# A BEHAVIOURAL GENETIC MODEL OF THE MECHANISMS UNDERLYING THE LINK BETWEEN OBESITY AND DIMENSIONAL MEASURES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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## Abstract

**Objective**: The purpose of this study was to investigate genetic and psycho-behavioural mechanisms contributing to the strong ADHD symptom-obesity association. Genetic variants associated with hypo-dopaminergic functioning have been implicated in ADHD, particularly the 7-repeat allele of a VNTR located on the DRD4 gene, likely due to the receptor's predominance in the prefrontal cortex. Based on this evidence, some experts have suggested that a shared aetiology of a dysfunctional dopamine (DA) system is responsible for the link. However, this conflicts with accumulating evidence that it is actually an *amplified* DA signal that increases the risk for overeating and weight gain due to a stronger appetitive response to food cues. It seems plausible that individuals with ADHD symptoms who are predisposed overeat are those who also possess a high sensitivity to, and greater motivation to seek out, rewarding stimuli, as reflected by increased DA availability in the brain reward pathways. Accordingly, the current study tested the hypothesis that symptoms of ADHD, predicted by hypo-dopaminergic functioning in the prefrontal cortex, in combination with an enhanced appetitive drive, predict hedonic eating, and in turn, higher BMI.

**Methods**: Functional markers of the DRD2 and DRD4 were genotyped to determine their contributions to ADHD symptoms and various indices of hedonic eating, respectively. The model was tested using Structural Equation Modeling procedures in a general population sample (n=421 adults) representing a broad range of body mass index (BMI) values.

**Results**: Overall, the fit indices indicated that the proposed model was a good fit to the data. Controlling for education level, all parameter estimates were in the expected direction and

statistically significant with the exception of the pathway from the DRD4 marker to ADHD symptoms. The indirect effect was significant, indicating that overeating mediated the association between ADHD symptoms and BMI.

**Conclusions**: Results lend support to the hypothesis that overeating and an elevated DA signal in the ventral striatum – representative of a greater reward response – are responsible for the link between ADHD symptoms and obesity. The current study was the first to connect the most prominent and supported theories of ADHD with evidence-based models of hedonic eating.

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# Introduction

## 1. Rationale and Purpose

Examining risk factors for obesity is essential considering the substantial and growing health and financial burden this condition imposes on Canadians (Cawley & Meyerhoefer, 2012; Donald & Behan, 2012; Haslam & James, 2005). Recently, it has been established that Attention-Deficit Hyperactivity Disorder (ADHD) and obesity often co-exist (Alfonsson, Parling & Ghaderi, 2012; Cortese et al., 2013; Erhart et al., 2012; Gungor, Celiloglu, Raif, Ozcan & Selimoglu, 2014; Holtkamp et al., 2004), suggesting that the symptoms or biological factors associated with ADHD increase the risk for overeating and/or may impede successful weight-loss intervention (Cortese & Castellanos, 2014). However, the majority of studies on this relationship have been limited to estimates of prevalence (Altfas, 2002; Gruss, Mueller, Horbach, Martin & Zwaan, 2012; Erhart et al., 2012). Regrettably, the mechanisms underlying the association between ADHD and adiposity have not received adequate attention, to date. A better understanding of the link has clear economic and health relevance to Canadians. For instance, individuals with both ADHD and obesity were found to have higher level of health services utilization and psychotherapy contact, compared to overweight subjects without ADHD (Erhart et al., 2012; Gruss et al., 2012). The primary purpose of the current study was to investigate genetic and psycho-behavioural mechanisms contributing to the strong ADHD-obesity connection.

Previous reports suggest that links between ADHD symptoms and body weight may be mediated by hedonic eating – that is, eating for reasons other than physiological need or energy requirements (Davis, Levitan, Smith, Tweed & Curtis, 2006; Dempsey, Dyehouse & Schafer, 2011; de Zwaan et al., 2011; Ivan, Azarbad, Corsica & Hood, 2009; Strimas et al., 2008).

However, many of these studies are limited by small sample sizes, the lack of controls for medication status, or the use of third-party reporting for the identification of ADHD (Yang et al., 2012). Accordingly, the **first objective** of the current study was to clarify whether various forms of overeating explain the association between ADHD symptoms and body mass index ($kg/m^2$; BMI) among a large non-medicated sample, employing ADHD symptom-assessment measures with high psychometric validity (Taylor, Deb & Unwin, 2011).

A logical next step in the investigation of contributing mechanisms is to focus on the aetiology of ADHD. Both genetic (Bobb et al., 2005) and neuro-imaging (Sergeant, Geurts & Oosterlaan, 2002) research has lead to the *dopamine (DA) dysfunction* hypothesis of the disorder (Wu et al., 2012). For example, candidate gene studies have demonstrated an association between ADHD and genetic markers predictive of dampened DA signaling in the brain reward pathways (Gizer, Ficks & Waldman, 2009; Thapar, Cooper, Eyre & Langley, 2013; Wu et al., 2012). In particular, and based on support from meta-analyses (Gizer et al., 2009; Smith, 2010; Wu et al., 2012), the DA D4 receptor gene (DRD4) has been strongly implicated in the disorder because D4 receptors are heavily expressed in the prefrontal regions of the cortex – areas that regulate attentional processes, decision-making, and inhibitory control (Ariza et al., 2012; Meador-Woodruff et al., 1996).

Genetic variation in the responsiveness of the DA mesolimbic system has also been a major target for research on vulnerability to overeating and excess weight gain, due to DA's involvement in the motivation and reinforcement of food-seeking behaviour (Berridge, Ho, Richard, DiFeliceantoni, 2010; Wise, 2006). Akin to drugs of abuse, palatable food increases DA in the striatum – the central structure in the mesocorticolimbic brain reward pathways (Le Foll, Gallo, Le Strat, Lu & Gorwood, 2008) – and individuals differ in the degree to which food elicits

this response (Berridge et al., 2010; Tomasi et al., 2014). Current evidence indicates that an amplified DA signal increases the initial risk for engagement in overeating, due to a stronger appetitive response to food cues (Davis et al., 2013; Filbey, Myers & Dewitt, 2012; Wang et al., 2011).

In terms of reward mechanisms, the DA D2 receptor has received the most intense research interest, as it is heavily expressed in the striatal area of the basal ganglia (Zhang et al., 2009) and has clearly demonstrated links with a broad range of addiction disorders (Chen et al., 2011; Doehring, Kirchof & Lotsch, 2009). A recent study genotyped multiple functional markers of the DRD2 genes (DRD2/ANKK1) and found support for a hypersensitivity to reward among those prone to hedonic overeating (Davis et al., 2012).

A strong appetitive motivation could be especially problematic in the context of ADHD, particularly in our current environment of abundantly available, calorically-dense foods. Indeed, hedonic overeating is believed to result when one's drive to consume palatable food exceeds one's capacity for inhibitory control of eating (Appelhans et al., 2011). Supporting this claim, higher food reward-sensitivity predicted greater palatable food intake (Appelhans et al., 2011) and weight gain over a one-year period (Nederkoorn, Houben, Hofmann, Roefs & Jansen, 2010), but only among women exhibiting diminished levels of inhibitory control. There was no association among those with adequate inhibitory control. Theoretically, and based on this evidence, it seems plausible that the individuals with ADHD who are predisposed to engage in overeating are those who also possess a high sensitivity to, and greater motivation to seek out, rewarding stimuli.

While a number of studies have examined the association between eating behaviour and either reward sensitivity or impulsivity/inhibitory control – besides the two aforementioned

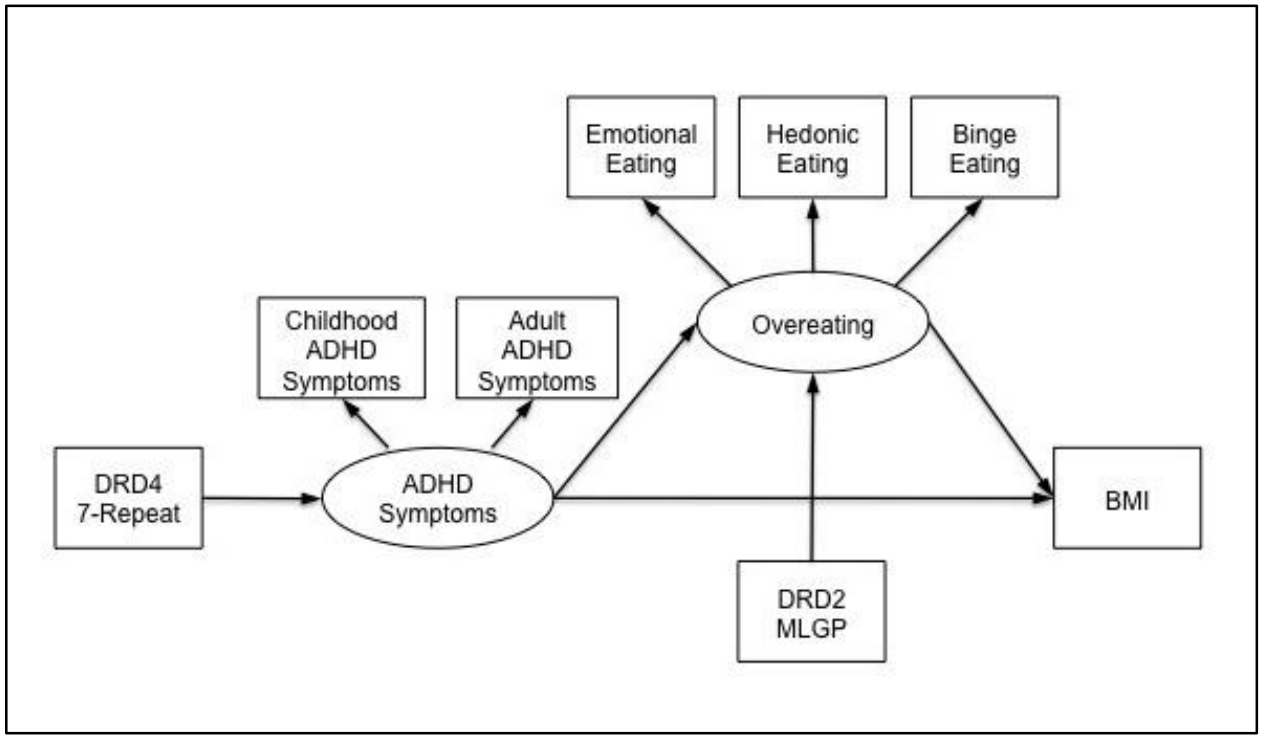
studies (Appelhans et al., 2011; Nederkoorn et al., 2010) – the joint involvement of these two factors has yet to be tested in the same study. Likewise, to the author's knowledge, no study has investigated the neurobiological mechanisms regulating these psychological characteristics. Despite extensive research on the role of DA in ADHD in general (Gizer et al., 2009; Li, Sham, Owen & He, 2006; Smith, 2010), such studies on both weight status and ADHD are scarce.

Relatedly, much of the neuroscientific study of obesity has used neuro-imaging technology, which only reveals the current state of brain-circuitry activation, limiting the ability to separate casual factors from those that may be consequent to the process of overeating (Hommer, Bjork & Gilman, 2011). This factor is particularly relevant, considering the neuro-adaptations, such as down regulation of receptor activation that can result from abnormally sustained activation of the reward system due to the abuse of DA stimulating substances (Koob & Simon, 2009). There is now substantial evidence that these changes may occur in response to the chronic overconsumption of high sugar and/or fat food in the same way as to habitual substance use (Bello & Hajnal, 2010). In order to determine the antecedent DA state without confounding neuro-adaptations, arguably genes can provide the best available index.

Therefore, the **second and main objective** of the current study was to test the hypothesis that symptoms of ADHD, in combination with an enhanced appetitive drive, predict hedonic eating, and in turn, higher body mass index (BMI). As part of the behavioural genetic model (see Figure 1), functional markers of the DRD4 and DRD2 were genotyped to determine their contributions to ADHD symptoms (adult and childhood ADHD symptoms) and multiple indices of overeating (i.e., emotional eating, hedonic eating, and binge eating), respectively. For the DRD4 gene, a 48-base pair (bp) Variable Number Tandem Repeat (VNTR) was analyzed based on meta-analyses supporting a role in ADHD and the lack of evidence for other polymorphisms

of the gene (Gizer et al., 2009; Li et al., 2014; Thapar et al., 2013; Wu et al., 2012). The 7-repeat allele of the marker has been associated with diminished-DA levels and was expected to predict greater ADHD symptomatology (Gizer et al., 2009; Li et al., 2014; Thapar et al., 2013; Wu et al., 2012). Several DRD2 markers were included based on their known functionality. Higher scores on a cumulative index of the DRD2 polymorphisms - reflective of increased ventral striatum activation potential - were expected to predict overeating (Davis et al., 2013; Nikolova et al., 2011). The model was tested using Structural Equation Modeling (SEM) and mediation procedures among a large sample recruited from the general population and representative of a range of BMIs. The use of a nonclinical sample avoids confounding treatment effects and is based on the theory that symptoms of disorder are best considered as dimensions that occur in varying degrees of severity within the population.

