inversely correlated with changes in fat-free mass in both the MPH group *(*$r = -0.617$) and the placebo

group *(r* = -0.640). This could perhaps be indicating that the decrease in TEF was not due to the drug, but to changes in fat-free mass. In theory TEF should be unaffected by the body weight of the participant, as TEF is associated with the digestion, absorption, and storage of food, and is mostly associated with the amount of energy a meal consists of (i.e. the more calories in a meal, the higher the TEF will be, in order to digest, absorb and store the food), as some studies have shown (D'Alessio et al., 1998). D'Alessio et al. (1998) studied the differences between lean individuals and individuals with obesity, and concluded that TEF increased linearly with caloric intake, and differences in TEF were indistinguishable between the two groups given the same meal size. In short, the cause for such variability in TEF is hard to determine, and could be due to a number of factors that have yet to be discovered as there is no established consensus among the literature (Granata & Brandon, 2002).

5.3 Physical Activity Energy Expenditure

Physical activity energy expenditure (PAEE) encompasses the remainder of TEE, and is approximately 15-30% of total daily energy expenditure (Poehlman, 1989). Based on other studies with stimulants such as caffeine (Astrup et al., 1990; Graham 2001), objective 2 in the current study was; 1) to determine if the MPH group exhibited greater free-living PAEE than the placebo group. PAEE encompasses activities of energy expenditure such as physical work, muscular activity such as shivering and fidgeting, as well as purposeful free-living physical activity. PAEE was found to not significantly change between or within groups after 60-days, with generally small effect sizes. Indeed, this was a pilot study and our hypotheses with PAEE were exploratory in nature; our study was not powered to specifically examine this relationship but it is an interesting question to pursue in future research. The very limited MPH and PAEE data are in clinical populations with ADHD, with no studies, to our knowledge, focusing on the

effects of MPH on PAEE in a non-ADHD population. Data have shown that taking this stimulant medication was significantly related to a decrease in PAEE in an ADHD population (Butte et al., 1999). Their findings could however be due to a decrease in hyperactivity, as opposed to an absolute decrease in total PA. Perhaps, in a non-ADHD population, such as the current study, this effect was not seen because the study population does not exhibit hyperactivity levels, as to be expected in a non-ADHD population (Wood et al., 2009). In comparison, the children in Butte et al.'s (1999) study saw reductions in their PA levels during tasks (such as playing video games, or watching a movie). This can be thought of as a reduction in their extra non-necessary movements during a task. Previous literature shows that individuals with ADHD tend to exhibit impulsivity and often fidget (American Psychiatric Association, 2013), leading to an increase in PA levels (hyperactivity). Through MPH administration, it is possible these children were able to perform the tasks more efficiently, with less movement, resulting in the decrease PAEE observed in the study. Taking those findings into account with the current study, showcasing no change in PAEE, it can be implied that MPH may not necessarily reduce free-living gross motor movement, but actually may inhibit non-necessary movements during a task, leading to an overall reduction in hyperactivity. These same effects would not be expected to be observed in a non-ADHD population, as they lack this hyperactivity (Wood et al., 2009). Additionally, although repeated measures ANOVA for sedentary behaviour (mins/day), light physical activity (mins/day), moderate physical activity (mins/day) and moderate-to-vigorous physical activity (mins/day) yielded no significant changes with small effect sizes, the repeated measures ANOVA for vigorous physical activity (mins/day) yielded a large effect size (d = 0.91) favouring the MPH group. Although effect sizes for changes in VPA were large in favour of MPH, the magnitude of these absolute changes (MPH; 1.49 ± 0.86 mins/day, placebo: (0.73 ±

0.82 mins/day) (see **Table 7**) is not meaningful given the amount of time spent in VPA was so low. Despite the acuteness of this trend, more research with a larger population is needed to further investigate this finding, as this could support the theory that MPH might exhibit excitatory effects, similar to caffeine (Graham, 2001; Astrup et al., 1990) and similar effects to that of MPH administration previously studied in rats (Thanos et al., 2015).

The present study also found that in relation to Objective 3, there were no significant correlations between changes in PAEE variables (sedentary behaviour, light physical activity, moderate physical activity, moderate-to-vigorous physical and vigorous physical activity) and changes in anthropometrics (body weight, body fat%, fat mass, and fat-free mass). This further highlights the effect of MPH on reducing adiposity is not influenced by changes in PAEE. Instead, it can be concluded that the beneficial changes to weight loss and body composition appear to be mostly driven by the changes in REE.

5.4 Limitations

The present study had several limitations. Although our assessment indicated 100% compliance to the medication, the reliability of this finding may be a limitation of this study, as the only accountable method to assess compliance was the participant bringing their pill boxes back to pharmacy, which in essence is no better than self-reporting consumption of the study drug. In order to promote compliance, the participant received daily electronic text/email reminders to take their medication, as well as an easily accessible and portable drug dispenser for the medication.

Another limitation of the present study, and the primary limitation, was the small sample size (10 participants) which underestimated the power of the study, as well as limiting the meaningfulness of the statistical significance of many of the findings. Effect sizes were reported

to aid interpretation of meaningfulness of the findings. Additionally, the 60-day study duration of this pilot trial, while representing an extension from laboratory research, is still much shorter than standard clinical trial designs of 1-year or longer. Further research using longer study durations are need to better evaluate the sustained effects of MPH on EE.

One more limitation of this study is generalizability of the findings. This thesis evaluated the effect of sustained MPH administration on EE in individuals with obesity not diagnosed with ADHD. As such, the participants recruited for this study were only those meeting the clinical definitions of Obesity, BMI over 30.0 kg/m^2 in adults, and 95^{th} percentile or higher in children (World Health Organizations growth curves; Cole et al., 2000). Therefore, the findings may not be representative of individuals that fall outside of these categories. Furthermore, individuals with certain lifestyle risk factors (i.e. smoking, alcoholism, etc.), diagnosed diseases (i.e. ADHD, diabetes, etc.) or individuals taking certain medications (i.e. MAO inhibitors, antidepressants, etc.) were excluded from this study. As such, the findings of this thesis may not apply to these individuals. Additionally, this project used indirect calorimetry as the method for measuring REE, and not a calorimeter. As such, room temperature and air flow in the room could not be controlled, which may affect the reproducibility of this study.

This study also lacked a mid-point REE/TEF/PAEE measurement, which can be considered a limitation as well. This data, if collected at the 30-day mark, could have provided a clearer picture of the trajectory effects of MPH and would have aided in the interpretation of the observed trends in the present study. This can be addressed in future studies by incorporating an REE/TEF/PAEE repeated measures at the present 30-day mark, or even in future studies incorporating longer duration to better establish trajectories.

These limitations of this study are balanced with many strengths, including the experimental, placebo-controlled design, which is rare in pilot studies and yields the highest quality of evidence (Moher et al., 2010; Ioannidis et al., 2004). In addition, the objective measurement of all components of EE and body composition employed gold standard measures, providing reliable and valid data. Additionally, very careful and thorough screening and side effect monitoring was employed that went above standard clinical care. The dosing and titration protocol was consistent with the American Academy of Pediatrics and ADHD alliance, which may be the reason the medication was very well tolerated in this study (Appendix I). The current thesis focused on EE, but data from the larger study were also collected on measures of EI, cognition, olfaction, food reward, so various mechanisms of action could be detected. Lastly, the experience of conducting a drug trial as part of a master's thesis provided invaluable clinical research experience to graduate students.

6.0 CHAPTER 6 - SIGNIFICANCE

Obesity is a continuously growing public health concern, affecting approximately one in four adult Canadians (Public Health Agency of Canada, 2011). Current behavioural interventions targeting diet and exercise have had limited efficacy, with weight regain being a significant factor undermining maintenance of weight loss. Current pharmacological methods have had either unwanted side effects or limited efficacy, perhaps due to the sole focus of reducing EI as opposed to targeting both EI and TEE (Chan et al., 2013). Therefore, increasing TEE, more specifically REE, with MPH may lead to greater weight loss and possibly better maintenance of weight loss than currently approved agents. The present study has shown for the first time that MPH had a measurable and potentially meaningful effect on relative REE in the presence of weight loss, and these changes in REE were moderately associated with reductions in body weight and adiposity. . With promising trends such as these, and a large effect size (d = 0.83 for relative REE), it suggests that with the addition of more participants, this study could have possibly resulted in a statistically and clinically significant findings. The present study also highlighted that, for the first time in a non-ADHD sample, MPH does not exhibit a significant reduction in physical activity levels. The findings of this study suggest preliminary evidence of the effect MPH could have in producing reductions in body weight and body fat, which may be driven by increases in REE, with virtually no impact on TEF or PAEE. Given the current limitations in weight loss medications, with none of them demonstrating effects on REE, the clinical implications of the study findings may be substantial, and warrant further investigation with larger sample sizes and longer duration to more accurately assess the utility MPH as a therapeutic option in the management of obesity.

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30.10.1097/CHI.0b013e3181b54612

Figures

Figure 1: Consort Flow Chart of participants enrollment, randomization, allocations and analysis from study beginning to end.