**Figure 1. Model to be tested using SEM, with functional markers of the DRD4 and DRD2 genes predicting ADHD symptoms and Overeating, respectively, and in turn, BMI**




MLGP = Multilocus Genetic Profile Score

## 2. Review of the Literature

### 2.1. Obesity

Obesity is one of the leading public health threats (Scully, 2014) and is now regularly referred to as an "epidemic". The World Health Organization (WHO) defines overweight and obesity as abnormal or excess fat accumulation that may impair health (Donald & Behan, 2012). Excess body weight causes and exacerbates a large number of health problems (Bray, 2004; Haslam & James, 2005; Kopelman, 2000), impairs quality of life (Kim & Kawachi, 2008) and is among the leading contributors to premature mortality (Danaei et al., 2009; Orpana et al, 2009; Kitahara et al., 2014; Scully, 2014). In a recent analysis of data pooled from 20 large studies from the United States, Australia, and Sweden (n=9564 adults with extreme obesity, and 304011 adults of normal weight), carrying an extra 45 kg or more predicted a reduction in life expectancy by 6.5 to 13.7 years, due to illnesses such as cancer, heart disease, stroke, diabetes, and kidney and liver disease (Kitahara et al., 2014). In regards to cancer, the largest study to date (n=5.24 million individuals in UK) reported a positive association between BMI and 10 of the most common forms, such as liver, colon, and uterine cancers (Bhaskaran et al., 2014). In addition, excess adiposity increases the risk for: sleep apnea, asthma, and other respiratory ailments (Beuther & Sutherland, 2007; McClean, Kee, Young & Elborn, 2008); pregnancy complications (Huda, Brodie & Sattar, 2010), infertility (Rich-Edwards et al., 2002), gynecological issues (e.g., abnormal menses), and erectile dysfunction (Johannes et al., 2000); Alzheimer's disease and dementia (Beydoun, Beydoun & Wang, 2008; Profenno, Porsteinsson & Faraone, 2010); and musculoskeletal disorders like osteoarthritis and other joint, muscle, and bone problems that impede mobility (Anandacoomarasamy, Caterson, Sambrook, Fransen & March, 2008). In addition to adverse physical health effects, wide-ranging social and emotional

health consequences are associated with obesity. For instance, overweight individuals are more likely to experience bullying (van Geel, Vedder & Tanilon, in press), depression (de Wit et al., 2010; Luppino et al., 2010), and stigma and discrimination (Puhl & Heuer, 2009, 2010).

Obesity also has substantial associated economic costs at both the individual and population levels; although calculating estimates of its price is complicated by the sizeable hidden and indirect losses (Trogdon, Finkelstein, Hylands, Dellea & Kamal-Bahl, 2008). Indirect costs refer to resources lost as a result of obesity-related health conditions, which account for the value of lost work wages and productivity due to the greater absenteeism of obese employees, higher life insurance premiums and payouts by employers for obese workers, and the lower wages and household incomes received by obese employees (Colditz & Wang, 2008; Trogdon et al., 2008). The direct health care costs of obesity have also risen steadily over time (Dor, Langwith & Tan, 2010). In the U.S., excess adiposity is estimated to account for 21% of overall medical spending (Cawley & Meyerhoefer, 2012). *Per capita*, people carrying excess body fat cost 150% or $2741 more annually than healthy-weight patients (Cawley & Meyerhoefr, 2012). Over the lifetime, these expenditures resemble those for individuals who smoke (Thompson, Edelsberg, Colditz, Bird & Oster, 1999). The financial and health impact will continue to escalate with time, especially with the earlier onset of obesity that has been occurring (Scully, 2014) and negligible improvement in its occurrence.

#### 2.1.1. The prevalence of obesity

Epidemiological evidence shows that the prevalence of obesity has more than doubled over the past few decades (Scully, 2014; Shields et al., 2010; WHO, 2003), with half this rise occurring between 2000 and 2008 (Scully, 2014). According to a “landmark” analysis of almost 1800 surveys, reports, and published studies, obesity rates increased substantially between 1980

and 2013 in children, adolescents, and adults in both developed and developing countries (Ng et al., 2014). In Canada, the prevalence of adult obesity rose from 6.1 to 18.3% between 1985 and 2011 (Twells, Gregory, Reddigan & Midodzi, 2014), with 1 in 4 adults now considered obese based on measured height and weight, or 62.1% when combined with those who are overweight (Shields et al., 2010). Particularly distressing is the parallel trend among children (de Onis, Blossner & Borghi, 2010; Ng, et al., 2013; Ogden, Carroll, Curtin, Lamb & Flegal, 2010; Popkin, Conde, Hou & Monteiro, 2006) and the emergence of serious health conditions originally thought to occur only in adulthood (e.g., type 2 diabetes and hypertension; Kaur, Kapil & Singh, 2005; SEARCH for Diabetes in Youth Study Group, 2006). For instance, the prevalence of type 2 diabetes climbed by 30% in children and adolescence between 2001 and 2009 (Dabelea et al., 2014).

Although there has been some recent discussion of obesity trends stabilizing (Flegal et al., 2012; Ogden, Carroll, Kit & Flegal, 2014; Yanovski & Yanovski, 2011), other research predicts that overall obesity rates in Canada will continue to rise at least into 2019, leading to half of the Canadian provinces having more overweight and obese residents than normal-weight adults (Twells et al., 2014). Based on U.S. data, the most recent report on obesity found the rates had increased in 6 states and did not improve in any of the other states (Levi, Segal, St. Laurent, & Rayburn, 2014). The overall average waist circumference also grew significantly from 1999-2000 to 2011-2012 (Ford, Maynard & Li, 2014). Moreover, individuals who are already carrying excess weight are getting heavier, with morbid or class III obesity (BMI > 40 $kg/m^2$) continuing to escalate exponentially (Sturm & Hattori, 2013; Yanovski & Yanovski, 2011), leading to even greater risk of adverse outcomes. Despite widespread acknowledgement of the issue, it is evident by these trends that intervention efforts remain inadequate and ineffective.

### 2.1.2. The obesogenic environment

The global rise in obesity appears primarily driven by coinciding changes in the food system (Cutler, Glaeser & Shapiro, 2003; Swinburn et al, 2011), and their interaction with polygenetic predispositions to weight gain (Kessler, 2013). The development of distribution systems and mass production contributed to what is now commonly referred to as the "obesogenic environment" – in which food has become a highly processed, convenient, inexpensive, and widely available commodity (Swinburn et al., 2011). Food availability has shown extensive growth since the 1960s (Scully, 2014), alongside sharp declines in the price of food (Swinburn et al., 2011). By the 1990s, an average of 450 more calories were available per person worldwide, rising to an excess of over 600 kcal in developing countries (Scully, 2014). Meanwhile, individuals now spend less than 1/10 of their disposable income on food, down from ¼ in the 1930s (Sturm & Ruopeng, 2014), and more processed, high sugar, and calorie-dense foods tend to be the cheapest options.

Amongst the reduced cost and greater availability, people started eating more frequently and larger amounts at each eating occasion (Nielsen & Popkin, 2003; Young & Nestle, 2002). Portion sizes grew in restaurants, grocery products, and cookbook recipes (Young & Nestle, 2002), which are shown to have sustained effects on energy intake, weight gain, and obesity (Berteus, Torgerson, Sjostrom & Lindroos, 2005; Chapelot, 2011; French et al., 2014; Koopman et al., 2014; Rolls, 2014). The composition of food also changed. Worldwide consumption of carbohydrates skyrocketed with the development of high fructose corn syrup and other low cost liquid sweeteners (Sturm & Ruopeng, 2014).

In addition, food products are now promoted using highly persuasive marketing strategies and multiple media outlets (Swinburn et al., 2011). In 2012, food marketing via social media and

mobile devices grew exponentially, with $4.6 billion spent on fast food advertising, compared to the relatively meager $116 million used to advertise fruits and vegetables (Yale Rudd Centre for Food Policy & Obesity, 2013). On average, teenagers in the U.S. viewed 4.8 fast food advertisements per day or approximately 6000 commercials each year (Yale Rudd Centre for Food Policy & Obesity, 2013). Moreover, fast food marketing targets black and Hispanic youth – populations already at high risk for obesity and related conditions (Yale Rudd Centre for Food Policy & Obesity, 2013).

In reaction to omni-present food cues, hedonic, habitual, and passive eating likely became more common, as opposed to consumption motivated by physical hunger and nutrition needs (Potenza, 2014). Experts have often attributed growing obesity rates to a 'clash' between our genes – adapted to survive seasonal food shortages or possible famines in times past – and the current obesigenic environment (Cummings & Schwartz, 2003; Peters, 2003; Pi-Sunyer, 2002). According to the "thrifty genotype" hypothesis, weight gain can be viewed as a normal biological adaptation to our modern food-abundant surroundings (Cummings & Schwartz, 2003; Peters, 2003; Swinburn et al., 2011). We have an innate drive to eat beyond caloric need when food is available and to store excess energy. Nowadays, this inherent motivation is problematic, because of the greater availability of calorically-dense foods (Jeffrey & Utter, 2003; Nestle, 2003; Piernas & Popkin, 2011). However, despite these drastic environment changes, some individuals remain able to maintain a healthy weight. It is critical to determine what differentiates them from the escalating proportion who are overweight. The ADHD-obesity relationship indicates that certain symptoms or biological mechanisms associated with the disorder predispose some sufferers to excess adiposity.

### 2.2. Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is characterized by persistent and pervasive developmentally age-inappropriate signs of impulsiveness, inattention, and/or hyperactivity (APA, 2013). Several sources indicate that an escalating number of youth are being diagnosed with the disorder (Atladottir et al., 2007; Boyle et al., 2011; Centers for Disease Control and Prevention, 2010). Prevalence estimates range from 8.7% to 10.6% of grade school-aged children (Atladottir et al., 2007; Boyle et al., 2011; Centers for Disease Control and Prevention, 2010; Wolraich et al., 2012), and these rates are believed to be conservative (Wolraich et al., 2012). Symptoms appear to persist into adulthood in approximately half of all childhood cases (Fischer, 1997; Searight, Burke & Rottnek, 2000). Worldwide, 2.5-3.4% of adults have been diagnosed with the disorder (Fayyad et al, 2007; Simon, Czobor, Balint, Meszaros & Bitter, 2009). The occurrence of adult ADHD is likely underestimated, as this disorder was originally considered a psychiatric disorder of childhood. However, it has now been reconceptualized as a "lifespan disorder" (Dalsgaard, 2013; Kordon & Kahl, 2004; McGough & Barkley, 2004) because symptoms do not necessarily remit with age. Accordingly, the DSM 5 (APA, 2013) moved ADHD to the Neurodevelopmental Disorders section, and added examples to facilitate application of diagnostic criteria across all ages and more accurately reflect the experience of affected adults (APA, 2013; Dalsgaard, 2013).

ADHD is a heterogeneous disorder in its presentation. The DSM 5 divides 18 core symptoms into 2 categories: *inattention symptoms* and *hyperactive-impulsive symptoms* (APA, 2013). Symptoms of hyperactivity include restlessness, and excessive fidgeting and talking, and examples of impulsive symptoms are a tendency to interrupt and extreme impatience. Inattention symptoms consist of difficulty paying attention to detail, finishing tasks, and staying organized, and a tendency to be forgetful and easily distracted (APA, 2013). Based on the type and number

of symptoms displayed, diagnoses are divided into: *Combined Presentation*, *Predominately Inattentive Presentation*, *Predominately Hyperactive-Impulsive Presentation*, and *ADHD Not Otherwise Specified* or *Unspecified*. To be classified as having a particular presentation, 5 or 6 symptoms are required to undermine functioning in 2 or more settings among individuals older than age 17, or younger than 17, respectively (APA, 2013).

ADHD can have a devastating impact on all life domains. In children, the disorder is associated with delayed school achievement, low self-esteem, and problematic family and peer relations (Davies, 2014; Efron et al., 2014; Nigg, 2013). Adolescents and adults with ADHD are more likely to exhibit impaired social functioning and employment difficulties, and sometimes, antisocial behaviour and criminality (APA, 2013; Davies, 2014; Nigg, 2013). In addition, other mental health problems often co-exist, including depression, substance use disorders, disruptive behaviour disorders (conduct disorder and oppositional defiant disorder), self-harm, and suicidal behaviours (Efron et al., 2014).

ADHD also has debilitating physical health consequences, although they have not been well studied (Spencer, Faraone, Tarko, McDermott & Biederman, 2014). Nigg (2013) declared the disorder to be an early warning sign for the secondary prevention of several health complications, such as hypertension and type 2 diabetes. Similarly, after assessing various health outcomes in cases and matched controls, Spencer et al. (2014) concluded that adults with ADHD should be considered a high-risk group for adverse medical morbidities, based on differences in lipid profiles, vital signs, BMI, asthma, and muscoskeletal disorders. The authors called for research investigating the mechanisms through which ADHD impacts physical health, and to test whether treatment of the disorder will mitigate risks. Many of the cited health conditions relate to excess adiposity, and ADHD symptoms have been shown to impede successful weight loss

(Cortese & Castellanos, 2014). ADHD patients may also have trouble following health recommendations, similar to difficulties seen with medication compliance (Adler & Nierenberg, 2010; Alfonsson et al., 2012).

### 2.3. ADHD and Obesity

The link between ADHD and obesity was not formerly recognized until fairly recently, with the first two studies to report their co-occurrence published in 2002 (Altfas, 2002; Fleming & Levy, 2002). Some researchers have claimed their association was simply overlooked (Cortese et al., 2008), while Davis (2010) deemed an oversight unlikely, and proposed the association was largely absent before the past decade, and only emerging as a consequence of the current obesogenic environment.

In prevalence studies, ADHD and its symptoms were found in a substantially higher percentage of both children (Cortese et al., 2008; Erhart et al., 2012) and adults (Alfonsson et al., 2010; Altfas, 2002; Fleming & Levy, 2002) receiving treatment for obesity compared to the general population, and the occurrence is especially high among individuals with morbid obesity (BMI>40; Gruss et al., 2012), representing almost half of the sample in one study (42.6%; Altfas, 2002). In children with ADHD, the elevated body weight tends to continue into adulthood (Anderson, Cohen, Naumova & Must, 2006; Cortese et al., 2013). A 33-year prospective study found that men who had childhood ADHD were twice as likely to be obese in middle age (Cortese et al., 2013). This finding is supported by large population-based epidemiological and clinical studies presenting elevated obesity rates among children, adolescents, and adults with the disorder (Cortese et al., 2008; Gungor et al., 2014; Nigg, 2013; Pagoto, et al., 2009; Schwartz et al., 2014; Waring & Lapane, 2008; Yang, Mao, Zhang, Li & Zhao, 2013). The association remains regardless of obesity measurement (BMI, body fat %, waist circumference) or ADHD

assessment tool used, and after controlling for socio-economic status and depression (Erhart et al., 2012; Nigg, 2013).

Most reports present the ADHD-obesity link with the assumption that ADHD symptoms lead to increased adiposity, ignoring a plausible bi-directional relationship or the prospect that excess weight may trigger ADHD symptoms. To test the directionality, Khalife et al. (2014) analyzed a large, medically untreated, population cohort (n=8106) over an eight-year period from childhood to adolescence. Results verified presumptions – inattention and hyperactivity symptoms at the age of 8 predicted obesity at age 16, and not vice-versa. However, a bi-directional relationship was found between symptoms of inattention and physical inactivity, where reduced levels of physically-active play in childhood predicted adolescent inattention symptoms, and childhood ADHD symptoms were linked to physical inactivity in adolescence. Relatedly, engaging in physical activity shows potential as an adjunct intervention for ADHD symptoms based on evidence of improved executive functioning among children who participated in exercise interventions (Hillman et al., in press; Hoza et al., in press).