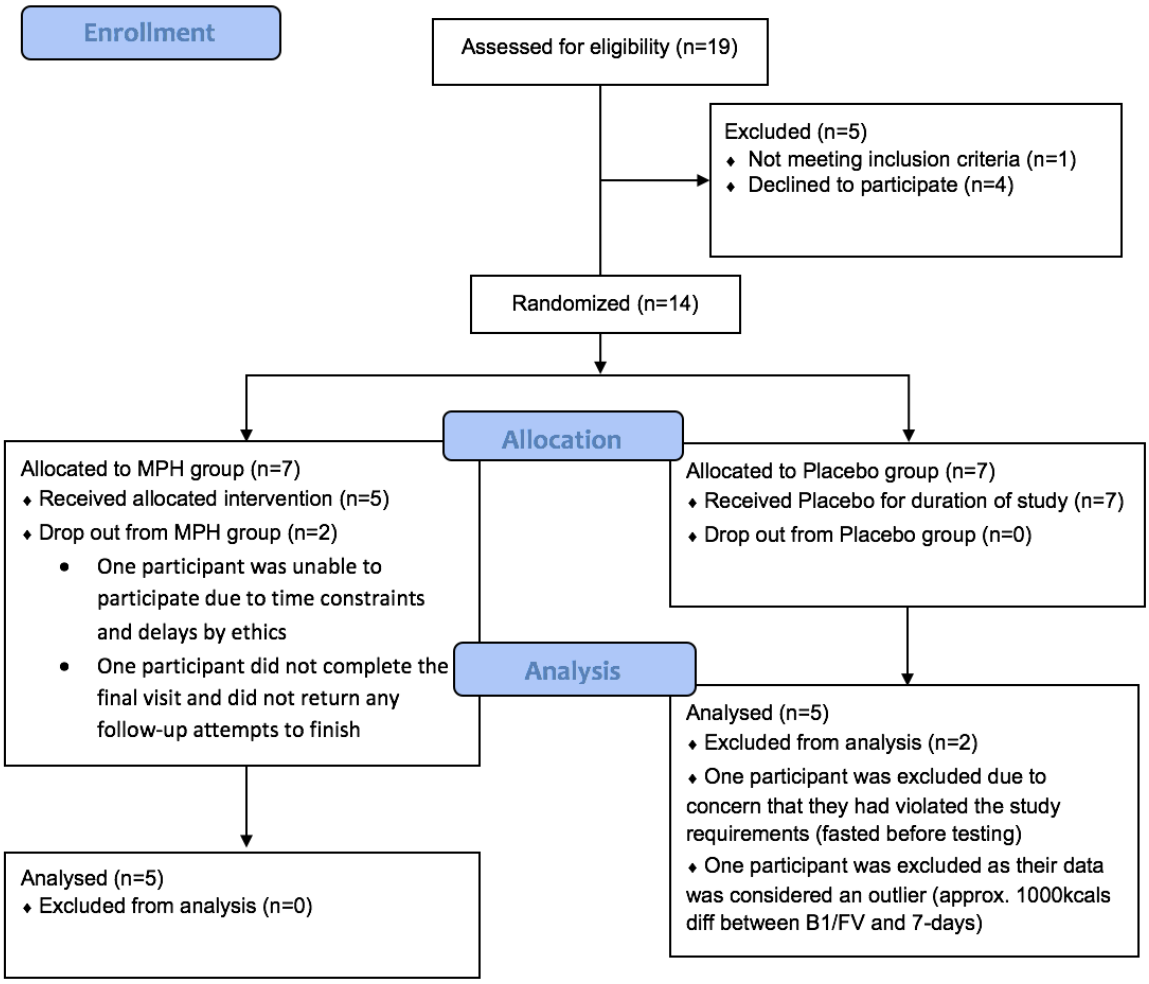
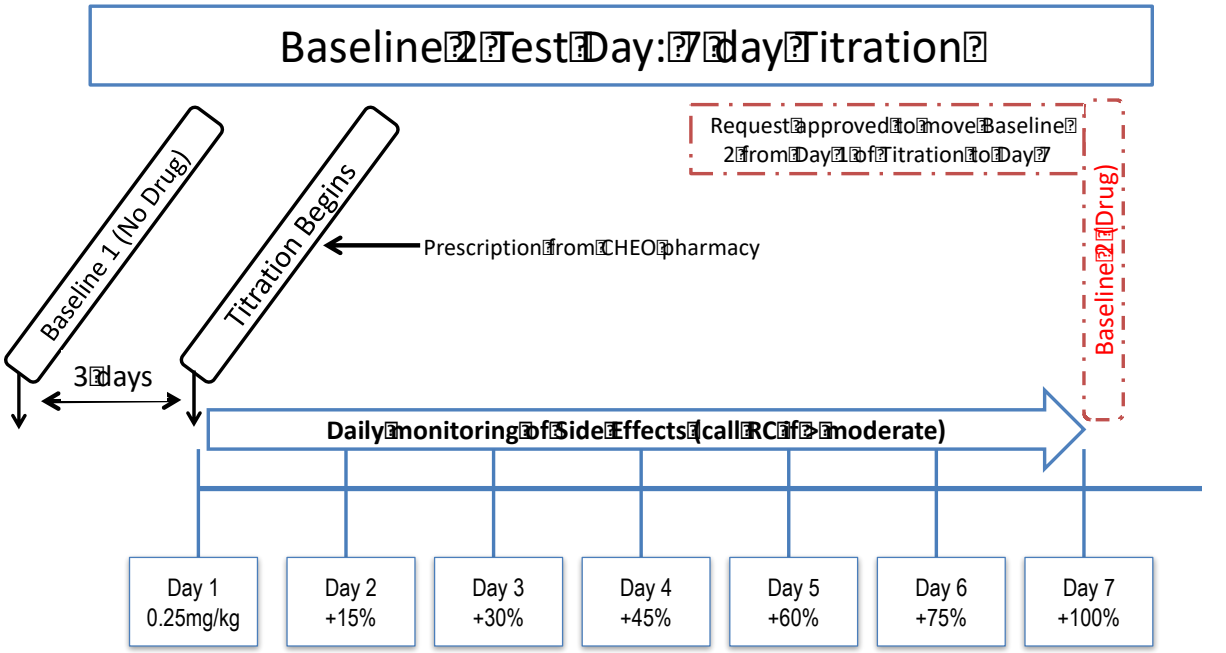


Figure 2: Titration Protocol



Participants will be rating their side effects at home and if they rate any of the side-effects greater than moderate they will be told to contact the study coordinator. The study coordinator will have a side effects management check list and if the side effect(s) are deemed to be Minor (e.g. expected and tolerable), then the participant will be told to carefully monitor the side effects for another day and then report back. If the side effect(s) are persisting, the study coordinator will have the study-affiliated psychiatrist call the participant who will determine the proper course of action. The psychiatrist may be able to properly assess the participant's needs over the phone, or they may deem it necessary that the participant comes into the laboratory for immediate assessment and dose titration to a lower dose that eliminates the side effect symptoms.

Figure 3: Study Timeline

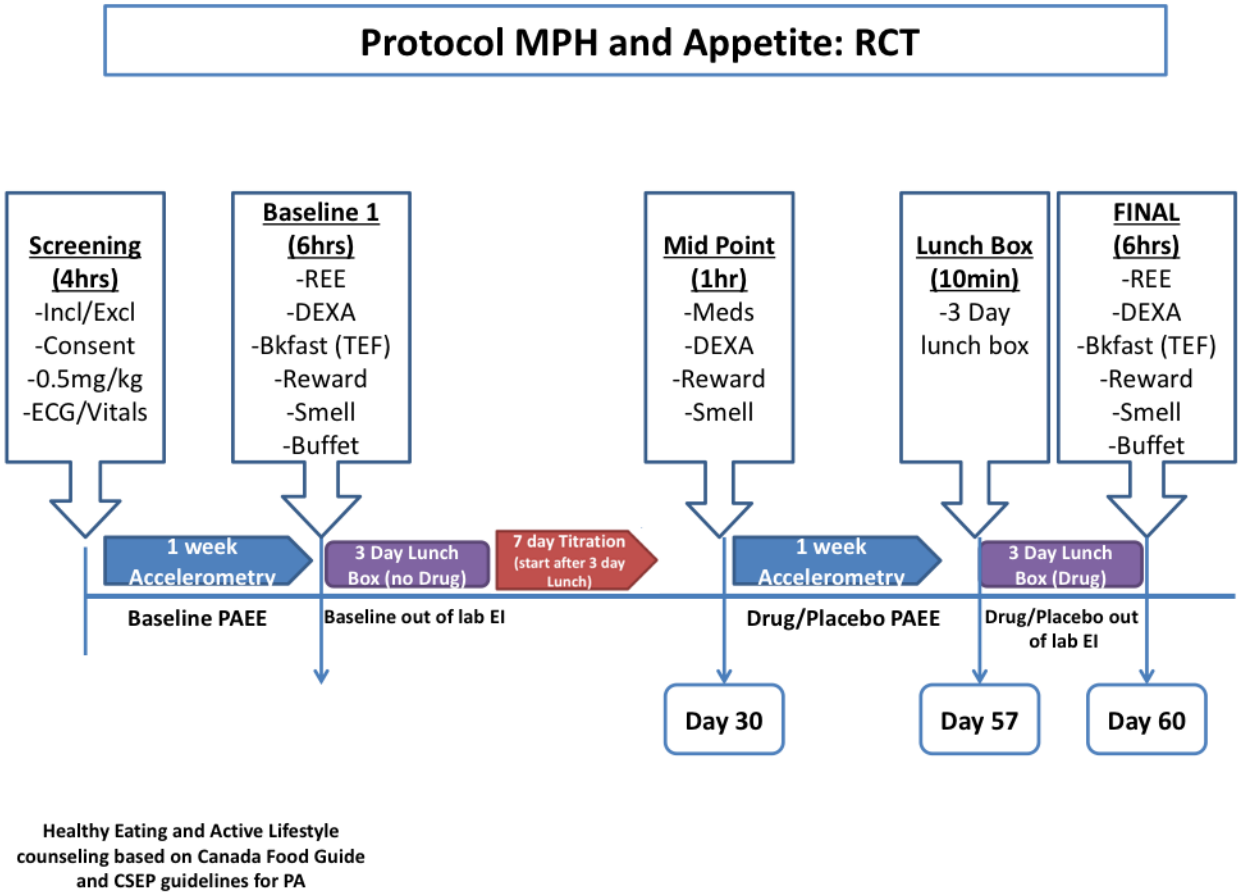


Figure 4: Relative Resting Energy Expenditure (REE) for MPH and Placebo groups as shown over study duration.