At first glance, the relationship between ADHD and adiposity may seem counterintuitive considering the hyperactivity symptoms experienced by some patients; however, contrary to expectations, symptoms do not demonstrate a protective effect against weight gain in children with the disorder (Holtkamp et al, 2004), and the risk for obesity appears to remain even when childhood ADHD symptoms have remitted (Donald & Behan, 2012). Moreover, hyperactive symptoms tend to subside in adulthood to a greater degree than other symptoms (Biederman, Mick & Faraone, 2000). Regardless, ratings of hyperactivity and sluggishness are positively correlated, suggesting children with ADHD exhibit only bursts of overactivity interspersed with

underactivity, and not the sustained activity that promotes healthy body weights (McBurnett, Pfiffner & Frick, 2001).

In fact, several studies have found lower levels of physical activity in children with ADHD relative to peers, especially in terms of regular, vigorous exercise and organized sports (Harvey et al., 2009; Kim & Mutyala, 2011). For example, using structured parental interviews, a recent study of boys aged 6 to 10 years found that those with ADHD engaged in less regular physical activity and spent more hours in front of a television or computer compared to age-matched healthy controls (Ptacek et al., 2014). Similarly, in a sample of 1331 cases and 1331 controls below the age of 18, children with ADHD were significantly less likely to do a daily physical activity/sport or to be active for over 30 minutes a day (Bener & Kamal, 2014). In a large U.S. sample (n=45,897 youth aged 10 to 17 years), youth with ADHD also had higher than expected obesity rates, and a lower probability of meeting recommended levels of activity, but only among those who were not medicated (Cook, Li & Heinrich, 2014).

The poor motor skills and coordination difficulties often exhibited among affected individuals may discourage their participation in sports or exercise (Cook et al., 2014). In addition, executive function deficits can interfere with prolonged commitment to programs. Adhering to diet and exercise regimens requires planning and continued effort to be effective. However, these studies have primarily relied on parental report of children's height, weight, activity, and ADHD status, and these relationships have yet to be tested among adults. Besides, while being physically active has substantial health benefits, it is not likely a key factor in the ADHD-obesity link. Scientific literature consistently demonstrates that exercise does not sufficiently compensate for overeating in determining adiposity (Cessa et al., 2014), but can be an essential component of weight loss maintenance (Sciamanna et al., 2011).

The influence of sex/gender on the ADHD-obesity association is worthy of investigation, considering that males and females vary in both the disorder and in overeating behaviours. Boys outnumber girls in ADHD diagnosis and treatment, particularly at younger ages. Estimated male to female ratios range from 2:1 to 9:1, depending on the subtype and setting (Rucklidge, 2010). Clinic-referred ADHD cases are more likely to be male (Rucklidge, 2010). A large community-based sample reported a male to female ratio of 2.28:1 (Ramtekkar, Reiersen, Todorov & Todd, 2010). Also, girls tend to be identified later and exhibit more inattention and/or internalizing symptoms than hyperactivity/impulsivity, although, these trends may be due to gender role socialization and stereotypes (Efron et al., 2014; Rucklidge, 2010; Skogli, Teicher, Anderson, Hovik & Oie, 2013). Two reports support a potential sex effect on association between ADHD symptoms and adiposity. Compared to the general population, boys with ADHD were at increased risk of being overweight, whereas, the relationship was age dependent in girls (Fliers et al., 2013). There was a 4-fold greater risk of being obese in girls aged 10 to 12 with the disorder, but ADHD seemed to be protective against excess weight gain among younger girls (aged 5-9 years) and female teenagers (13-17 years of age; Fliers et al., 2013). However, medication status was not controlled for, and it may explain the gender and/or age effect due to estrogen's interaction with dopamine (Pal, Pal, Nandda & Saurabh, 2007). That is, among the medicated participants, post-puberty females may have experienced greater appetite suppressing effects from the stimulant drugs, which may explain why the older girls did not have an increased risk of obesity. In a non-clinical sample, ADHD symptoms in female adolescents were associated with compensatory behaviours (i.e., dysfunctional eating habits), while in males, signs of inattention and hyperactivity/impulsivity predicted later overweight status (Petrone, Prunas, Dazzi &

Madeddu, 2013). Sex/gender differences have not been tested in most other studies due to samples that were either inadequate in size, or consisted solely of males or females.

ADHD and overweight both have high rates of co-morbid psychopathology, and individuals with both conditions appear particularly prone to additional emotional or mental health problems. For instance, among bariatric surgery candidates (n=93) and obese inpatients (n=63) from a psychotherapy unit, participants categorized into the "emotionally dysregulated/undercontrolled" cluster had higher rates of ADHD, as well as other psychopathology (i.e., eating disorder symptoms, binge eating disorder [BED], and more severe depression), compared to the "resilient/high functioning" group (Muller, Claes, Wilderjans, & de Zwaan, 2014). Likewise, in a retrospective cohort of children and youth with diagnosed ADHD (n=22452), heavier individuals were more likely to later develop Major Depressive Disorder (MDD; Jerrell, McIntyre & Park, 2014). Such results raise ambiguity about whether the ADHD-obesity link results from the depression or other mental health conditions that often co-occur with them, hence the importance of screening for additional psychological problems, or controlling for possible depression. The use of a nonclinical sample would lessen the probability of confounding mental illness.

Moving beyond prevalence estimates, emerging research has questioned the role of sleep in ADHD, which has also been recently implicated in obesity. A lack of sleep is shown to both exacerbate ADHD symptoms (Lundahl & Nelson, 2014), and predict higher BMIs (Carter et al., 2011). Lundahl and Nelson (2014) argue that sleep deprivation could potentially play both a causal and maintaining role in the co-morbidity. However, the only study to date that has tested the theory found no significant relationships (Fliers et al., 2013).

### 2.4. ADHD and Overeating

Only a few studies have examined behavioural mechanisms, and results have suggested that hedonic overeating may mediate the link between ADHD symptoms and obesity (Davis et al., 2006; Dempsey et al., 2011; de Zwaan et al., 2011; Ivan et al, 2009; Pagoto et al., 2009; Strimas et al., 2008). In contrast to homeostatic eating, hedonic overconsumption can occur in several ways and for different reasons. For instance, *emotional eating* – food consumption in response to emotions such as boredom or sadness, rather than for energy needs or perceived hunger – has been positively associated with ADHD symptoms and degree of impulsivity (Alfonsson et al., 2012; Davis et al., 2006; Dempsey et al., 2011). ADHD symptoms were also related to *external eating* – eating that is prompted by environmental cues (Davis et al., 2006; Strimas et al., 2008).

Considering the delay aversion associated with ADHD (Ernst et al., 2003) – that is, a tendency to choose immediate gratification over delayed larger rewards – these patients may prefer fast foods with high sugar and fat content. Studies do suggest that ADHD symptoms influence food preferences or choices. For example, a greater adherence to "fast food" and "sweet" dietary patterns was associated with higher risk of having ADHD among school-aged children (Azadbakht & Esmaillzadeh, 2012). A recent study also found that boys (n=100, age 6-10 years) with *Combined Presentation* consumed more sweetened beverages and less fruit and vegetables compared to age-matched, healthy male controls (n=100; Ptacek et al., 2014). Likewise, ADHD symptoms have been linked to consumption of foods with higher average energy densities and lower nutrient densities, as well as an overall diet containing greater total energy and fat intakes, lower nutritional quality, and larger volumes of food and beverages (Howard et al., 2011; Van Egmond-Frohlich, Weghuber & de Zwaan, 2012). It is possible that

the food choices of individuals with ADHD reflect taste preference, occur due to convenience, or result from a greater sensitivity to the advertising of processed foods.

On the other hand, some researchers (Seitz et al., 2013; Fleming & Levy, 2002) have proposed that ADHD patients may be relatively inattentive to internal signs of hunger and satiety, and as a result, eat past the point of physical satiety or will forget about eating when engaged in interesting activities. If the latter occurs, when these individuals do eventually eat, they will likely be ravenously hungry, which may lead to greater caloric intakes than would have occurred otherwise. A newly published report lends some support to this theory. In comparison to an age-matched control group, boys with combined-type ADHD had less adherence to a traditional meal schedule by often skipping breakfast, lunch, &/or dinner, yet they ate more frequently throughout the day at irregular eating times (Ptacek et al., 2014). However, reasons other than attention to hunger cues could also account of these findings, such as the difficulties in planning typically seen in the disorder. Furthermore, another study found that ADHD patients were *more* susceptible to perceptions of hunger (Dempsey et al., 2011).

Of the forms of overconsumption, binge eating has received the most research attention in relation to ADHD. Bingeing refers to eating what would be considered an excessive amount of food for most people within a limited time span, and is associated with feelings of loss of control. Children (Erhart et al., 2012) and adolescents (Neumark-Sztainer, Story, Resnick, Garwick & Blum, 1995) with ADHD are more likely to report binge eating compared to their nonclinical counterparts. Some experts have suggested that binge eating itself could be included in the framework for hyperactivity-impulsivity symptoms (Cortese, Bernardina & Mouren, 2007).

Both Ivan et al. (2009) and Pagoto et al. (2009) found that binge eating partially mediated the association between ADHD symptoms and weight status. Similarly, Among Korean elementary school children (n=12350), a new report using SEM found unhealthy food intake (i.e., soft drinks, fast food, instant noodles) and "bulimic" dietary behaviours (including overeating and diet speed) mediated a positive total effect of ADHD symptoms on BMI, while the direct effect of ADHD symptoms on BMI was actually negative because they predicted both underweight and overweight BMIs (Kim et al., 2014). However, only 4.5% of the sample was classified as obese, and the report did not provide information on medication history or any fit index statistics in order to judge model fit. While not formally tested, a partial mediation is also supported by a retrospective review of patients (n=252, mean age 10.8 years) at two pediatric mental health clinics, in which adjusting for bingeing attenuated the relationship between ADHD and BMI z-scores (Reinblatt et al., 2014). Children with the disorder had 16 times the odds of presenting with binge eating, and the association persisted after controlling for co-morbid diagnosis, medications, demographics, and clinic (Reinblatt et al., 2014). However, the authors note that many inflicted children did not binge eat (74%), and speculate on a distinct subgroup of individuals possessing both ADHD symptoms and binging behaviours.

Impulsivity – a hallmark of ADHD – has long been studied in relation to binge eating (e.g., Nasser, Bluck & Geliebter, 2004), and thought to contribute to difficulties inhibiting strong urges or cravings. Among girls with ADHD, signs of impulsiveness were found to be the strongest predictor of pathological eating (Mikami, Hinshaw, Patterson & Lee, 2008). A recent study using bootstrap analyses tested whether impulsivity (as measured by self-report questionnaires and a behavioural task) mediated the association between ADHD symptoms and binge eating (Steadman & Knouse, in press). The indirect effect was insignificant. ADHD symptoms

positively correlated with both binge eating and impulsivity measures, but the impulsivity measures were not significantly associated with binge eating when controlling for the effect of ADHD. The authors concluded that other factors linked to both ADHD and binge eating may explain their connection, such as depression and emotional regulation. Despite using powerful statistical methods, interpretations are limited by the small sample (n=50) of undergraduate students, with a higher than average SES and low levels of obesity (BMI ranged from 17 to 33.9 $kg/m^2$).

Two different studies have reported that only inattention symptoms predicted the severity of binge eating (Ivan et al., 2009; Seitz et al., 2013). Certain characteristics of the disorder may be associated with bingeing, while other symptoms predict other forms of eating behaviour. In a secondary data analysis of disordered eating in relation to either diagnosed or subclinical (presence of behaviours/symptoms but not all diagnostic criteria) ADHD, youth meeting diagnostic criteria were more likely to experience a clinical eating disorder, bingeing and/or purging behaviours, and restrictive eating, while youth with subclinical inattention or hyperactivity/impulsivity symptoms were more likely to experience subclinical bingeing and/or purging, but not eating restriction (Bleck, DeBate & Olivardia, 2014).

Binge eating is also a hallmark of bulimia nervosa (BN) – an eating disorder characterized by binge and purge episodes, and typically a body weight within the normal range. Both adolescent (Biederman et al., 2007) and adult females (Nazar et al., 2008) with ADHD appear to be more vulnerable to developing co-morbid eating disorders, especially BN. In a meta-analysis the prevalence of BN in ADHD groups ranged from 1 to 12%, compared to 0 to 2% in control groups. The authors concluded, however, that the evidence was limited by few studies, small sample sizes, and methodological heterogeneity (Nazar et al., 2008). A more recent study,

involving a large number of participants (n=12413) from 13 countries, reported that 6% of patients with a lifetime diagnosis of ADHD had a history of BN, and 15% respondents with lifetime diagnosis of BN had history of ADHD (Kessler et al., 2013). Likewise, Seitz et al. (2013) conducted a case-control trial in which females with BN had a higher probability of meeting ADHD diagnostic criteria (OR=4.2) than controls. In summary, the link between ADHD and disordered eating does appear to be exclusive to the impulsive binging/purging behaviours, as opposed to the restrictive eating (Bleck & DeBate, 2013).

Another eating disorder, known as Night Eating Syndrome (NES), has also been connected to ADHD. Individuals with NES engage in excessive nighttime eating on a frequent or nightly basis, and may feel doing so is essential in order to get back to sleep. The majority of their calorie consumption occurs at night, while having little appetite or food intake in the morning. Surveying 10 U.S. universities (n=1636), researchers found that students with NES were more likely to have ADHD and be taking related medications (Runfola, Allison, Hardy, Lock & Peebles, 2014). No other studies investigating NES and ADHD have been conducted to date. Overall, current research findings suggest that the combination of ADHD symptoms and disturbed eating behaviours reflect a general level of greater psychopathology.

A number of other studies have failed to find an association between ADHD and eating behaviour (Dubnov-Raz, Perry & Berger, 2011; Lingineni et al., 2012; Pauli-Pott, Becker, Albayrak, Hebebrand & Pott, 2013), possibly due to small sample sizes, confounding factors such as socio-economic status and depression, or the method of ADHD assessment used (Cortese, Moreira, Rhode, Morcillo-Peñalver & Faraone, 2014; Khalife et al., 2014; Yang et al., 2012). For instance, the common use of self or parental report of past ADHD diagnosis as the primary measurement of the disorder is unreliable, as many cases go overlooked, misdiagnoses

may also be present, and associated variables beyond formal diagnosis could be missed (Agranat-Meged et al., 2005; Alfonsson et al., 2012; Fliers et al., 2013; Wolraich et al., 2012). In fact, the disorder had gone previously undiagnosed among 60% and 83% of children comprising the samples of two separate studies (Agranat-Meged et al., 2005; Efron et al., 2014). Moreover, the use of categorical variables does not allow for analysis across the full continuum of symptom severity; whereas, the validated scales used in the current study reflect ADHD symptoms as continuous measures.

The current study will further clarify inconsistencies by using a medication naïve sample. Several existing studies are limited by the lack of controls for medication status, despite the known impact that ADHD pharmacological treatments have on appetite and weight (Fliers et al., 2013; Graziano et al., 2012; McElroy et al., 2013). They have either included participants who have taken or are currently taking stimulants, or have failed to assess and/or provide information on medication history. In general, current literature points to ADHD pharmaceutical interventions having a protective effect on obesity while continuing to administer them (Byrd, Curtin & Anderson, 2013; Cook, Li & Heinrich, 2014; Waring & Lapane, 2008). Notably, the ADHD stimulant drug Vyvanse was just newly accepted for a Food and Drug Administration (FDA) priority review for the treatment of binge eating. It remains unknown if the improvements in weight are produced by the medications' suppressive effect on appetite, or occur as an indirect result of diminished ADHD symptoms, and thereby better regulation of eating behaviour. Others have also raised the possibility that the improved cognitive functioning requires less caloric intake (Davis, 2010), as additional mental work has been associated with greater *ad libitum* food consumption (Riverin & Tremblay, 2009).

On the other hand, some null and conflicting evidence on the effect of ADHD drug treatments also exists. For instance, Fliers et al. (2013) found no influence of stimulant use on obesity risk, and Reinblatt et al. (2014) reported the medications were associated with a 3-fold increase (OR 3.16, p=0.006) in the odds of binge eating, but not related to BMI. Moreover, certain researchers have reservations regarding the cessation of stimulant drugs – a relevant concern considering about half of childhood methylphenidate prescriptions are terminated before adulthood (Goodman, 2013). In a case study of a patient with childhood ADHD, the authors detailed how he gained 30 kgs in the year following discontinuation of methylphenidate, and theorized that the interruption of long-term stimulant use may have a rebound effect resulting in appetite enhancement, metabolic readaptation, and weight gain (Bernard, Cottencin, Guardia, Vaiva & Rolland, 2014). Likewise, the results of a longitudinal study using the health records of 163,820 children suggested a weight-rebound effect after stopping stimulant use, as well as dose-response relationship for age at first use and duration of use (Schwartz et al., 2014). Specifically, younger age and longer duration predicted slower BMI growth earlier in childhood, but a more rapid "BMI rebound" in late childhood, leading to higher BMIs in late adolescence than controls without a history of ADHD or stimulant naïve subjects with ADHD (Schwartz et al., 2014). These findings may reflect an enhanced appetite for the reinforcing properties of sugar as a result of earlier stimulant use, akin to the cross-sensitization that occurs among different drugs of abuse or between intermittent sugar intake and addictive drugs (Davis, 2010). Alternatively, weight gain after stopping ADHD medications could simply be due to the reemergence of inattention and hyperactivity/impulsivity symptoms (Bernard et al., 2014).

### 2.5. The Neurobiology of ADHD

In addition to similar behavioural tendencies, ADHD and overeating display some neurobiological commonalities, which suggest plausible mechanisms underlying their co-occurence. Research has established that individuals with ADHD exhibit structural and functional brain abnormalities, and they appear to result from delayed maturation (Baroni & Castellanos, 2014). More specifically, various findings signify decreased volumes or hypoactivation in the frontal-striatal-cerebellar or ventral striatal-limbic circuits, and/or altered relationships amongst the various regions or networks responsible for the tasks that are impaired in ADHD (Baroni & Castellanos, 2014; Sripada, Kessler & Angstadt, 2014). Despite a consensus that the disorder's symptoms have neurological underpinnings, how or why the pathophysiology originates remains a matter of debate.

Difficulties establishing its aetiology stem from the probable varied and multiple sources, with proposed contributors ranging from genes and psychosocial factors, to environmental toxins, and prenatal and early life exposures (Thapar et al., 2013). The risk factors with the most consistent findings include: having a biological relative with ADHD, large rare copy number variants (CNVs; i.e., variations in the number of copies of certain sections of DNA), certain candidate gene variants, extreme early adversity, pre- and peri-natal exposure to lead, and low birth weight or prematurity (Thapar et al., 2013). While no single factor is known to be definitively causal (Thapar et al., 2013), genome wide analyses, and structural and functional imaging work, undeniably refute notions that ADHD is solely a social construct (Williams et al., 2010). Several family, twin, and adoption studies suggest a significant influence of genetics (Faraone et al., 2005; Nikolas & Burt, 2010; Thapar et al., 2013; Wu et al., 2012), with heritability estimates in the range of 71-76% for the disorder, along with some as high as 90%

(Faraone et al., 2005; Nikolas & Burt, 2010; Wu et al., 2012). Genes regulating the DA system have been recognized as the most important contributors to ADHD (Gizer et al., 2009; Wu et al., 2012).

DA is a catecholaminergic neurotransmitter involved in several motor activities and cognitive functions. DA neurons in the mesolimbic and mesocortical systems originate in the ventral tegmental area (VTA) and respectively project to limbic structures including the nucleus accumbens and amygdala, and to the frontal cortex (Koob, 1992). Along these pathways, DA is responsible for reinforcing certain behaviours and directing attention to relevant environmental cues by associating them with feelings of reward or pleasure (Blum, Cull, Braverman & Comings, 1996). The strength of the DA signal is under polygenetic control, and determined by many factors such as the affinity and density of the DA transporters and receptors, and the amount of DA synthesized and secreted into the synapse. While having a complex biology and signal transduction mechanisms, DA receptors primarily belong to a family of 7-transmembrane spanning, G-protein-coupled receptors (for review, see Beaulieu & Gainetdinov, 2011). The five subtypes of DA receptors are divided into D1-like (D1 and D5) and D2-like (D2, D3, and D4) classes according to their activating or inhibiting effect on adenylate cyclase, respectively. The D1-like and the D4 receptors are exclusively expressed on DA-target cells of postsynaptic neurons, while D2 and D3 subtypes are found both presynaptically as autoreceptors on DA neurons, and postsynaptically on DA-receptive cells (for review, see Beaulieu & Gainetdinov, 2011).

The effectiveness of pharmacological treatments in alleviating symptoms of inattention and impulsivity/hyperactivity first lead to the idea that a deficiency or impaired DA system underpins the disorder (Bradley, 1937). Stimulant medications such as methylphenidate – the first line of

treatment for ADHD – act by increasing DA in the mesocorticolimbic pathways of the brain (Spencer et al., 2005). Varied responses to methylphenidate occur, in part, because of individual variation in DA transporter (DAT) and DA receptor density and affinity (Krause, la Fougere, Krause, Ackenheil & Dresel, 2005). Research on genes contributing to these differences demonstrates an association between ADHD and variants associated with dampened DA levels (Bobb, Castellanos, Addington & Rapoport, 2006; Gizer et al., 2009; Thapar et al., 2013; Wu et al., 2012). Compared to research on other psychiatric disorders, a relatively large body of replicated findings exists for candidate genes for ADHD, although the effect size of risk variants is often small (Thapar et al., 2014). Among the candidate genes identified, recent reviews and meta-analyses report the strongest findings for the DAT1, DRD4 and DRD5 in relation to the disorder (Bobb et al., 2006; Li et al., 2006; Thapar et al., 2013; Wu et al., 2012).

#### 2.5.1. Dopamine D4 receptor gene (DRD4)

The D4 receptors are abundantly expressed in the prefrontal cortex, as well as brain regions involved in the reward circuits such as the hippocampus, amygdala and hypothalamus (Ariza et al., 2012; Meador-Woodruff et al., 1996). The DRD4 gene is the most well studied gene in response to methylphenidate and other stimulant medications (Froehlich et al., 2010), and has the most consistent support for a role in ADHD among the DA genes (Gizer et al., 2009; Thapar et al., 2013; Wu et al., 2012). According to a recent review of studies on ADHD candidate genes, the DRD4 is one of the few "hot genes" – reported by at least 5 association studies (Li, Chang, Zhang, Gao & Wang, 2014). Among the 67 identified reports on the gene and ADHD, 49 had significant results and 18 studies had nonsignificant findings (Li et al., 2014).

The DRD4 gene is localized to the short arm of chromosome 11 (11p15.5) and contains 3 introns in the coding region (Gelernter, Kennedy, Van Tol, Civelli & Kidd, 1992; Gingrich &

Caron, 1993; Petronis, Van Tol, Lichter, Livak & Kennedy, 1993). The large majority of research on the DRD4 has focused on the functional 48-bp VNTR in exon three, which encodes the third intracellular loop of the receptor (Van Tol et al., 1992). Of the 9 variants identified worldwide (Chang, Kidd, Livak, Pakstis & Kidd, 1996), the 4-repeat allelic polymorphism occurs most frequently, with rarer variants containing 2- to 11-repeats. *In vitro* studies indicate receptors encoded by the 7-repeat allele have both reduced receptor densities and a decreased binding affinity for DA due to a longer intracellular loop compared with receptors encoded by other variants (Asghari et al., 1995; Schoots & Van Tol, 2003), and as a result, likely undersupply the postsynaptic cell with DA (Swanson et al., 2000). Strong evidence supports the association of the 7-repeat allele with ADHD (Langley et al., 2005; Li et al., 2006; Thapar et al., 2013; Wu et al., 2012), as well as endophenotypes of the disorder, such as impulsivity and executive functioning. For instance, individuals possessing the 7-repeat variant display diminished brain activity and performances on behavioural measures of attention (Albrecht et al., 2014; Gizer & Waldman, 2012), and higher scores of trait impulsivity on psychometric scales (Varga et al., 2012). Other DRD4 mutations produced null results in the most recent meta-analysis on ADHD candidate genes (Wu et al., 2012).

Only a handful of studies has been done on the DRD4 in relation to obesity. In a sample of overeating women with Seasonal Affective Disorder, the 7-repeat allele of the DRD4 VNTR (the high-risk variant for ADHD) was associated with increased maximal lifetime BMI and obesity (Levitan et al., 2004). Interestingly – and by contrast – a recent study found a greater risk for Anorexia Nervosa among individuals possessing the 7-repeat/7-repeat genotype (Gervasini et al., 2013). Otherwise, the few studies that exist have failed to find differences for the DRD4 gene in relation to weight or disordered eating (Ariza et al., 2012; Yilmaz, Kaplan, Levitan, Zai &

Kennedy, 2012). For example, a recent longitudinal analysis reported there was no relationship between the gene and weight status of overweight youth before and after a lifestyle intervention, or an effect of genotype or allele frequency when comparing this sample to lean adult controls (Roth, Hinney, Schur, Elfers & Reinehr, 2013). However, the hypofunctional variant does seem to predict more severe ADHD symptoms in persons with eating disorders or obesity. For instance, Yilmaz et al. (2012) reported no difference in DRD4 allele frequency between patients with Bulimia Nervosa (BN) and controls, yet the 7-repeat variant was more likely in BN probands who also had ADHD, leading the authors to conclude that co-morbid BN-ADHD may represent a homogeneous group that is more impulsive or inattentive. Likewise, while another report indicated obese and control participants did not vary in the frequency of DRD4 alleles, individuals in the obese group who possessed the 7-repeat allele performed worse on executive functioning tasks (Ariza et al., 2012). Also, increased food intake, cravings, binge eating, and weight gain have been reported in response to treatment with clozapine (Bromel et al., 1998; Kluge et al., 2007; Theisen et al., 2003) – an anti-psychotic DA antagonist with a high affinity for the DRD4 (Naheed & Green, 2001; Seeman & Van Tol, 1994). While a direct role of the DRD4 in obesity or overeating does not appear likely based on the available evidence, more research is worthwhile to establish whether the gene contributes indirectly through traits that place individuals at greater risk for dysfunctional eating patterns.

### 2.6. Dopamine and Obesity

Reduced DA availability is also believed to place some individuals at increased risk for addictive behaviours according to the *Reward Deficiency Syndrome* viewpoint (Blum et al., 1996, 2000). According to this theory, individuals with a hypo-functioning reward circuitry are said to require a “DA-fix” to feel good, and therefore, are more likely to seek out stimuli which

increase available DA in the brain such as illicit drugs (e.g., cocaine). Experts have argued that chronic overeating can been modeled as an addictive behaviour, based on several physiological and behavioural similarities with chronic drug abuse (Davis & Carter, 2009; Davis et al, 2013; Filbey et al., 2012; Garcia-Garcia et al., 2014; Volkow, Wang, Tomasi & Baler, 2013). The subcortical brain's response to reward displays little differentiation between addictive drugs and reinforcers such as highly palatable foods (Kelley, Schiltz & Landry, 2005).

DA neurotransmission is involved in both the hypothalamic control of homeostatic eating and hedonically motivated eating mediated by the brain reward pathways (Lutter & Nestler, 2009; Schwartz et al., 2000; Wise, 2008). In particular, DA in the ventral striatum (which includes the nucleus accumbens and olfactory tubercle) is primarily responsible for mediating the rewarding properties of highly palatable food that drive their obsessive overconsumption (Cohen, 2008; Haber & Knutson, 2010; Hetherington, 2008; Mela, 2001; Kessler 2013; Wise, 2013). In the dorsal striatum (caudate, putamen), DA is linked to motivation for food and plays a permissive role in eating behaviour (Caudate, Putamen; Garcia-Garcia et al., 2014; Palmiter, 2008).