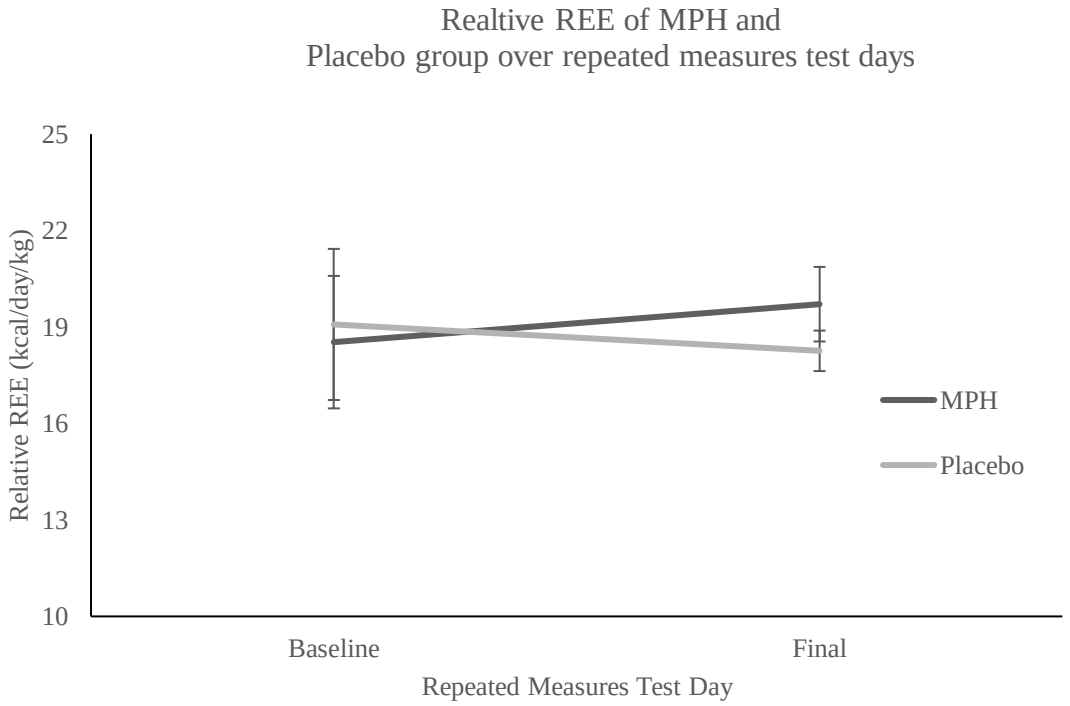


Figure 5: Thermic Effect of Food (TEF) Area Under the Curve (AUC) for MPH and Placebo groups as shown over study duration.

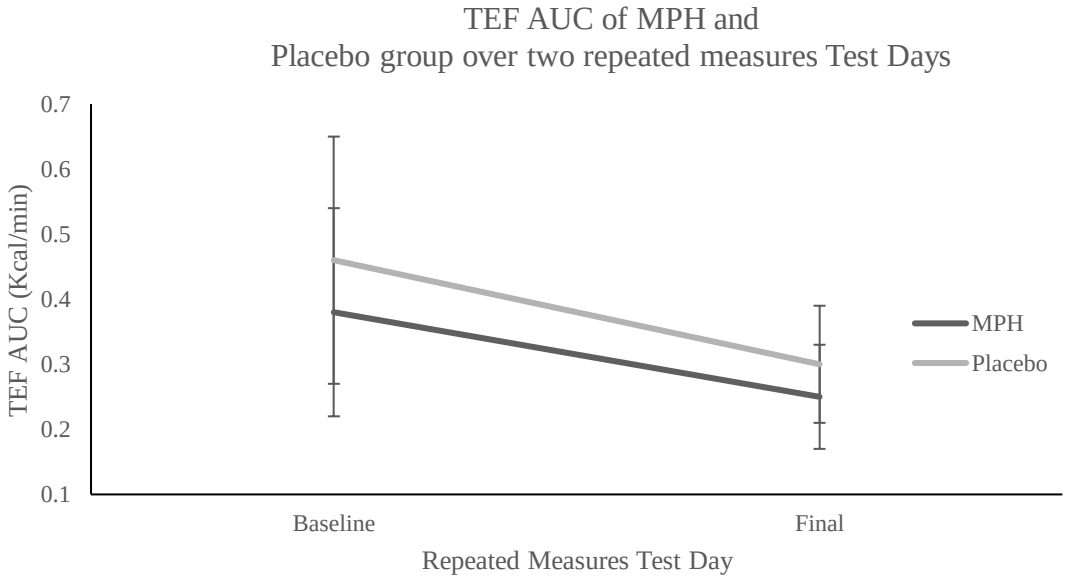


Figure 6: Relative Resting Energy Expenditure of individuals in the MPH group as shown over study duration.

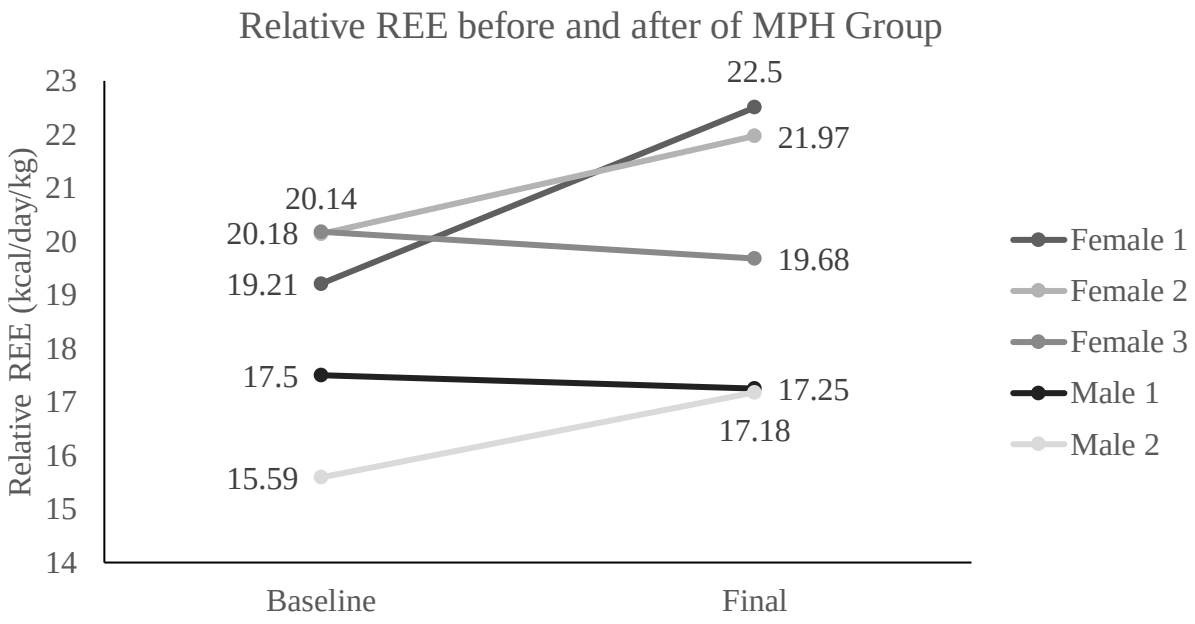


Figure 7: Relative Resting Energy Expenditure of individuals in the Placebo group as shown over study duration.