Based on this evidence, and in view of the aetiology of ADHD, some researchers have proposed that the addiction-ADHD co-morbidity results from a shared underlying basis of sub-optimal DA levels (Campbell & Eisenberg, 2007; Choudhry et al., 2013; Cortese & Morcillo, 2010). That is, diminished DA signaling contributes to both ADHD symptoms and to overeating, as a means to compensate or self-medicate an anhedonic state. Research support largely comes from neuro-imaging studies, which indicate similarities in frontal cortex structural abnormalities (Mana, Paillere & Martinet, 2010; Raji et al., 2010). In addition, patients with ADHD have reduced DA receptor binding capacity in the hypothalamus, which regulates hunger and satiety

(Volkow & Swanson, 2008). Likewise, reductions in DA receptors have been reported in the striatum of obese populations (Stice, Spoor, Bohon & Small, 2008; Volkow et al., 2008; Wang et al., 2001); however, researchers now generally agree that these findings are reflective of neuro-adaptations that occur in response to abnormally prolonged stimulation of the DA system due to chronic overconsumption of highly palatable foods, rather than a casual factor of obesity (Corwin, Avena & Boggiano, 2011). For instance, mice models of diet-induced obesity result in decreased striatal DA receptor availability that occurs in response to the high fat and/or sugar intake, and not in association with the level of adiposity (Narayanaswami, Thompson, Cassis, Bardo & Dwoskin, 2013; Van De Giessen et al., 2013).

Moreover, accumulating evidence indicates that it is an *amplified* DA signal that tends to increase the risk for binge eating and obesity due to a stronger appetitive response to food cues (Davis et al., 2013; Filbey et al., 2012; Tomasi et al., 2014). According to this perspective, these individuals are more responsive to the prospect or delivery of reward, more easily pleased by rewarding stimuli, and tend to be novelty seekers (Hommer et al., 2011). In support, compared to normal-weight controls, exposure to high calorie taste cues elicited greater activation in brain reward areas among overweight participants, and the response increased in relation to greater binge eating severity (Filbey et al., 2012; Stice et al., 2008). Longitudinal imaging studies verified the direction of the reward sensitivity and obesity association – that is, activity in reward-related areas (i.e., caudate, nucleus accumbens, putamen) in response to palative food images positively correlated with BMI changes over a 6 month or 1 year follow up (Demos, Heatherton & Kelly, 2012; Stice, Yokum, Bohon, Marti & Smolen, 2010; Yukom, Gearhardt, Harris, Brownell & Stice, 2014). Also, participants with higher BMIs displayed significantly elevated cerebrospinal fluid levels of homovanillic acid – the main metabolite of DA – in

comparison to subjects with BMIs falling in the lower and middle quartiles (Markianos, Evangelopoulos, Koutsis & Sfagos, 2013), while levels were reduced among a sample of anorexia nervosa patients, even after recovery (Kaye, Frank & McConaha, 1999). In a recent report, amphetamine-induced striatal and nigral DA release was found to correspond with increasing participant BMIs from normal weight to mildly obese (19 to 35 $kg/m^2$), while there was little difference in receptor density (Kessler, Zald, Ansari & Cowan, 2014). Other studies have linked reward sensitivity to stronger food cravings (Franken & Muris, 2005), preferences for sweet and fatty foods (Davis et al., 2007), greater food intake (Applehans et al., 2011), emotional overeating (Davis, Strachan & Berkson, 2004), and higher weight status (Davis et al., 2004, 2007; Temple, Legierski, Giacomelli, Salvy & Epstein, 2008).

Efforts to reconcile these conflicting theories point to the dynamic nature of addictions and the likelihood that risk factors differ over the developmental course – as people transition from the initial pleasure of casual use to compulsive need and treatment resistance (Davis et al., 2013; Koob & Le Moal, 2005). Both views regarding DA and addictive behaviours may be correct – albeit at different stages – where high reward sensitivity associated with an amplified DA signal increases the risk of initiation and escalation of the behaviour and the consequent down regulation of the DA system contributes to maintenance and proneness to relapse (Davis et al., 2013; Koob & Le Moal, 2005). The same line of reason can be applied to eating behaviour and the development of obesity. Similar to addiction, the factors contributing to excess body weight are complex and may vary overtime. In the case of the ADHD-obesity link, the explanation of a common mechanism of DA dysfunction appears too simplistic, and conflicts with evidence of elevated DA among those prone to overeating and weight gain. A dampened DA system could

plausibly reinforce continued overconsumption and mar weight loss efforts; however, it does not necessarily play a direct role in the initial engagement in, or risk for, overconsumption.

In the proposed model, a greater tendency to overeat is hypothesized to occur among individuals with increased striatal DA – reflecting a greater reward responsivity – but lower cortical DA, resulting in more ADHD symptoms. Support for this theory comes from a recent fMRI analysis. Compared to healthy-weight controls (n=9), children with obesity (n=9) had greater functional connectivity between the left middle frontal gyrus (associated with cognitive control and response inhibition) and reward-related regions in the left ventromedial prefrontal cortex (vmPFC) and the left lateral OFC (Black et al., in press). In deciphering the results, the researchers refer to past reports in which obese children viewing motivationally-salient food advertisements exhibited less activity in brain regions associated with inhibitory control, along with their finding of greater input to these regions from the reward neurocircuitry, and reason that these children are prone to overeating due to an increased susceptibility to food-related stimuli and less self control (Black et al., in press) – resembling the hypothesis of the current study. Similarly, in two previously mentioned studies, higher food reward-sensitivity predicted greater palatable food intake (Appelhans et al., 2011) and weight gain over a one-year period (Nederkoorn et al., 2010), but only among women exhibiting diminished inhibitory control. Applying the same model to attribution in a weight management program, researchers found participants with stronger reward response had a higher likelihood of dropping out, while ADHD-related traits of impulsivity, delay of gratification, and risk taking were not related (Koritzky, Dieteri, Rice, Jordan & Bechara, in press). However, these protocols did not involve measurement of the neurobiology underlying sensitivity to reward.

### 2.6.1. Dopamine D2 receptor gene (DRD2)

The DA D2 receptor gene has been a common focus of addiction and obesity research, being the most prominent receptor localized in the mesolimbic pathways, particularly, the nucleus accumbens. These receptors appear to determine responsivity to food and drug-related stimuli in the striatum (Tomasi et al., 2014). The encoding gene (DRD2) is positioned on chromosome 11 (11q23.1) and contains 6 intros (Gingrich & Caron, 1993). Unlike the DRD4, the DRD2 has 2 alternatively spliced isoforms (D2-short and D2-long) with distinct properties. The D2-short primarily functions as an autoreceptor presynaptically, while the D2-long is predominantly a postsynaptic receptor (Beaulieu & Gainetdinov, 2011).

A large majority of this work has concentrated on the TaqIA (rs1800497) polymorphism, as it has been reported to alter D2 receptor binding affinity and density, with reports of up to 30% reduction of the receptors in the striatum of individuals possessing at least one copy of the minor A1 (T) allele (Noble, 2003; Jonsson et al., 1999; Pohjalainen et al., 1998; Ritchi & Noble, 2003). However, some uncertainty has surfaced regarding the impact of the polymorphism, as it was thought to be located in the 3' UTR of the DRD2 (Noble, 2000), but is now known to reside 10 kb downstream of the DRD2 (on chromosome band 11q23.1), on an adjacent gene denoted the ankyrin repeat and kinase domain containing 1 (ANKK1; Morton et al., 2006; Neville, Johnstone & Walton, 2004). The A1 allele has been associated with addictive disorders (Munafo, Matheson & Flint, 2007; Young, Lawford, Nutting & Noble, 2004) and non-bingeing subtypes of obesity (Davis et al., 2012; Wang et al., 2011). Some reports suggest a positive association between the A1 allele and weight status (Carpenter, Wong, Li, Noble & Heber, 2013; Chen et al., 2011), while others found no relationship (Hardman, Rogers, Timpson & Munafo, 2013; Southon et al., 2003). However, many studies on the polymorphism lacked statistical power due to small sample

sizes (Hardman et al., 2013). Recent meta-analyses indicate significant heterogeneity across studies on the TaqIA, which indicates a high likelihood of false positives and limits interpretation (Hardman et al., 2013; Munafo, Clark, Johnstone, Murphy & Walton, 2004).

Davis and colleagues (2013) analyzed multiple markers of the DRD2/ANKK1 genes. Results indicated that genotypes of two of the polymorphisms – the TaqIA (rs1800497) and C957T (rs6277) – were associated with enhanced DA neurotransmission, were more frequent among participants with Binge Eating Disorder than weight-matched controls, and were significantly related to binge eating, hedonic eating, food cravings, and emotional eating. In the current study, four of these same single nucleotide polymorphisms (SNPs) of the DRD2/ANKKI1 genes were genotyped, chosen because of their known functionality (Hirvonen et al., 2004, 2005, 2009; Zhang et al., 2009). For the C957T (rs6277) marker, the T allele has been associated with greater DRD2 receptor density and striatal binding potential (Hirvonen et al., 2004, 2005, 2009). Both the -141 Ins/Del (rs1799732) and rs12364283 markers are located in the promoter region of the DRD2 gene. The DelC minor allele of the former predicted increased ventral striatal reactivity (Forbes et al., 2009); whereas, the minor C allele of the latter was related to greater transcription and D2 receptor density over the major T allele (Zhang et al., 2007). In the model tested in the current study, these 4 markers comprise a DRD2 composite variable reflecting striatal responsiveness to rewarding stimuli.

### 2.6.2. Multilocus Genetic Profile Score (MLGP)

Multiple genes and their polymorphisms determine the heritability of complex quantitative traits, such as BMI, with individual markers accounting for only a minute proportion of their phenotypic variance (Plomin, Haworth, & Davis, 2009). Therefore, analyzed independently, many candidate genes are unlikely to have effect sizes that reach significance,

even in studies of reasonable sample sizes (Nikolova, Ferrell, Manuck, & Hariri, 2011; Plomin, 2013). Considering that the signaling mechanisms of neurological systems appear to be due to multiple polymorphisms and/or genes, some researchers have advised the use of composite scores in order to represent the cumulative effect of several independent loci of known functionality (Nikolova et al., 2011). Otherwise, important individual contributions may go undetected or falsely dismissed due to difficulty replicating. The larger effect sizes of biologically-informed multilocus genetic profile scores (MLGPs) allows for more reliable results and analyses of greater power (Plomin, 2013).

Nikolova et al. (2011) tested the validity of such polygenic scores in reflecting individual variability in brain function. Specifically, the researchers considered both the independent and simultaneous impact of five genetic markers known to influence DA signaling in the ventral striatum. The loci did not produce significant effects when analyzed independently, while their aggregate scores accounted for 10.9% of individual variability in ventral striatal reactivity (Nikolova et al., 2011). Davis and colleagues have since used the MLGP procedure in studying addictive and overeating behaviours (Davis & Loxton, 2013; Davis et al., 2013). Considering four of the DRD2 polymorphisms contribute to the same variable – that is, striatal responsiveness to rewarding stimuli – is makes logical sense to sum the relative impact of their genotypes into MLGP scores. The calculation of this composite variable is described in more detail in the Methods section.

### 3. Summary

Several prevalence studies have established the ADHD-obesity connection (e.g., Alfonsson et al., 2012; Cortese et al., 2013; Holtkamp et al., 2004). Meanwhile, the current understanding of the underlying mechanisms remains largely speculative. The present study

tested the contribution of both behavioural and neurogenetic factors to the ADHD-obesity link. In terms of the former, the strongest studies suggest that overeating behaviour mediates the association between ADHD symptoms and adiposity (Davis et al., 2006; Ivan et al., 2009; Pagoto et al., 2009; Strimas et al., 2008), but most of these analyses have only included binge eating as an index of excessive consumption. Other reports have relied on third-party reporting of a past ADHD diagnosis, or this research has failed to control for stimulant medications and relevant confounders such as socio-economic status and depression. With the aim to confirm support for the view that hedonic eating explains, at least in part, the association between ADHD symptoms and BMI, a mediation model was tested that built on previous reports by including other measures of overeating, and by utilizing well-validated assessments of ADHD symptomatology. A large sample was recruited from the general population and thoroughly screened for co-morbid psychiatric conditions and related medication use in order to control for their known impact on eating and body weight.

The current model also represents the first analysis to test genetic mechanisms that may account for the ADHD-obesity link. Based on the accepted aetiology of ADHD (Wu et al., 2012), and 'reward deficiency' theories of addiction and obesity, various experts have suggested that both conditions share sub-optimal DA signaling, which is responsible for their co-morbid connection (Campbell & Eisenberg, 2007; Choudhry et al., 2013; Cortese & Morcillo, 2010). However, current evidence on hedonic eating contradicts this hypothesis. Support for a reward deficit in obesity risk is largely derived from imaging studies and is now believed to reflect neuroadaptations that occur in response to chronic overstimulation of the mesolimbic pathways due to excessive intake of hyperpalatable foods (Corwin et al., 2011). With respect to an innate predisposition to overeating, research increasingly reinforces 'reward surfeit' models (Davis et

al., 2013; Filbey et al., 2012; Wang et al., 2011). That is, individuals prone to hedonic overeating and obesity are believed to possess a genetic profile indicative of heightened reward responsivity (Davis et al., 2013).