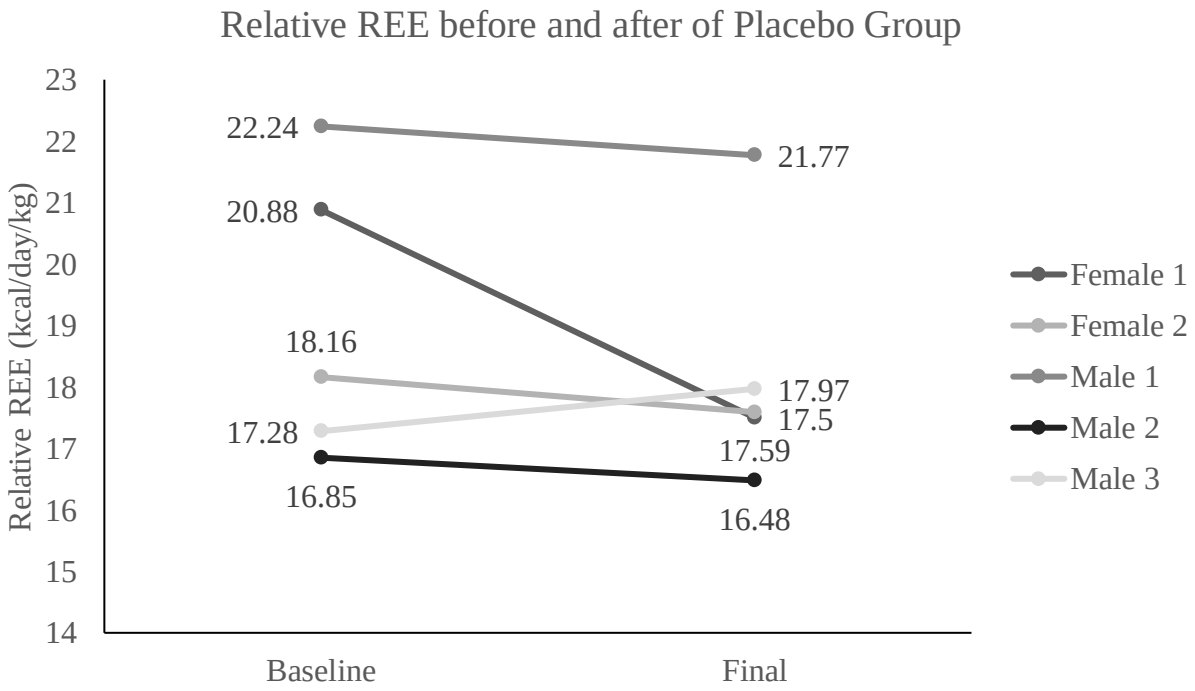
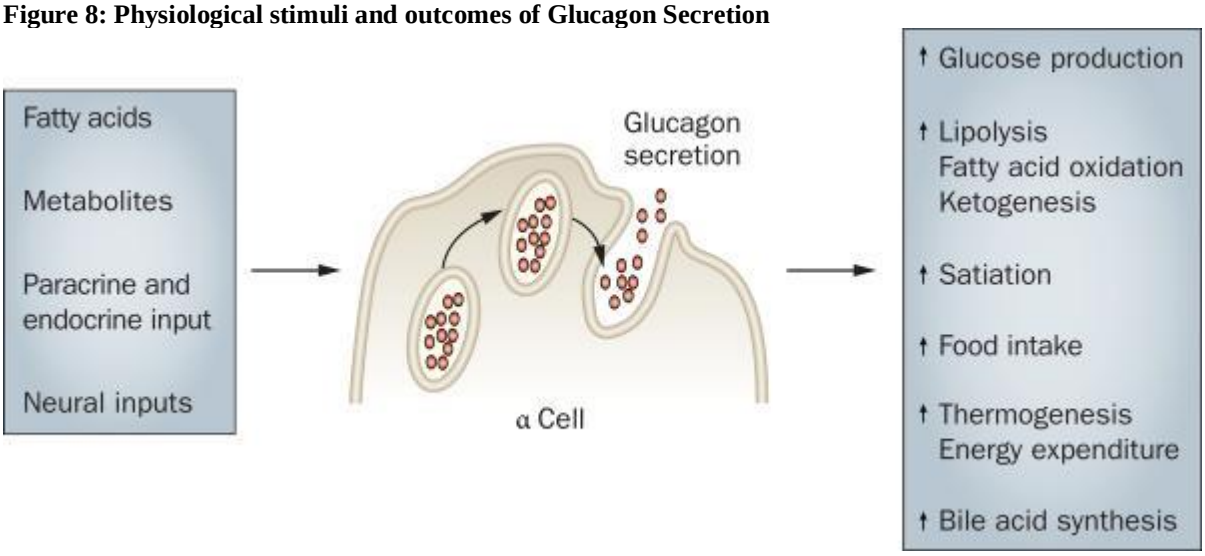


Figure 8: Physiological stimuli and outcomes of Glucagon Secretion



Physiological stimuli and outcomes of Glucagon secretion (Habegger et al., 2010)

Tables

Table 1: Actical Physical Activity Cut-offs for children as described by Puyau et al. (2002)

Type of Physical Activity	Cut-offs (counts•minute)
Sedentary	0-100 (c•min)
Light	100-1499 (c•min)
Moderate	1500-6499 (c•min)
Vigorous	≥6500 (c•min)

Note: Sample: n=32 (age 7–18); Activities: rest, playing videogames, working at computer, dusting, aerobics, ball toss, walking (2 and 3 mph), running (4.5 to 7 mph). Criterion: room calorimetry. Method: regression model

Table 2: Actical Phyiscal Activity cut-offs for adults as described by Colley & Tremblay (2011) and Wong et al. (2011)

Type of Physical Activity	Cut-offs (counts•minute)
Sedentary	0-100 (c•min)
Light	100-1534 (c•min)
Moderate	1535-3959 (c•min)
Vigorous	≥3960 (c•min)

Table 3: Baseline Characteristics of study population, showcasing anthropometric and energy expenditure values (n = 10)

Variables	Condition			Difference Between groups	Effect Sizes
	Grouped	Placebo	MPH		
	Mean (SD)	Mean (SD)	Mean (SD)	*p*	*d*
Sample size	n = 10	n = 5	n = 5		
Sex	5 Male (50%)	3 Male (60%)	2 Male (40%)	0.58	
Age (years)	28.8 ± 6.89	29 ± 7.9	28.6 ± 6.7	0.933	0.055
Height (cm)	170.0 ± 10.2	171.3 ± 9.7	168.7 ± 11.6	0.711	0.243
Baseline Body Weight (kg)	107.31 ± 22.3	112.26 ± 20.13	102.36 ± 25.5	0.515	0.431
Baseline BMI (kg/m^2)	36.82 ± 4.43	37.99 ± 2.76	35.64 ± 5.74	0.432	0.522
Baseline Fat-Mass (kg)	47.83 ± 11.88	50.18 ± 14.15	45.49 ± 10.18	0.564	0.381
Baseline Fat-Free Mass (kg)	54.48 ± 12.10	55.53 ± 8.68	53.43 ± 15.86	0.802	0.164
Baseline Body-Fat (%)	45.04 ± 5.19	45.1 ± 7.35	45.00 ± 2.56	0.982	0.018
Baseline REE (Kcal/day)	1994.54 ± 333.77	2122.6 ± 301.5	1866.4 ± 344.5	0.246	0.791
Baseline Relative REE (Kcal/day/kg)	18.80 ± 2.07	19.08 ± 2.36	18.53 ± 1.97	0.696	0.253
Baseline TEF (Kcal/min)	0.42 ± 0.17	0.46 ± 0.16	0.38 ± 0.19	0.513	0.455

Table 4: Post-Treatment Final Characteristics of study population, showcasing anthropometrics, and energy expenditure (n = 10)

	Condition			Difference Between groups	Effect Sizes
	Grouped	Placebo	MPH		
Variables	Mean (SD)	Mean (SD)	Mean (SD)	*p*	*d*
Sample Size	n = 10	n = 5	n = 5		
Final Body Weight (kg)	105.16 ± 23.04	110.62 ± 19.9	99.7 ± 26.8	0.486	0.463
Final BMI (kg/m^2)	36.06 ± 4.63	37.45 ± 2.97	34.67 ± 6.28	0.397	0.566
Final Fat-Mass (kg)	46.78 ± 13.81	50.31 ± 16.62	43.25 ± 11.02	0.452	0.501
Final Fat-Free Mass (kg)	54.42 ± 12.96	55.94 ± 9.83	52.89 ± 16.59	0.733	0.224
Final Body-Fat (%)	44.71 ± 6.47	45.5 ± 9.25	43.92 ± 2.68	0.723	0.232
Final REE (Kcal/day)	1959.82 ± 272.64	2000.8 ± 262.8	1918.8 ± 306.5	0.662	0.287
Final Relative REE (Kcal/day/kg)	18.99 ± 2.29	18.26 ± 2.04	19.71 ± 2.52	0.345	0.632
Final TEF (Kcal/min)	0.27 ± 0.09	0.30 ± 0.08	0.25 ± 0.09	0.510	0.587
Change in Body Weight (kg)	-2.2 ± 1.71	-1.64 ± 1.41	-2.66 ± 2.00	0.378	0.589
Change in BMI (kg/m^2)	-0.75 ± 0.6	-0.54 ± 0.47	-0.96 ± 0.73	0.311	0.684
Change in Fat-Mass (kg)	-1.05 ± 2.59	0.132 ± 2.81	-2.23 ± 2.37	0.279	0.909
Change in Fat-Free Mass (kg)	-0.06 ± 1.19	0.41 ± 1.28	-0.54 ± 0.99	0.227	0.830
Change in Body-Fat (%)	-0.33 ± 2.08	0.42 ± 2.32	-1.08 ± 1.71	0.632	0.736

Table 5: Comparison of Placebo and MPH groups within and between subjects for absolute and relative Resting Energy Expenditure, and Thermic Effect of Food

			Mean ± SD		Mean Differences			
Variables	Condition	n	Baseline	Final	Within Group Change from Baseline to Final	Between Group Change at Final (Placebo - MPH)	*p*	Cohens d
REE								
(Kcal/day)	Placebo	5	2122.6 ± 301.5	2000.8 ± 262.8	-121.80 ± 69.48	———	0.15	———
	MPH	5	1866.4 ± 344.5	1918.8 ± 306.5	52.36 ± 53.26	———	0.38	———
	MPH Vs Placebo	10	———	———	———	-174.17 ± 276.84	0.082	0.49
Relative REE								
(Kcal/day/kg)	Placebo	5	19.08 ± 2.36	18.26 ± 2.04	-0.821 ± 0.677	———	0.29	———
	MPH	5	18.53 ± 1.97	19.71 ± 2.52	1.189 ± 0.704	———	0.17	———
	MPH Vs Placebo	10	———	———	———	-2.01 ± 3.09	0.074	0.83
TEF (AUC)								
(Kcal/min)	Placebo	5	0.46 ± 0.16	0.30 ± 0.08	-0.164 ± 0.09	———	0.134	———
	MPH	5	0.38 ± 0.19	0.25 ± 0.09	-0.13 ± 0.10	———	0.266	———
	MPH Vs Placebo	10	———	———	———	-0.034 ± 0.07	0.785	0.15

Note: * indicates statistical significance. ($p \leq 0.05$)

Abbreviations: AUC, area under the curve; MPH, Methylphenidate; REE, Resting energy expenditure; TEF, thermic effect of food;

Table 6: Individual Changes in Relative REE and body weight as shown by group

Participant	Group	Age	Baseline Relative REE (kcal/day/kg)	Final Relative REE (Kcal/day/kg)	Relative REE change from Baseline to Final (Kcal/day/kg)	Body Weight Change from Baseline to Final (kg)
Participant 1	MPH	28	19.21	22.5	3.29	-4.5
Participant 2	MPH	27	20.14	21.97	1.82	-5.1
Participant 3	MPH	23	20.18	19.68	-0.51	-1.7
Participant 4	MPH	25	17.5	17.25	-0.25	-1.3
Participant 5	MPH	40	15.59	17.18	1.59	-0.7
Participant 6	Placebo	24	20.88	17.5	-3.38	-0.6
Participant 7	Placebo	35	18.16	17.59	-0.57	-0.1
Participant 8	Placebo	37	22.24	21.77	-0.46	-3.7
Participant 9	Placebo	18	16.85	16.48	-0.38	-2.1
Participant 10	Placebo	31	17.28	17.97	0.68	-1.7

Note: MPH, Methylphenidate; MVPA, Moderate-Vigorous Physical Activity; REE, Resting Energy Expenditure;

Table 7: Comparison of Placebo and MPH groups within and between subjects for weighted variables of Physical Activity Energy Expenditure

Variables	Condition	n	Mean ± SD		Mean Differences			
			Baseline	Final	Within Group Change from Baseline to Final	Between Group Change at Final (Placebo - MPH)	*p*	Cohens d
SB								
(Mins/day)	Placebo	5	447.32 ± 28.11	455.91 ± 37.88	8.59 ± 11.12	———	0.48	———
	MPH	5	456.02 ± 33.06	465.36 ± 53.86	9.35 ± 24.16	———	0.72	———
	MPH Vs Placebo	10	———	———	———	-0.76 ± 13.30	0.52	0.02
LPA								
(Mins/day)	Placebo	5	125.27 ± 15.99	117.01 ± 26.76	-8.26 ± 10.65	———	0.48	———
	MPH	5	114.09 ± 18.11	108.75 ± 36.75	-5.34 ± 15.93	———	0.75	———
	MPH Vs Placebo	10	———	———	———	-2.92 ± 9.58	0.50	0.16
MPA								
(Mins/day)	Placebo	5	27.11 ± 21.11	26.05 ± 20.52	-1.06 ± 8.87	———	0.91	———
	MPH	5	29.15 ± 21.95	23.66 ± 22.96	-5.50 ± 8.63	———	0.56	———
	MPH Vs Placebo	10	———	———	———	4.44 ± 6.19	0.61	0.19
MVPA								
(Mins/day)	Placebo	5	27.42 ± 21.31	27.08 ± 20.38	-0.33 ± 9.41	———	0.97	———
	MPH	5	29.89 ± 21.90	25.89 ± 23.92	-4.01 ± 8.31	———	0.66	———
	MPH Vs Placebo	10	———	———	———	3.68 ± 6.28	0.74	0.15
VPA								
(Mins/day)	Placebo	5	0.31 ± 0.69	1.03 ± 1.56	0.73 ± 0.82	———	0.43	———
	MPH	5	0.74 ± 0.83	2.23 ± 2.21	1.49 ± 0.86	———	0.16	———
	MPH Vs Placebo	10	———	———	———	-0.76 ± 0.59	0.098	0.91

Note: * indicates statistical significance. ($p \leq 0.05$)
Abbreviations: LPA, Light Physial Activity; MPA, Moderate Physical Activity; MPH, Methylphenidate; MVPA, Moderate-Vigorous Physical Activity; SB, Sedentary Behaviour; VPA, Vigorous Phyiscal Activity

Table 8 Correlations of both Placebo and MPH groups changes in energy expenditure components and changes in anthropometrics

Variables	Sample size	Change in BW	Change in %BF	Change in FM	Change in FFM
Change in absolute REE	n = 10				
r value		-0.353	-0.397	**-0.401**	-0.153
p		0.317	0.256	0.251	0.673
Change in Relative REE	n = 10				
r value		**-0.599**	**-0.522**	**-0.555**	-0.145
p		0.067	0.121	0.096	0.689
Change in TEF AUC	n = 10				
r value		-0.170	0.072	0.021	**-0.594**
p		0.663	0.842	0.954	0.070
Change in SB	n = 10				
r value		0.257	-0.279	-0.153	0.096
p		0.473	0.436	0.673	0.798
Change in LPA	n = 10				
r value		**-0.502**	0.107	-0.045	-0.173
p		0.14	0.768	0.901	0.632
Change in MPA	n = 10				
r value		0.208	**0.418**	0.382	0.093
p		0.564	0.229	0.276	0.798
Change in MVPA	n = 10				
r value		0.221	**0.424**	0.391	0.61
p		0.54	0.222	0.264	0.866
Change in VPA	n = 10				
r value		0.158	0.115	0.138	-0.319
p		0.663	0.753	0.704	0.368

Note:. * indicates statistical significance. ($p \leq 0.05$), **Bold** indicates a moderate or higher correlation
Abbreviations: LPA, Light Physial Activity; MPA, Moderate Physical Activity; MPH, Methylphenidate; MVPA, Moderate-Vigorous Physical Activity; REE, Resting Energy Expenditure; SB, Sedentary Behaviour; TEF, Thermic Effect of Food; VPA, Vigorous Phyiscal Activity

Table 9: Correlations of MPH and Placebo (separately) group changes in energy expenditure components and changes in anthropometrics

Variables	Sample Size	Changes in BW		Changes in %BF		Changes in FM		Changes in FFM	
		Placebo	MPH	Placebo	MPH	Placebo	MPH	Placebo	MPH
Change in absolute REE	n = 5								
r value		-0.204	-0.259	-0.206	-0.288	-0.193	-0.191	0.25	-0.101
p		0.742	0.674	0.74	0.638	0.756	0.759	0.685	0.871
Change in Relative REE	n = 5								
r value		-0.388	**-0.653**	-0.223	**-0.643**	-0.241	**-0.586**	0.272	-0.023
p		0.518	0.232	0.719	0.242	0.696	0.299	0.658	0.971
Change in TEF AUC	n = 5								
r value		0.165	-0.358	0.216	0	0.188	-0.055	**-0.64**	**-0.617**
p		0.835	0.554	0.727	1	0.762	0.93	0.244	0.267
Change in SB	n = 5								
r value		0.14	0.324	**-0.86**	-0.015	**-0.806**	0.155	**-0.309**	0.382
p		0.823	0.595	0.061	0.981	0.099	0.803	0.613	0.525
Change in LPA	n = 5								
r value		**-0.842**	-0.356	0.308	0.001	0.16	-0.17	0.102	**-0.416**
p		0.074	0.557	0.614	0.998	0.797	0.784	0.87	0.487
Change in MPA	n = 5								
r value		**0.762**	-0.238	**0.669**	0.042	**0.768**	-0.117	-0.302	-0.297
p		0.134	0.7	0.217	0.946	0.13	0.851	0.622	0.628
Change in MVPA	n = 5								
r value		**0.788**	-0.259	**0.668**	0.04	**0.771**	-0.124	0.249	-0.315
p		0.114	0.674	0.218	0.948	0.127	0.842	0.687	0.606
Change in VPA	n = 5								
r value		**0.794**	-0.117	**0.425**	-0.034	**0.541**	-0.022	**-0.415**	-0.065
p		0.108	0.851	0.476	0.956	0.346	0.971	0.487	0.918

Note:. * indicates statistical significance. ($p \leq 0.05$), **Bold** indicates a moderate or higher correlationAbbreviations: LPA, Light Physial Activity; MPA, Moderate Physical Activity; MPH, Methylphenidate; MVPA, Moderate-Vigorous Physical Activity; REE, Resting Energy Expenditure; SB, Sedentary Behaviour; TEF, Thermic Effect of Food; VPA, Vigorous Phyiscal Activity

Appendices

Appendix A—Three Factor Eating Questionnaire

FOOD HABITS QUESTIONNAIRE

(Stunkard et Messick, 1984)

This questionnaire contains a certain number of propositions.