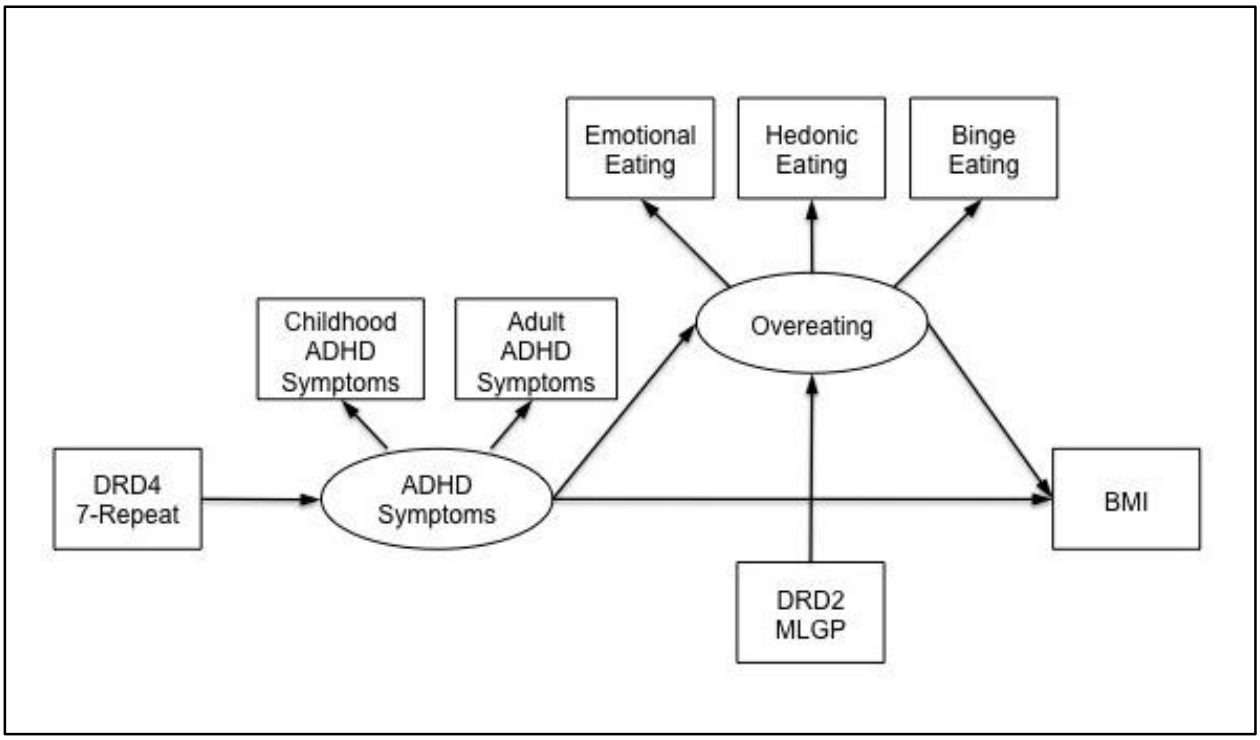
Understanding the ADHD-obesity link is complicated by these two seemingly opposing neurobiological states. However, the DA activation driving hedonic overeating is largely regulated by the subcortical reward pathways in the mesolimbic areas of the brain, particularly in the ventral striatum where the DA D2 receptors are heavily expressed (Davis et al., 2012); whereas, the DA D4 receptors are predominantly expressed in the prefrontal cortical regions associated with the reduced executive functioning seen in ADHD (Ariza et al., 2012; Meador-Woodruff et al., 1996). Likewise, the research literature supports the DRD4 gene's involvement in ADHD symptoms (e.g., Gizer et al., 2009; Li et al., 2014; Thapar et al., 2013), but fails to verify a role in overeating (e.g., Ariza et al., 2012; Yilmaz et al., 2012), and vice-versa for the DRD2 gene (e.g., Davis et al., 2013; Wang et al., 2011). Accordingly, the current study tested a model in which these two genetic mechanisms co-occur to give rise to hedonic eating, and in turn, weight gain, based on the hypothesis that ADHD symptoms predict excess consumption among those who also possess a high sensitivity to reward.

The added influence of a responsive reward circuitry is hypothesized to render individuals with ADHD symptoms particularly vulnerable to excessive caloric intake and adiposity. The joint involvement of reward sensitivity and ADHD symptoms in overeating is supported by a few recent studies. For instance, greater food reward-sensitivity was found to predict increased palatable food intake (Appelhans et al., 2011) and weight gain (Nederkoorn et al., 2010), but only among those who also displayed diminished inhibitory control. The current

report expanded on these studies, representing the first to examine neurogenetic in addition to behavioural mechanisms.

Of the DRD2-related polymorphisms, research has most frequently analyzed the ANKK1 TaqIA, but several others are also related to reward activation, eating behaviour, and/or adiposity (Davis et al., 2013; Yokum et al., 2015). Based on their known functionality, and positive links to addictive and hedonic eating behaviours (Davis & Loxton, 2013; Davis et al., 2013), four DRD2 polymorphisms were included in the model. All four markers predict ventral striatal activation potential (Nikolova et al., 2011). A composite MLGP score was calculated to represent their cumulative impact, allowing for greater powered analyses and larger effect sizes than typically gained individually (Plomin, 2013). Each of the DRD2 polymorphisms included in the MLGP index was also tested individually in the model for their independent effects. Unlike the DRD2, only one functional polymorphism of the DRD4 gene – the 48-bp VNTR – has consistently demonstrated a role in ADHD symptomatology (Wu et al., 2012), and therefore, was the only marker of the gene analyzed. In summary, the model tested the overall hypothesis that a greater tendency to overeat occurs among individuals with increased striatal DA – reflecting a greater reward responsivity – but lower cortical DA, resulting in more ADHD symptoms. SEM procedures were used to allow for the simultaneous analysis of multiple regressions among both latent and observed variables. Gender differences were also assessed.

**Figure 1. Model to be tested using SEM, with functional markers of the DRD4 and DRD2 genes predicting ADHD symptoms and Overeating, respectively, and in turn, BMI**




MLGP = Multilocus Genetic Profile Score

## 4. Hypotheses

4.1. The model shown in Figure 1 is a good fit to the data according to accepted fit indices, and all pathways are positive and significant.

4.2. Carrying at least one copy of the 7-repeat allele of the DRD4 48-bp VNTR predicts greater ADHD symptomatology.

4.3. Both ADHD symptoms and the MLGP score positively predict overeating.

4.4. Overeating positively predicts BMI.

4.5. Overeating mediates the association between ADHD symptoms and BMI.

4.6. Each of the four DRD2 polymorphisms comprising the MLGP index positively and significantly predict overeating when tested in the model individually.

# Methods

## 1. Participants

The sample consisted of 421 adult males (25.1%, n=106) and females (74.8%, n=315) between 24 and 50 years of age (mean age = 33.56, standard deviation = 6.66). Exclusion criteria included any serious medical illnesses (e.g., cancer, heart disease, paralysis), prescription medications except for oral contraceptives, or history of, or current treatment for, any Axis I disorder, including any psychotic disorder, ADHD, and substance abuse or dependence. One exception was made for unipolar depression, due the high co-morbidity with obesity. Only two (0.5%) participants met diagnosis for a current Major Depressive Episode, 9.7% (n=41) had suffered a past single episode, and 2.9% (n=12) had experienced more than one episode. Women were required to not have been pregnant in the previous 6 months, and to be premenopausal as indicated by self-reporting regular menstrual cycles. Also, participants were required to be fluent in English and had lived in North America for at least 5 years prior to their enrolment.

The majority of subjects was single (65.1%, n=274), Caucasian (i.e. European or East Indian; n=336, 79.8%), born in Canada (n=308, 73.2%), and had completed at least some university (n = 263, 62.5%). The sample represented a wide range of BMIs (17.80-75.19 $kg/m^2$), with an overall sample mean of 32.47 $kg/m^2$ (standard deviation = 9.34). Among males and females the mean BMI was 32.45 $kg/m^2$ (standard deviation = 8.95) and 32.48 $kg/m^2$ (standard deviation = 9.48), respectively.

See table 1 for more detailed sample demographics.

**Table 1. Sample demographics**

| Demographic | N | % |
|---|---|---|
| Gender | | |
| Male | 106 | 25.2 |
| Female | 315 | 74.8 |
| Marital Status | | |
| Single | 274 | 65.1 |
| Married/Common Law | 114 | 27.0 |
| Divorced/Separated | 31 | 7.4 |
| Widow | 1 | 0.2 |
| Missing | 1 | 0.2 |
| Education | | |
| Some high school/high school diploma | 35 | 8.4 |
| Trade school/some college | 32 | 7.6 |
| College degree/certificate | 90 | 21.4 |
| Some university | 45 | 10.7 |
| University degree | 154 | 36.6 |
| Graduate/professional school | 64 | 15.2 |
| Missing | 1 | 0.2 |
| Ethnicity | | |
| Caucasian | 336 | 79.8 |
| African American | 60 | 14.3 |
| Oriental | 6 | 1.4 |
| Hispanic | 16 | 3.8 |
| Native Indian | 3 | 0.7 |

## 2. Design and Procedure

The study was part of a larger CIHR-funded research project at the Centre for Addiction and Mental Health (CAMH) that involved 3 separate days of testing. Participants were recruited through web postings, newspaper advertisements, and posters at various universities, hospitals, and other public institutions throughout the Toronto area. Some recruitment materials specifically requested "overweight" participants in order to ensure the sample represented a large range of body sizes, particularly those at the higher end of the BMI continuum. Initial contact was made with participants by telephone to conduct an initial screening interview and to schedule an in-person appointment. At the time of the appointment, informed consent, general demographic information, and anthropometric measurements were obtained. Also, a psychiatric screening interview that included the Structural Clinical Interview for the *Diagnostic and Statistical Manual – IV* (SCID; First, Spitzer, Williams & Gibbon, 2002) was conducted to confirm eligibility. Participants were given self-report questionnaires to complete, and venous blood samples were taken for DNA extraction (20-30 ml) at the on-site laboratory. The 319 (74.8%) participants who finished the full 3-day protocol were paid an honorarium of $100 to cover travel and out-of-pocket expenses, and the remaining proportion of the sample received a portion of this amount prorated for amount of the protocol completed. The procedures employed in the study were approved by the institutional (CAMH and York University) Research Ethics Boards and carried out in accordance with the Declaration of Helsinki.

## 3. Genotyping

Genotyping of the DNA was performed at the Neurogenetics Laboratory at CAMH, with lab staff blind to other study measures. Genomic DNA was extracted from whole blood using non-enzymatic high-salt procedures (Lahiri & Nurnberger, 1991). For the ANKK1/DRD2

markers (rs1800497[Taq1A], rs6277[C957T], rs12364283, rs1799732[-141delC]), DNA fragments containing the polymorphisms of interest were amplified using polymerase chain reaction (PCR) techniques and Applied Biosystems Inc (AB; LifeTechnologies, Burlington, ON) TaqMan assays for SNPs and the ABI 7500. The sequence information for the three assays that were available on demand is: CACAGCCATCCTCAAAGTGCTGGTC[A/G]AGGCAG GCGCCCAGCTGGACGTCCA for rs1800497 (ABI assay ID: C___7486676_10), TCTTCTCT GGTTTGGCGGGGCTGTC[A/G] GGAGTGCTGTGGAGACCATGGTGGG for rs6277 (ABI assay ID: C__ 11339240_10), and TTACCAACT GTCCTCAGTTTGCCAG[A/G]TTCTGT-GTC AGATTCAGAAGTCACA for rs12364283 (ABI assay ID: C__31503501_10). The assay for rs1799732 was custom designed, with the following sequences: forward primer CAAAA-CAAGGGATGGCGGAATC, reverse primer CCACCAAAGGAGCTGTACCT, VIC probe TACCCGTTC[−/C]AGGCCG, and FAM probe CTACCCGTTCAGGCCG. The total volume of the PCR reaction was 10 µl, which consisted of 1 µl (20 ng/µl) of DNA, 5 µl of 2× TaqMan Buffer, 0.25 µl of 40× Assay and 3.75 µl of dH2O. The PCR cycling conditions included initial denature for 10 min at 95 °C followed by 50 cycles of the following: 92 °C for 15 s and 60 °C for 1 min. Post-amplification products were analyzed on the ABI Prism 7500 Sequence Detection System using the allelic discrimination option, and genotype calls determined by comparing to No Template Controls (Grandy, Zhang & Civello, 1993).

For the DRD4, the 48-bp VNTR region in the third exon (Lichter et al., 1993) was amplified using PCR conditions, and DNA bands separated on 3.5% agarose gel (Bishop Canada, Burlington, ON) and sized by comparison to a standard 100 bp ladder (MBI Fermentas, Burlington, ON).

In order to ensure quality control at the genotyping step, 5% of the samples were re-genotyped.

## 4. Measures

### 4.1. ADHD Symptoms

The *Wender Utah Rating Scale* (WURS; Ward, Wender & Reimherr, 1993) is a widely used self-report questionnaire developed to assess retrospective childhood ADHD symptoms in adults. The 25-item version of the scale consists of the items from the original 61-item version that had the highest mean difference between patients with ADHD and a comparison group (Ward et al., 1993). Higher scores reflect a greater number and severity of ADHD symptoms. Individuals with ADHD score significantly higher on the scale than both healthy controls and unipolar depression patients (Ward et al., 1993). A cutoff score ≥ 46 correctly distinguished 99% of non-clinical participants, 86% of patients with ADHD, and 81% of patients with depression (Taylor et al., 2011; Ward et al., 1993). The WURS demonstrates acceptable internal consistency, test-retest reliability, and convergent validity (Ward et al., 1993). The Cronbach's alpha in our sample was 0.94.

*Conners' Adult ADHD Rating Scale – Self-report Screening Version* (CAARS-SSV; Conners et al., 1999) was developed for the assessment of current ADHD symptoms in adults. The scale consists of three subscales: ADHD Index (12 items), DSM-IV Inattentive Symptoms (9 items) and DSM-IV Hyperactive-Impulsive Symptoms (9 items). Items comprising the ADHD index were those found to best differentiate adults with ADHD from controls from a 93-item pool developed from various sources including the DSM symptom criteria, the Conners' rating scales for children and adolescents (Conners, 1997), and clinical impressions of adult ADHD (Wender, 1995). The CAARS demonstrates high internal consistency, concurrent validity, test-

retest reliability and other forms of validity (Erhardt, Epstein, Conners, Parker & Sitarenios, 1999; Taylor et al., 2011). The alpha co-efficient in our sample was 0.92.

**4.2. Overeating**

Binge eating was assessed by the *Binge Eating Questionnaire* (BEQ; Halmi, Falk & Schwartz, 1981), which reflects the severity and frequency of symptoms associated with binge eating such as the loss of control over eating and negative affect following a binge. An index was created using the sum of 5 (yes/no) questions, such as "are there times when you feel you cannot voluntarily stop eating?" The internal consistency in our sample was 0.85 for the 5-item scale.