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

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

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

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

	TRUE	FALSE
10. Life is too short to worry about dieting.	☐	☐
11. Since my weight goes up and down, I have gone on reducing diets more than once.	☐	☐
12. I often feel so hungry that I just have to eat something.	☐	☐
13. When I am with someone who is overeating, I usually overeat too.	☐	☐
14. I have a pretty good idea of the number of calories in common food.	☐	☐
15. Sometimes when I start eating, I just can't seem to stop.	☐	☐
16. It is not difficult for me to leave something on my plate.	☐	☐
17. At certain times of the day, I get hungry because I have gotten used to eating them.	☐	☐
18. While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	☐	☐
19. Being with someone who is eating often makes me hungry enough to eat also.	☐	☐
20. When I feel "blue", I often overeat.	☐	☐
21. I enjoy eating too much to spoil it by counting calories or watching my weight.	☐	☐
22. When I see a real delicacy, I often get so hungry that I have to eat right away.	☐	☐
23. I often stop eating when I am not really full as a conscious means of limiting the amount that I eat.	☐	☐
24. I get so hungry that my stomach often seems like a bottomless pit.	☐	☐
25. My weight has hardly changed at all in the last 10 years.	☐	☐
26. I am always hungry so it is hard for me to stop eating before I finish the food on my plate.	☐	☐

	TRUE	FALSE
27. When I feel lonely, I console myself by eating.	☐	☐

28.	**I consciously hold back at meals in order not to gain weight.**	☐	☐
29.	**I sometimes get very hungry late in the evening or at night**	☐	☐
30.	**I eat anything I want, anytime I want.**	☐	☐
31.	**Without even thinking about it, I take a long time to eat.**	☐	☐
32.	**I count calories as a conscious means of controlling weight.**	☐	☐
33.	**I do not eat some foods because they make me fat.**	☐	☐
34.	**I am always hungry enough to eat at any time.**	☐	☐
35.	**I pay a great deal of attention to changes in my figure.**	☐	☐
36.	**While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods.**	☐	☐

PART 2

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

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

Rarely	**Sometimes**	**Usually**	**Always**
1	**2**	**3**	**4**

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

Not at all	**Slightly**	**Moderately**	**Very much**
1	**2**	**3**	**4**

39. How often do you feel hungry ?

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

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

Never	**Rarely**	**Often**	**Always**
1	**2**	**3**	**4**

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

Easy	Slightly Difficult	Moderately Difficult	Very Difficult
1	2	3	4

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

Not at all	Slightly	Moderately	Extremely
1	2	3	4

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

Almost Never	Seldom	Usually	Almost always
1	2	3	4

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

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

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

Never	Rarely	Often	Always
1	2	3	4

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

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

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

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

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

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

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

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

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

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

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

What number would you give yourself?

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

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

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

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

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

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

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

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

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

Appendix B—Wender Utah Rating Scale for the Attention Deficit Hyperactivity Disorder

Overview:

The Wender Utah Rating Scale can be used to assess adults for Attention Deficit Hyperactivity Disorder with a subset of 25 questions associated with that diagnosis.

Wender Utah Rating Scale

- 61 questions answered by the adult patient recalling his or her childhood behavior
- 5 possible responses scored from 0 to 4 points

	As a child I was (or had):	not at all or very slightly	mildly	moder-ately	quite a bit	very much
1	active restless always on the go	0	1	2	3	4
2	afraid of things	0	1	2	3	4
3	concentration problems easily distracted	0	1	2	3	4
4	anxious worrying	0	1	2	3	4
5	nervous fidgety	0	1	2	3	4
6	inattentive daydreaming	0	1	2	3	4
7	hot- or short-tempered low boiling point	0	1	2	3	4
8	shy sensitive	0	1	2	3	4
9	temper outbursts tantrums	0	1	2	3	4
10	trouble with stick-to-it-tiveness not following through. failing to finish things started	0	1	2	3	4
11	stubborn strong-willed	0	1	2	3	4
12	sad or blue depressed unhappy	0	1	2	3	4
13	incautious. dare-devilish involved in pranks	0	1	2	3	4
14	not getting a kick out of things dissatisfied with life	0	1	2	3	4
15	disobedient with parents rebellious sassy	0	1	2	3	4
16	low opinion of myself	0	1	2	3	4
17	irritable	0	1	2	3	4
		not at all or very	mildly	moder-ately	quite a bit	very much

		slightly				
18	outgoing friendly enjoyed company of people	0	1	2	3	4
19	sloppy disorganized	0	1	2	3	4
20	moody ups and downs	0	1	2	3	4
21	angry	0	1	2	3	4
22	friends popular	0	1	2	3	4
23	well-organized tidy neat	0	1	2	3	4
24	acting without thinking impulsive	0	1	2	3	4
25	tendency to be immature	0	1	2	3	4
26	guilty feelings regretful	0	1	2	3	4
27	losing control of myself	0	1	2	3	4
28	tendency to be or act irrational	0	1	2	3	4
29	unpopular with other children didn't keep friends for long didn't get al.ong with other children	0	1	2	3	4
30	poorly coordinated did not participate in sports	0	1	2	3	4
31	afraid of losing control of self	0	1	2	3	4
32	well-coordinated picked first in games	0	1	2	3	4
33	tomboyish (for women only)	0	1	2	3	4
34	running away from home	0	1	2	3	4
35	getting into fights	0	1	2	3	4
36	teasing other children	0	1	2	3	4
37	leader bossy	0	1	2	3	4
38	difficulty getting awake	0	1	2	3	4
39	follower led around too much	0	1	2	3	4
40	trouble seeing things from someone else's point of view	0	1	2	3	4
41	trouble with authorities trouble with school visits to principal's office	0	1	2	3	4
42	trouble with police booked convicted	0	1	2	3	4

	Medical problems as a	not at all	mildly	moder-	quite	very

	child	or very slightly		ately	a bit	much
43	headaches	0	1	2	3	4
44	stomachaches	0	1	2	3	4
45	constipation	0	1	2	3	4
46	diarrhea	0	1	2	3	4
47	food allergies	0	1	2	3	4
48	other allergies	0	1	2	3	4
49	bedwetting	0	1	2	3	4
	As a child in school I was (or had)	not at all or very slightly	mildly	moder-ately	quite a bit	very much
50	overall a good student fast	0	1	2	3	4
51	overall a poor student slow learner	0	1	2	3	4
52	slow in learning to read	0	1	2	3	4
53	slow reader	0	1	2	3	4
54	trouble reversing letters	0	1	2	3	4
55	problems with spelling	0	1	2	3	4
56	trouble with mathematics or numbers	0	1	2	3	4
57	bad handwriting	0	1	2	3	4
58	able to read pretty well but never really enjoyed reading	0	1	2	3	4
59	not achieving up to potential	0	1	2	3	4
60	repeating grades	0	1	2	3	4
61	suspended or expelled	0	1	2	3	4

Questions Associated with ADHD

- 25 of the questions were associated with ADHD as follows:

	As a child I was (or had):
3	concentration problems easily distracted
4	anxious worrying
5	nervous fidgety
6	inattentive daydreaming
7	hot- or short-tempered low boiling point
9	temper outbursts tantrums
10	trouble with stick-to-it-tiveness not following through. failing to finish things started
11	stubborn strong-willed
12	sad or blue depressed unhappy
15	disobedient with parents rebellious sassy
16	low opinion of myself
17	irritable
20	moody ups and downs
21	angry
24	acting without thinking impulsive
25	tendency to be immature
26	guilty feelings regretful
27	losing control of myself
28	tendency to be or act irrational
29	unpopular with other children didn't keep friends for long didn't get al.ong with other children
40	trouble seeing things from someone else's point of view
41	trouble with authorities trouble with school visits to principal's office
	As a child in school I was (or had)
51	overall a poor student slow learner
56	trouble with mathematics or numbers
59	not achieving up to potential

Wender Utah rating scale subscore = _____(sum of 25 questions associated with ADHD)

Interpretation:

- minimum score for the 25 questions is 0
- maximum score 100
- if a cutoff score of 46 was used 86 of patients with ADHD 99 of normal persons and 81% of depressed subjects were correctly classified

References: Ward MF Wender PH Reimherr FW. The Wender Utah Rating Scale: An aid in the retrospective diagnosis of childhood Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 1993; 150: 885-890.

Appendix C: Beck Depression Inventory

The Beck Depression Inventory-II (BDI-II) is the most widely used instrument for detecting depression. It is a brief, criteria-referenced assessment for measuring depression severity and is in line with the depression criteria of the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* (DSM–IV). Administration: 5 minutes; self-administered.

Beck

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.
- 0 I am no more irritated by things than I ever was.
- 1 I am slightly more irritated now than usual.
- 2 I am quite annoyed or irritated a good deal of the time.
- 3 I feel irritated all the time.

12.
- 0 I have not lost interest in other people.
- 1 I am less interested in other people than I used to be.
- 2 I have lost most of my interest in other people.
- 3 I have lost all of my interest in other people.

13.
- 0 I make decisions about as well as I ever could.
- 1 I put off making decisions more than I used to.
- 2 I have greater difficulty in making decisions more than I used to.
- 3 I can't make decisions at all anymore.

14.
- 0 I don't feel that I look any worse than I used to.
- 1 I am worried that I am looking old or unattractive.
- 2 I feel there are permanent changes in my appearance that make me look unattractive
- 3 I believe that I look ugly.

15.
- 0 I can work about as well as before.
- 1 It takes an extra effort to get started at doing something.
- 2 I have to push myself very hard to do anything.
- 3 I can't do any work at all.