Emotional eating was assessed using the *Dutch Eating Behavior Questionnaire* (DEBQ; van Strien, Frijters, Bergers & Defares, 1986). The subscale consists of 13 items and reflects the degree to which eating occurs in response to emotional states rather than to hunger, for example "Do you have the desire to eat when you are emotionally upset?". Items are scored on a 5-point likert scale. The DEBQ has high internal consistency, factorial validity (van Strien et al., 1986), and convergent and divergent validity (van Strien, Schippers & Cox, 1995). The emotional eating subscale had a Cronbach's alpha coefficient of 0.96 in our sample.

Hedonic eating was assessed by the *Power of Food Scale* (PFS; Lowe et al., 2009). This 21-item questionnaire reflects appetitive drive and responsiveness to the food-abundant environment, separate from actual food consumption. That is, the scale does not measure a tendency to (over)eat, but rather the feeling of being controlled by food. Examples of items are: "It seems like I have food on my mind a lot" and "If I see or smell a food I like, I get a powerful urge to have some." The scale has demonstrated high Cronbach's alpha coefficients in multiple data sets, high test-retest reliability, and has been related to several measures of overeating (Cappelleri et al., 2009; Lowe et al., 2009). Scores were also predictive of food cravings (Forman

et al., 2007). Items are scored on a 5-point likert scale and summed to produce a total score. The Cronbach's alpha was 0.97 in our dataset.

### 4.3. Anthropometry

*BMI* (weight[kg]/height[$m^2$]) was calculated from height and weight measured with the participants wearing light indoor clothing and no shoes.

### 4.4. Multilocus Genetic Profile Score (MLGP)

For the 4 DRD2 markers, a multilocus genetic profile (MLGP) score was calculated based on known functional changes in brain DA transmission and/or responsiveness in the reward pathways. Individual MLGP scores represent the sum of the value assigned to each DA genotype across the 4 functional polymorphic loci included in this study (see Table 3), with a plausible range from 0 to 4. As done previously by researchers (Davis et al., 2013; Nikolova et al., 2011), genotypes known to be associated with a higher DA signal in the brain reward pathways received a MLGP score of 1, while genotypes predictive of a lower DA signal were scored a 0.

4.4.1. *The ANKK1 Taq1A (rs1800497)* is a C/T Single Nucleotide Polymorphism (SNP) where the T (A1) allele predicts reduced D2 receptor binding affinity and lower striatal receptor densities in comparison to the C (A2) variant (Jonsson et al., 1999). As a result, the T (A1) allele is associated with a relatively decreased DA signal (Noble, Blum, Ritchie, Montgomery & Sheridan, 1991) and striatal glucose metabolism (Noble, Gottschalk, Fallon, Ritchie & Wu, 1997). The absence of the A1 allele was scored 1, while both the A1/A1 and A1/A2 genotypes were given a score of 0, based on evidence of a dominant pattern of inheritance (Voisey et al., 2012).

4.4.2. *The DRD2 C957T (rs6277)* is a SNP in exon 7 for which the T allele has been associated with greater DRD2 receptor density and striatal binding potential (Hirvonen et al, 2004, 2005; 2009). Participants without a copy of the T allele (i.e. genotypes CC and TC) were given a score of 0, and those with the homozygous T genotype received a score of 1.

4.4.3. The DelC minor allele of the DRD2 promoter region marker *-141 Ins/Del* has been associated with increased ventral striatal reactivity (Forbes et al., 2009). Possession of at least one copy of the DelC minor allele resulted in a score of 1, with the remaining genotypes receiving a score of 0.

4.4.4. Also located in the promoter region of the DRD2 gene, the minor C allele of the *rs12364283* is associated with higher transcription and D2 receptor density compared with the major T allele (Arinami et al., 1997; Parsian et al., 2000). Accordingly, genotypes CC and TC received a score of 1, and the TT genotype was coded zero.

### 4.5. Dopamine D4 Receptor Gene (DRD4)

The DRD4 variable was scored by a 1 or 0, according to the presence or absence of the 7-repeat allele, respectively.

## 5. Statistical Analysis

### 5.1. Descriptive Statistics

A dataset was created using SPSS version 21. First, to determine how representative the sample was of the general population, descriptive statistics of relevant demographic variables were calculated. Next, descriptive statistics were examined to ensure scores were within the valid range of values and bi-variate correlations among the questionnaire measures used in the model were analyzed to establish the strength of their interrelationships. Pair-wise t-tests were used to test for mean differences in the model variables between males and females. For the five genetic

markers used in the model, allele and/or genotype frequencies were computed, and compared to those of other similar samples.

### 5.2. Structural Equation Modeling

The hypothesized model was tested using Structural Equation Modeling (SEM) – a statistical technique that assesses adequacy of predetermined theoretical models to explain the relationships among observed and latent variables (Kline, 2005). It is an extension of the general linear model that enables the simultaneous testing of multiple inferential pathways in cross-sectional data (Byrne, 2001). A good model fit indicates theoretically sound relationships.

SEM was performed using SPSS AMOS software version 21. First, skewness and kurtosis scores of the measures in the model were examined to ensure SEM assumptions of normality were met. Also, the data were tested for the presence of multivariate outliers using the squared Mahalanobis' distance ($D^2$; Mahalanobis, 1927; 1936) for each case – a metric for estimating how far, in standard deviation units, a set of scores for one case is from the centroids (i.e., multivariate sample means), accounting for the different scale and variance of each of the variables. AMOS also provides the probability ($p_2$ value) that the largest squared distance of any observation from the centroid would exceed the $D^2$ value computed (Blunch, 2012). A case is considered a multivariate outlier if the probability associated with its $D^2$ value is 0.001 or less. If, upon further examination, these cases are determined to be valid data points, a decision is often made to retain them in the data set (Arbuckle, 1997).

There has been considerable debate regarding how to determine model fit in SEM, particularly about the use of the chi-square test. In SEM the chi-square statistic is known as the "exact-fit" test as it analyzes whether all discrepancies (i.e., residuals) between the model-implied population covariance matrix and the actual sample observed covariance matrix are 0

(Barrett, 2007; Goffin, 2007). In large samples (n>200), experts agree that a nonsignificant chi-square is unrealistic given the increased sensitivity, the complexity of psychological processes (Bentler, 2007; Goffin, 2007), and the expected random sampling fluctuations (Hayduk, Cummings, Boadu, Pazderka-Robinson, & Boulianne, 2007). Moreover, researchers are advised to prioritize the theoretical validity of the model over achieving a nonsignificant chi-square through modification indices that capitalize on sample specific fluctuations (Goffin, 2007; Hayduk et al., 2007; Markland, 2007). According to recommendations, the chi-square test result in the current analysis was reported for the model, followed by a number of different "approximate" or "global" fit tests (Goffin, 2007; Hayduk et al., 2007; Markland, 2007).

A set of threshold values developed by Hu and Bentler (1999) have typically been seen as the "golden rules" to determine "acceptable fit" in SEM, but more recent evidence found considerable heterogeneity among these fit indices under varying data conditions, calling into question the validity of rigid single-value cut-offs (Barrett, 2007). Current recommendations in SEM literature generally include reporting a range or multiple fit indices as part of a comprehensive approach using additional information (i.e., the residual matrix, theoretical meaningfulness; Beauducel & Wittmann, 2005; Fan & Sivo, 2005; Goffin, 2007; Markland, 2007; Yuan, 2005). For example, Bentler (2007) recommends that researchers provide at least two indices of fit (e.g., CFI and RMSEA) and the largest residuals or the entire residual matrix. On average, a good-fitting model will have small residuals (Hu & Bentler, 1995). Accordingly, several fit indices and the residuals were reported in the results below.

To control for any possible effect of confounding variables, the model was retested with the addition of age, ethnicity, and level of educational attainment to the model.

### *5.2.1. Mediation*

The hypothesized model includes a proposed mediation in which Overeating partially explains the relationship between ADHD Symptoms and BMI. While earlier methods for testing mediation included a series of regression equations, SEM allows the simultaneous testing of multiple regression equations. According to current recommendations outlined by Preacher and Hayes (2004), the significance of the mediated (i.e. indirect) effect was determined using bias-corrected bootstrapped confidence intervals. Bootstrapping is a non-parametric method that involves drawing a large number of random samples with replacement from the original sample. The indirect effect is estimated in each of these samples, and their distribution generates an empirical sampling distribution of the effect. A correction for bias is usually made to increase the likelihood that the population value of the effect is encompassed within the interval in the expected proportion of cases, because the mean of the bootstrapped distribution will not exactly equal the indirect effect. A confidence interval (CI) can be determined, and if zero is not in the interval, the indirect (i.e., mediated) effect is said to be significant. If determined significant, the parameter estimate can then be used to indicate effect size and direction.

### *5.2.2. Gender analyses*

The model was retested for significant differences between males and females using the Multiple-Group Analyses function in AMOS 21. This analysis fits a model simultaneously to multiple groups, and tests models for significant group differences in the parameter categories of: measurement weights, structural weights, structural covariances, structural residuals, and measurement residuals. The models were assumed to be unconstrained, allowing males and females to have separate estimates on all parameters.

### *5.2.3. Individual DRD2/ANKK1 markers*

*Post-hoc* analyses were conducted to test the significance of each of the 4 individual markers that comprise the MLGP score. That is, the model was re-run 4 times, each time with a different individual marker (i.e., ANKK1 Taq1A, DRD2 C957T [rs6277], DRD2 rs12364283 T/C, DRD2 -141 Ins/Del [rs1799732]) in place of the overall MLGP score. The purpose of these *post-hoc* analyses was to test the assumption that each of the markers contributed significantly to the MLGP score and in the direction expected based on their believed association with brain DA availability.

# Results

## 1. Descriptive Statistics

Table 2 presents the descriptive statistics (i.e. mean, standard deviation, minimum, maximum, kurtosis, skewness, SEM) of all measured variables that were included in the model. The mean and standard deviations resembled those obtained among similar samples (e.g., Davis et al., 2007; Lowe et al., 2009), and skewness and kurtosis scores ranged from -1.346 to 1.070 – well within acceptable limits to continue with SEM (i.e. less than 2.00 and greater than -2.00; see Table 2; West, Finch & Curran, 1995).

Pair-wise t-tests were used to test for differences between males and females on all measured variables that were included in the model (see Table 3). Females had significantly higher mean scores on the BEQ, DEBQ Emotional Eating subscale, and PFS. There were no significant sex/gender differences on the MLGP, BMI, CAARS, or WURS; although, there was a trend toward males having higher childhood ADHD symptoms as measured by the WURS ($p = 0.059$).

One multivariate outlier was identified with a $D^2$ value of 42.330 and an associated probability of $< 0.0001$. The next largest $D^2$ values were 28.521 ($p_2$ value = 0.012), 25.284 ($p_2 = 0.022$), 23.503 ($p_2 = 0.031$), 22.452 ($p_2$ value = 0.032), with all other $p_2$ values 0.395 and greater. In examining the identified multivariate outlier more closely, it was determined that particularly high BMI and WURS scores were accountable for this effect. As the BMI, WURS, and other scores were valid data points, the decision was made to retain the case in the dataset.

**Table 2. Central tendency and distribution statistics for BMI, the MLGP, and the overeating and ADHD scales**

| | PFS | BEQ | CAARS | WURS | DEBQ | BMI | MLGP |
|---|---|---|---|---|---|---|---|
| **Mean** | 58.05 | 2.08 | 27.88 | 28.17 | 2.95 | 32.44 | 1.26 |
| **Standard Deviation** | 21.30 | 1.89 | 13.70 | 19.39 | 1.07 | 9.34 | 0.84 |
| **Minimum** | 21.00 | 0 | 0 | 0 | 1 | 17.80 | 0 |
| **Maximum** | 105.00 | 6 | 83.00 | 100 | 5 | 75.19 | 3 |
| **Kurtosis** | -1.022 | -1.350 | 1.061 | -0.075 | -0.808 | 0.926 | -0.881 |
| **Skewness** | 0.268 | 0.347 | 0.673 | 0.683 | 0.054 | 0.723 | -0.092 |
| **SEM** | 1.04 | 0.09 | 0.67 | 0.95 | 0.05 | 0.46 | 0.04 |

PFS = Power of Food Scale; BEQ = Binge Eating Questionnaire; CAARS = Conner's Adult ADHD Rating Scale; WURS = Wender Utah Rating Scale; DEBQ = Dutch Eating Behaviour Questionnaire; MLGP = Multilocus Genetic Profile Score.

**Table 3. Means, standard deviations, and t-test comparisons between males and females**

| | Females Mean (SD) | Males Mean (SD) | t | p |
|---|---|---|---|---|
| **PFS** | 59.63 (20.92) | 53.36 (21.82) | 2.639 | 0.009 |
| **BEQ** | 2.23 (1.91) | 1.61 (1.75) | 2.954 | 0.003 |
| **CAARS** | 27.64 (13.53) | 28.58 (14.24) | -0.605 | 0.546 |
| **WURS** | 27.13 (18.48) | 31.25 (21.70) | -1.895 | 0.059 |
| **DEBQ** | 3.06 (1.06) | 2.64 (1.04) | 3.575 | <0.001 |
| **BMI** | 32.48 (9.48) | 32.45 (8.95) | .023 | .981 |
| **MLGP** | 1.28 (0.83) | 1.22 (0.86) | 0.662 | 0.509 |

PFS = Power of Food Scale; BEQ = Binge Eating Questionnaire; CAARS = Conner's Adult ADHD Rating Scale; WURS = Wender Utah Rating Scale; DEBQ = Dutch Eating Behaviour Questionnaire; MLGP = Multilocus Genetic Profile Score.

## 2. Genotype Frequencies and MLGP Scores

The genotype frequencies of the five genetic markers (see Table 3) resembled those of comparable samples (e.g., Ariza et al., 2012; Fuemmeler et al., 2012).