16.
- 0 I can sleep as well as usual.
- 1 I don't sleep as well as I used to.
- 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
- 3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
- 0 I don't get more tired than usual.
- 1 I get tired more easily than I used to.
- 2 I get tired from doing almost anything.
- 3 I am too tired to do anything.

18.
- 0 My appetite is no worse than usual.
- 1 My appetite is not as good as it used to be.
- 2 My appetite is much worse now.
- 3 I have no appetite at all anymore.

19.
- 0 I haven't lost much weight, if any, lately.
- 1 I have lost more than five pounds.
- 2 I have lost more than ten pounds.
- 3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

Appendix D: Drug Abuse Screening Test

The purpose of the DAST is 1) to provide a brief, simple, practical, but valid method for identifying individuals who are abusing psychoactive drugs; and 2) to yield a quantitative index score of the degree of problems related to drug use and misuse. DAST scores are highly diagnostic with respect to a DSM diagnosis of psychoactive drug dependence and takes approximately 5 minutes to complete.

Adult Version

These questions refer to the past 12 months.	**Circle Your Response**	
1. Have you used drugs other than those required for medical reasons?	Yes	No
2. Have you abused prescription drugs?	Yes	No
3. Do you abuse more than one drug at a time?	Yes	No
4. Can you get through the week without using drugs?	Yes	No
5. Are you always able to stop using drugs when you want to?	Yes	No
6. Have you had "blackouts" or "flashbacks" as a result or drug use?	Yes	No
7. Do you every feel bad or guilty about your drug use?	Yes	No
8. Does your spouse (or parents) ever complain about your involvement with drugs?	Yes	No
9. Has drug abuse created problems between you and your spouse or your parents?	Yes	No
10. Have you lost friends because of your use of drugs?	Yes	No
11. Have you neglected your family because of your use of drugs?	Yes	No
12. Have you been in trouble at work (or school) because of drug abuse?	Yes	No
13. Have you lost your job because of drug abuse?	Yes	No
14. Have you gotten into fights when under the influence of drugs?	Yes	No
15. Have you engaged in illegal activities in order to obtain drugs?	Yes	No
16. Have you been arrested for possession of illegal drugs?	Yes	No
17. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?	Yes	No
18. Have you had medical problems as a result of your drug use (e.g. memory loss, hepatitis, convulsions, bleeding, etc.)?	Yes	No
19. Have you gone to anyone for help for drug problem?	Yes	No
20. Have you been involved in a treatment program specifically related to drug use?	Yes	No

Drug Abuse Screening Test

Adolescent Version

These questions refer to the past 12 months.	**Circle Your Response**	
1. Have you used drugs other than those required for medical reasons?	Yes	No
2. Have you abused prescription drugs?	Yes	No
3. Do you abuse more than one drug at a time?	Yes	No
4. Can you get through the week without using drugs?	Yes	No
5. Are you always able to stop using drugs when you want to?	Yes	No
6. Have you had "blackouts" or "flashbacks" as a result or drug use?	Yes	No
7. Do you every feel bad or guilty about your drug use?	Yes	No
8. Do your parents ever complain about your involvement with drugs?	Yes	No
9. Has drug abuse created problems between you and your parents?	Yes	No
10. Have you lost friends because of your use of drugs?	Yes	No
11. Have you neglected your family because of your use of drugs?	Yes	No
12. Have you been in trouble at school because of drug abuse?	Yes	No
13. Have you missed school assignments because of drug abuse?	Yes	No
14. Have you gotten into fights when under the influence of drugs?	Yes	No
15. Have you engaged in illegal activities in order to obtain drugs?	Yes	No
16. Have you been arrested for possession of illegal drugs?	Yes	No
17. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?	Yes	No
18. Have you had medical problems as a result of your drug use (e.g. memory loss, hepatitis, convulsions, bleeding, etc.)?	Yes	No
19. Have you gone to anyone for help for drug problem?	Yes	No
20. Have you been involved in a treatment program specifically related to drug use?	Yes	No

Appendix E: Pre-Screening Questionnaire

Pre-Screening Questionnaire

THE EFFECTS OF METHYLPHENIDATE ON THE REDUCTION OF FOOD ENERGY INTAKE AND ON THE AUGMENTATION OF ENERGY EXPENDITURE

Researchers:
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Children's Hospital of Eastern Ontario and the Faculty of Health Sciences, University of Ottawa
School of Human Kinetics

1) **Whats is your age?** _____
2) **Do you smoke?** **Yes □ No□**
3) **Have you maintained a stable body weight (± 2kg) over the last 6 months?** **Yes □ No□**
4) **Do you take medications?** **Yes □ No□**
   a. **If so, which ones** _____
5) **Do you, or have you ever been diagnosed with having ADHD** **Yes □ No□**
6) **Have you ever taken Methylphenidate?** **Yes □ No□**
7) **Do you have known allergies to Methylphenidate?** **Yes □ No□**
8) **Any personal or family of motor tics or Tourette's Syndrome?** **Yes □ No□**

9) Do you have any other known food allergies? **Yes □ No□**

10) Do you have diabetes? **Yes □ No□**

11) Do you have any hearts problems? **Yes □ No□**

12) Do you have high or low blood pressure? **Yes □ No□**

13) Do you have asthma or any other respiratory problems? **Yes □ No□**

14) Has your doctor ever diagnosed you with thyroid gland abnormalities? **Yes □ No□**

15) How many alcoholic beverages do you normally consume in a week **_____**

16) Have you ever been diagnosed with glaucoma? **Yes □ No□**

17) Do you have any other health problems that were not mentioned in this questionnaire? **Yes □ No□**

a. If yes, please specify **_____**

Appendix F: Case Report Form—Screening Visit

Case Report Form (CRF)
SCREENING VISIT

CONSENT INFORMATION

Date Consent Signed _ _ / _ _ _ / _ _
DD / MMM / YY

Demographic Information

Date of Visit: _ _ /_ _ _ /_ _
DD / MMM / YY

Date of Birth: _ _ /_ _ _ /_ _
DD / MMM /YY

Inclusion and Exclusion Criteria:
BMI≥30

Weight:_ _ _ . _ **Pounds ☐** **Kilograms ☐**

Height: _ _ _ **cm ☐** **Inches ☐**

Waist Circumference: _ _ _ **cm ☐** **Inches ☐**

BMI: _ _ _ **Is BMI ≥30.0? Yes ☐** **No ☐**

If no, participant is excluded.

CONCOMMITTANT MEDICATIONS

THE EFFECT OF METHYLPHENIDATE ON ENERGY EXPENDITURE IN INDIVIDUALS WITH OBESITY

Is patient presently on any medication? No ☐ Yes ☐ If yes please add to Concommitant Med page _____

Inclusion and Exclusion Criteria:
Summary Checklist

Inclusion Criteria: **All must be checked "YES" for the patient to be eligible**

Yes	No	
☐	☐	1 Written informed Consent or Assent
☐	☐	2 Between the age of 16 and40 (must be ≥16 or ≤40 when starting trial)
☐	☐	3 BMI>29.9 (class I obesity or greater)

Exclusion Criteria: **All must be checked "NO" for the patient to be eligible**

Yes	No	
☐	☐	1 Is a current smoker
☐	☐	2 Known food allergies (e.g. lactose, gluten, etc.)
☐	☐	3 History of Methylphenidate use or known allergy to Methylphenidate
☐	☐	4 History of ADHD or current diagnosis of an axis 1 psychiatric disorder (e.g., depression, panic disorder, schizophrenia) as measured by clinical interview and self-report, the Wender-Utah Rating Scale and the Beck Depression Inventory
☐	☐	5 Current use of antidepressants, thyroid medication, or any medication that could affect appetite
☐	☐	6 Pre-existing cardiovascular disorders including uncontrolled hypertension, angina pectoris, arterial occlusive disease, heart failure, cardiomyopathies, myocardial infarction, and cardiac arrhythmia
☐	☐	7 Diabetic
☐	☐	8 Excessive use of alcohol or alcoholism, or current addictions to opiates, cocaine or stimulants as measured by the Drug Abuse Screening Test
☐	☐	9 Restrained Eater (score of ≥11 from Three Factor Eating Questionnaire
☐	☐	10 Glaucoma
☐	☐	11 High Blood Pressure
☐	☐	12 Personal or family history of seizure disorders
☐	☐	13 Currently taking MAO inhibitors, pressor agents, coumarin, anticonvulsants, phenylbutazone, or tricyclic antidepressants
☐	☐	14 History of thyroid disease
☐	☐	15 Personal or family history of motor tics or Tourettes's Syndrome
☐	☐	16 After test dose of MPH, systolic blood pressure exceeding baseline reading by 20mmHg
☐	☐	17 After test dose of MPH diastolic blood pressure exceeding the baseline reading by 10mmHg
☐	☐	18 After test dose of MPH heart rate exceeds 20 beats per minute above baseline
☐	☐	19 Pregnant or breastfeeding

Inclusion and Exclusion Criteria:
Psychological Self-Report

1) ***Depression:*** **Has the participant been diagnosed or is the participant currently diagnosed as having clinical depression?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:

_____

_____

2) ***Schizophrenia:*** **Has the participant been diagnosed or is the participant currently diagnosed as having schizophrenia?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:

_____

_____

3) ***Panic Disorder:*** **Has the participant been diagnosed or is the participant currently diagnosed as having panic disorder?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:

_____

_____

4) ***Restrained Eating:*** **Did the participant score 11 or higher on the restraint subscale of the Three Factor Eating Questionnaire?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:

_____

_____

Inclusion and Exclusion Criteria:
Alcohol Use—AUDIT-C Questionnaire

1. **How often do you have a drink containing alcohol?**

   ☐ **a. Never**
   ☐ **b. Monthly or less**
   ☐ **c. 2-4 times a month**
   ☐ **d. 2-3 times a week**
   ☐ **e. 4 or more times a week**

2. **How many standard drinks containing alcohol do you have on a typical day? A standard drink is defined as a 12oz beer or cooler (~5% alcohol), 8-9oz malt liquor (~7% alcohol), 5oz table wine (~12%), or 1.5oz spirits (~80% alcohol).**

   ☐ **a. 1 or 2**
   ☐ **b. 3 or 4**
   ☐ **c. 5 or 6**
   ☐ **d. 7 to 9**
   ☐ **e. 10 or more**

3. **How often do you have six or more drinks on one occasion?**

   ☐ **a. Never**
   ☐ **b. Less than monthly**
   ☐ **c. Monthly**
   ☐ **d. Weekly**
   ☐ **e. Daily or almost daily**

Scoring: Each question has 5 answer choices and points allotted are: a=0 points, b=1 point, c=2 points, d=3 points, e=4 points.

Did the participant score 8 or higher on the AUDIT-C questionnaire? Yes ☐ No ☐

****If yes was answered above the participant is excluded**

Comments:
_____
_____
_____

Inclusion and Exclusion Criteria:
Clinical Assessment Questionnaires

Beck Depression Inventory: **Was the participant's score on the Beck Depression Inventory 17 or greater?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:
_____
_____
_____

Wender-Utah Rating Scale (ADHD screening): **Was the participant's score on the Wender-Utah Rating scale 46 or greater?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:
_____
_____
_____

Drug Abuse Screening Test: **Was the participant's score on the Drug Abuse Screening Test 11 or higher?** **Yes ☐ No ☐**

****If yes was answered above the participant is excluded**

Comments:
_____
_____
_____

Note: **If the participant is excluded due to a clinically relevant diagnostic score for any of the 3 above Axis 1 Disorder Tests they will be advised to follow-up with their family doctor and if they do not have a family doctor they will be encouraged to visit a walk-in clinic to follow up.**

Inclusion and Exclusion Criteria:
LAB TESTS

Date of Urine for Pregnancy _ _ / _ _ _ / _ _ Neg ☐ Pos ☐ if positive, exclude
DD / MMM / YY

Date EKG Performed _ _ / _ _ _ / _ _ Abnormalities Yes ☐ No ☐
If Yes Specify:_____

_____

_____

_____
____

NOTE : QTc > 440 msec or arrhythmia other than sinus bradycardia; conduction abnormalities, Prolonged QTc or other, exclude **

BASELINE VITAL SIGNS

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Comments:

_____

_____

_____

Inclusion and Exclusion Criteria:
VITAL SIGNS AT 30min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:
_____
_____
_____

VITAL SIGNS AT 60min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:
_____
_____
_____

VITAL SIGNS AT 90min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:

_____

_____

_____

VITAL SIGNS AT 120min Post Drug

Temperature: _ _ . _ °C **oral ☐** **tympanic ☐**

Heart Rate: Lying _ _ _ **Blood Pressure: Lying _ _ _ / _ _ _**

Heart Rate : Standing _ _ _ **Blood Pressure: Standing _ _ _ / _ _ _**

Did Heart Rate rise 20 beats per minute above baseline? **Yes ☐** **No ☐**

Did systolic blood pressure rise 20mmHg above baseline? **Yes ☐** **No ☐**

Did diastolic blood pressure rise 10mmHg above baseline? **Yes ☐** **No ☐**

****If yes was answered in any of the above the participant is excluded**

Comments:

_____

_____

MEDICAL HISTORY

None □

Body System	Past	Current	Condition	Treatment Yes/No	Code Data Use
Nervous					
Cardiovascular: uncontrolled hypertension, angina pectoris, arterial occlusive disease, heart failure, cardiomypathies, myocardial infarction, and cardiac arrhythmia					
Respiratory					
Endocrine: Thyroid, Diabetes					
Skin					
Digestive					
Musculoskeletal: Seizure Disorders					
Blood					
Urinary					
Female Reproductive					
Mental Health: axis 1 psychiatric disorder (e.g., depression, panic disorder, schizophrenia) as measured by self-report, the Wender-Utah Rating Scale[52-54] and the Beck Depression Inventory					

Other					

PHYSICAL EXAM

SYSTEM	NORMAL	ABNORMAL	Specify Abnormalities	Code Data Use
General Appearance				
Lymph Nodes				
Musculoskeletal/Extremities				
Cardiovascular				
Lungs				
Abdomen				
Eyes/Ears/Nose/Throat				
Other				

Final Eligibility

Patient meets all eligibility criteria? No ☐ Yes ☐

Signature (Cardiologist):_____ Date _____

Signature (Qualified Investigator):_____ Date _____

Appendix G—SIDE EFFECTS CHECKLIST: This side effects checklist will be introduced to the participant by the study nurse at the Clinical Screening Visit. Each participant will first rate all of these side effects prior to being administered the test dose of MPH (at 0.5mg/kg), and then 3 more times over the course of the screening visit while having vital signs monitored by the study nurse. Participants will then fill out the side effects checklist nightly for the first 2 weeks of the study and twice per month for the duration of the study trial.

Side Effect	None	Mild	Moderate	Severe
1. Insomnia/Disordered Sleeping				
2. Nausea				
3. Headache				
4. Anxiety				
5. Palpitations				
6. Drowsiness/Sedation				
7. Abnominal Pain/ Cramps				
8. Irritability				
9. Confusion/Disorientation				
10. Sweating				
11. Flushing				
12. Dryness of Mouth				
13. Blurred Vision				
14. Motor Tics				
15. Nervousness				
16. Restlessness				
17. Skin Rash				
18. Excessive Sweating				
19. Depression/Moodiness				
20. Sore Throat/Runny Nose				
21. Other				

Appendix H—Management rules for side effects: When the participant initially calls the study coordinator and it is deemed that the side effect falls under the "Minor (expected, tolerable) category, then the participant will be told to report back in one day if the side effect remains. If on the second day the symptoms remain the participant will call the coordinator once again and he will have the psychiatrist call the participant. The psychiatrist will use this table, along with their own clinical judgment, to determine the best course of action.

Prohibitive (Requires dose reduction or discontinuation)	**Major (May Require Dose Reduction; prohibits higher dose)**	**Minor (Expected, tolerable)**
Severe insomnia (>1.5 hrs)	Moderate insomnia (1-1.5hr)	Mild insomnia (<1hr)
Marked, severe tics causing impairment	Fleeting new tics	Fleeting, no impairment
Severe, unrelenting Headaches	Moderate headaches	Mild headaches
Intolerable GI Cramps	Moderate GI cramps	Mild GI cramps
Severe picking at skin, nail	Moderate picking at skin, nail	Mild picking at skin, nail
Severe anxiety	Moderate Anxiety	Mild anxiety
Severe irritability, leading to aggression	Moderate irritability	Mild irritability
Severe sedation, sleeping all day	Moderate sedation	Mild sedation
Severe depression not pre-existing	Moderate depression, not pre-existing	Mild depression
Rash (Exofoliative Dermatities, Erythema Multiforme)	Rash (Scalp Hair Loss, Hyperhidrosis)	Rash (small area)

Appendix I – Side Effects Checklist Reported

The reported side effects as reported by all participants

	MPH None | Mild | Moderate | Severe	Placebo None | Mild | Moderate | Severe	Percent of MPH with side effects	Percent of Placebo with side effects
Insomnia/Disordered Sleeping	2 | 2 | 1 | 0	4 | 2 | 0 | 0	60%	33%
Nausea	2 | 2 | 1 | 0	5 | 1 | 0 | 0	60%	17%
Headache	4 | 1 | 0 | 0	3 | 3 | 0 | 0	20%	50%
Anxiety	5 | 0 | 0 | 0	5 | 1 | 0 | 0	0%	17%
Palpitations	2 | 3 | 0 | 0	6 | 0 | 0 | 0	60%	0%
Drowsiness/Sedation	5 | 0 | 0 | 0	5 | 1 | 0 | 0	0%	17%
Abdominal Pain/ Cramps	4 | 1 | 0 | 0	5 | 1 | 0 | 0	20%	17%
Irritability	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%	33%
Confusion/Disorientation	4 | 1 | 0 | 0	5 | 1 | 0 | 0	20%	17%
Sweating	3 | 2 | 0 | 0	6 | 0 | 0 | 0	40%	0%
Flushing	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%	0%
Dryness of Mouth	3 | 1 | 1 | 0	4 | 2 | 0 | 0	40%	33%
Blurred Vision	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%	0%
Motor Tics	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%	0%
Nervousness	4 | 1 | 0 | 0	5 | 1 | 0 | 0	20%	17%
Restlessness	3 | 2 | 0 | 0	3 | 3 | 0 | 0	40%	50%
Skin Rash	5 | 0 | 0 | 0	5 | 1 | 0 | 0	0%	17%
Excessive Sweating	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%	33%
Depression/Moodiness	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%	33%
Sore Throat/Runny Nose	5 | 0 | 0 | 0	4 | 2 | 0 | 0	0%	33%
Other	5 | 0 | 0 | 0	6 | 0 | 0 | 0	0%	0%