**Table 4. Genotype frequencies, and composition and distribution of MLGP scores.**

| Polymorphism | Genotypes | N | % | MLGP Score |
|---|---|---|---|---|
| DRD4 7R | 7R+ | 135 | 32.1 | N/A |
| | 7R- | 286 | 67.9 | |
| ANKK1 Taq1A | CC | 252 | 59.9 | 1 |
| | TC | 148 | 35.2 | 0 |
| | TT | 21 | 5.0 | 0 |
| DRD2 rs12364283 | CC | 1 | 0.2 | 1 |
| | TC | 58 | 13.8 | 1 |
| | TT | 362 | 86.0 | 0 |
| DRD2 rs6277 (C957T) | CC | 144 | 34.2 | 0 |
| | TC | 185 | 43.9 | 0 |
| | TT | 92 | 21.9 | 1 |
| DRD2 -141C Ins/Del (rs1799732) | CC | 22 | 5.2 | 1 |
| | C/Ins | 106 | 25.2 | 1 |
| | Ins/Ins | 293 | 69.6 | 0 |

NB: Individual MLGP scores represent the sum of the value assigned to each DA genotype across the four functional polymorphic loci included in this study. "High" genotypes received a score of 1 and "low" genotypes a score of 0.

### 3. Bivariate Correlational Analyses of Measures

Pearson *r* bivariate correlation coefficients were calculated for variables in the SEM model (see Table 4). All measures demonstrated significant positive correlations, except for the MLGP, which was only significantly correlated with the Emotional Eating subscale of the DEBQ. In support of the measurement model, correlations were stronger among measures loading on the same latent variable (i.e. the WURS and CAARS on ADHD Symptoms, and the DEBQ Emotional Eating subscale, PFS, and BEQ on Overeating).

**Table 5. Bivariate correlation matrix for the MLGP score, overeating measures, ADHD scales, and BMI**

| | BMI | PFS | BEQ | CAARS | WURS | DEBQ |
|---|---|---|---|---|---|---|
| **BMI** | | | | | | |
| **PFS** | .359** | | | | | |
| **BEQ** | .381** | .741** | | | | |
| **CAARS** | .136** | .386** | .321** | | | |
| **WURS** | .270** | .353** | .289** | .599** | | |
| **DEBQ** | .375** | .621** | .630** | .374** | .332** | |
| **MLGP** | .005 | .042 | .075 | -.026 | -.009 | .104* |

** $p<0.0001$, * $p<0.05$

## 4. SEM

As required by SEM, all parameters of the model were determined *a priori* to testing.

### 4.1. Model Fit

#### *4.1.1. Chi-square*

The model had a significant chi-square value of 45.961 (d.f. = 18; $p<0.0001$); however, in samples of this size, the chi-square is almost always significant (Iacobucci, 2010). Relative chi-square (CMIN/DF) is an older measure of the chi-square statistic divided by its degrees of freedom. Although there is no universally agreed upon standard, some experts advise under 5 (Wheaton et al., 1977), while others suggest under 2 (Byrne, 1989) or 3 (Carmines & McIver, 1981; Iacobucci, 2010) as a maximum threshold. The current model had a CMIN/DF of 2.553.

#### *4.1.2. Root Mean Square Error Approximation (RMSEA)*

After the chi-square test, the RMSEA is currently the most popular measure of absolute fit reported by researchers. The RMSEA is advantageous because it is not overly sensitive to

sample size and accounts for the complexity of the model (i.e., the degrees of freedom; simpler models have better fit). The RMSEA is often positively biased (i.e., too large), but the known distribution properties of the statistic allow the calculation of Confidence Intervals (CI) in order to convey the preciseness of the statistic. Ideally, the lower CI should be less than 0.05 and the upper CI should not exceed 0.08 (Brown & Cudeck, 1993). According to Hu and Bentler (1999), a cut-off value of close to 0.06 is required to determine an acceptable fit. The current model resulted in an RMSEA of 0.061, with a CI of 0.039 to 0.083.

#### *4.1.3. Goodness of Fit Index (GFI)*

Older SEM reports often included the GFI (Joreskog & Sorbom, 1984), but the general consensus in the SEM literature no longer supports its use, as it is impacted by sample size (Sharma, Mukherjee, Kumar & Dillon, 2005). The GFI is a measure of the proportion of variance and covariance that the proposed model is able to explain (similar to $R^2$ in regression). It can be adjusted for the number of parameters (i.e., degree of parsimony) in the model (Adjusted Goodness of Fit Index [AGFI]). A GFI or AGFI of 1 indicates a perfect fit, while a good fitting model has a GFI of 0.95 or greater, and an AGFI of at least 0.90 (Hu & Bentler, 1999). The GFI and AGFI of the model were 0.974 and 0.948, respectively.

#### *4.1.4. Normed Fit Index (NFI)*

Using the Bentler-Bonnett NFI (Bentler & Bonnett, 1980) the best model is one with a chi-square of zero and the worst model has the chi-square of the null model. A drawback of this index is that it does not account for model parsimony. A NFI less than 0.90 is believed to indicate a poor fit (Bentler & Bonnett, 1980). The current model had value of .953.

#### *4.1.5. Tucker-Lewis Index (TLI)*

Unlike the NFI, the TLI (also known as the Bentler-Bonnett non-normed fit index [NNFI]) has a penalty for adding parameters. It depends on the average size of the correlations in the data. Possible TLIs range from 0 to 1, and larger values indicate a better fit. According to guidelines, the TLI should be at least 0.90, with a well-fitting model having a TLI of 0.95 or greater (Bentler & Bonnett, 1980; Hu & Bentler, 1999). The TLI value for the model was 0.955.

#### *4.1.6. Comparative Fit Index (CFI)*

The CFI (Bentler, 1990) is highly correlated with the TLI and interpreted in the same manner (Hu & Bentler, 1999). It evaluates the estimated model relative to a model with no estimated relationships between variables. A CFI of 0.971 was obtained in this study.

#### *4.1.7. Hoelter's Critical N*

Lastly, Hoelter's (1983) 'critical N' refers to the sample size at which the chi-square test would no longer be significant. Values should be at least 200, with a Hoelter of less than 75 indicating a very poor fit. A value of 264 was obtained for the model.

Overall, the fit indices indicate the proposed model is a good fit to the data (see Table 5).

**Table 6. Model fit indices**

| Fit Index | Threshold | Obtained Value | Value when Controlling for Education |
|---|---|---|---|
| **Chi-square** | $p > 0.05$ | 45.961 ($p<0.0001$) | 65.429 ($p<0.0001$) |
| **CMIN/DF** | <2 or <3 to <5 | 2.553 (df=18) | 2.617 (df=25) |
| **TLI** | $\geq 0.95$ | 0.955 | 0.926 |
| **GFI** | $\geq 0.95$ | 0.974 | N/A |
| **AGFI** | $\geq 0.90$ | 0.948 | N/A |
| **CFI** | $\geq 0.95$ | 0.971 | 0.959 |
| **NFI** | $\geq 0.95$ | 0.953 | 0.937 |
| **RMSEA** | <0.06 (<0.05-<0.08) | 0.061 (0.039-0.083) | 0.062 (0.044-0.081) |
| **HOELTER** | $\geq 200$ | 264 | 242 |

### 4.2. Residuals

Most of the residuals were fairly small (see table 6) with no standardized residuals exceeding 2.0, which would be indicative of a poor fitting model. Based on the largest residuals, there appeared to be considerable shared variance between both of the individual ADHD symptoms measures (i.e. the WURS and CAARS independently) and the DRD4 7R and BMI, that was not explained by the pathways from the DRD4 7R to the ADHD Symptoms latent variable, or from the ADHD Symptoms latent variable to BMI.

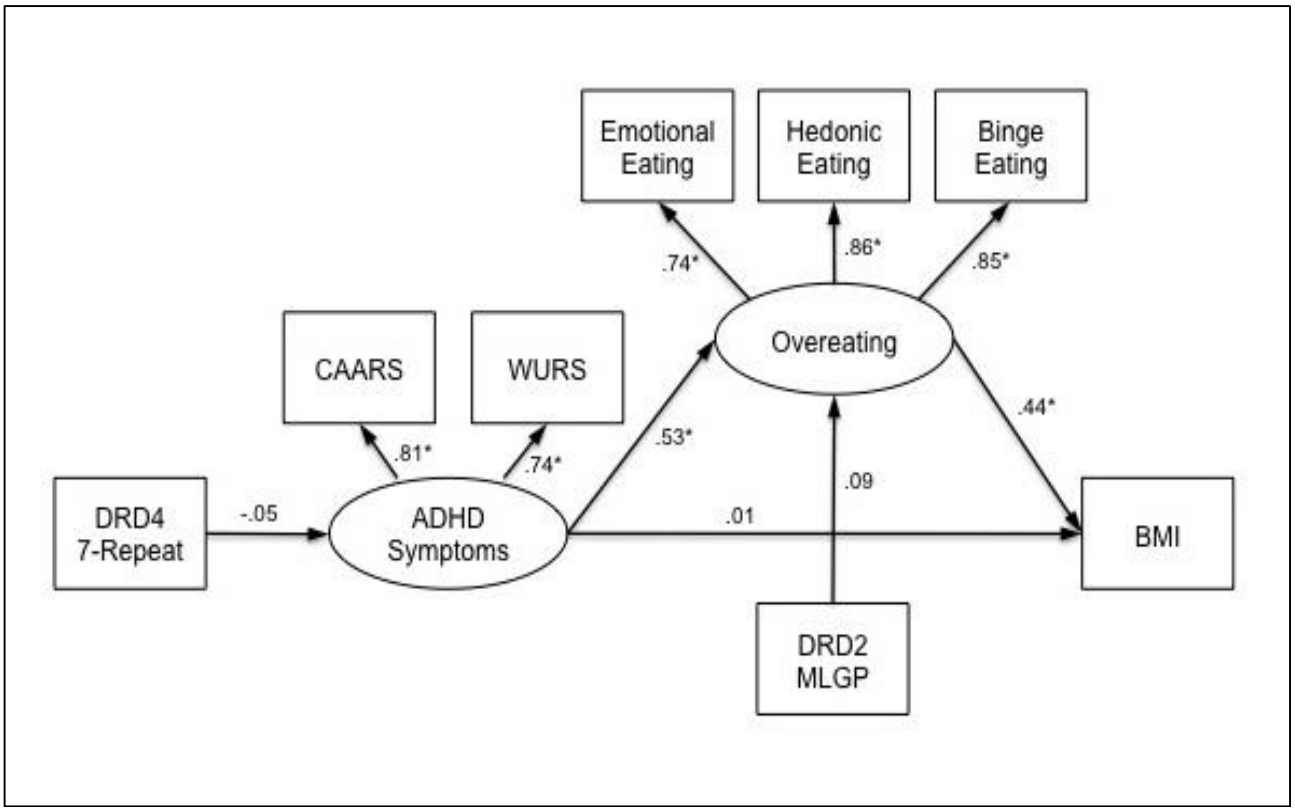
**Table 7. Standardized residual covariances among measures included in model.**

| | MLGP | DRD4 | BMI | BEQ | PFS | DEBQ | WURS | CAARS |
|---|---|---|---|---|---|---|---|---|
| **MLGP** | .000 | | | | | | | |
| **DRD4** | .673 | .000 | | | | | | |
| **BMI** | -.694 | .421 | -.005 | | | | | |
| **BEQ** | -.008 | .252 | .015 | -.018 | | | | |
| **PFS** | -.695 | -.616 | -.450 | .143 | -.019 | | | |
| **DEBQ** | .767 | -.906 | .853 | -.070 | -.301 | -.014 | | |
| **WURS** | -.175 | 1.600 | 1.791 | -.887 | .298 | .786 | .000 | |
| **CAARS** | -.524 | -1.000 | -1.268 | -.892 | .305 | 1.049 | .003 | .000 |

### 4.3. Estimates

Path coefficients assess the magnitude of the relationships in the model. See Figure 2 for the standardized regression weights of each path tested in the model. All parameter estimates were in the expected direction (positive) and the proposed pathways were statistically significant ($p<0.0001$), with the exception of the 3 parameters: between DRD4 7R and the ADHD Symptoms latent variable ($p=0.340$), between the DRD2 MLGP score and the Overeating latent variable ($p=0.058$), and the direct effect of the ADHD Symptoms latent variable on BMI ($p=0.864$).

**Figure 2. Model with standardized regression weights**




*p<0.0001

### 4.4. Mediation

In AMOS, 5000 bootstrap samples were created to estimate bias-corrected standard errors and 95% percentile CI for the indirect effect of ADHD Symptoms on BMI via Overeating. The indirect effect is significant at $p < .05$ if zero is not included in its 95% CI.

The bootstrap estimate of the standardized indirect (mediated) effect of ADHD Symptoms on BMI was 0.233 with a standard error of 0.044. Using the bias-corrected percentile method, the standardized lower bound of the CI was 0.156, and the upper bound was 0.336. The indirect effect was significant (p<0.0001) indicating that the effect of ADHD Symptoms on BMI occurs in part via the Overeating latent variable. As mentioned above, the direct effect from ADHD Symptoms to BMI was not significant (p=0.927; 95% BC CI: -0.160 to 0.200).

### 4.5. Controlling for Possible Confounders

The model was re-tested controlling for age, ethnicity, and highest level of education achieved. Due to some missing data in these 3 variables, it was necessary to estimate the means and some statistics were not possible to perform and/or calculate (i.e. bootstrapping, GFI, AGFI).

**Table 8. Standardized Regression Weights for Model Controlling for Age, Educational Attainment, and Ethnicity**

| | Standardized Estimate | P |
|---|---|---|
| ADHD←DRD4 7-Repeat | -0.055 | 0.336 |
| ADHD←Education | -0.089 | 0.164 |
| ADHD←Age | 0.035 | 0.568 |
| ADHD←Ethnicity | 0.045 | 0.423 |
| Overeating←ADHD | 0.520 | **0.000** |
| Overeating←MLGP | 0.096 | **0.040** |
| Overeating←Education | -0.092 | 0.067 |
| Overeating←Age | 0.048 | 0.338 |
| Overeating←Ethnicity | 0.015 | 0.755 |
| CAARS←ADHD | 0.807 | **0.000** |
| WURS←ADHD | 0.741 | **0.000** |
| DEBQ←Overeating | 0.742 | **0.000** |
| PFS←Overeating | 0.858 | **0.000** |
| BEQ←Overeating | 0.853 | **0.000** |
| BMI←ADHD | 0.009 | 0.889 |
| BMI←Overeating | 0.405 | **0.000** |
| BMI←Education | -0.212 | **0.000** |
| BMI←Age | 0.069 | 0.122 |
| BMI←Ethnicity | -0.022 | 0.606 |

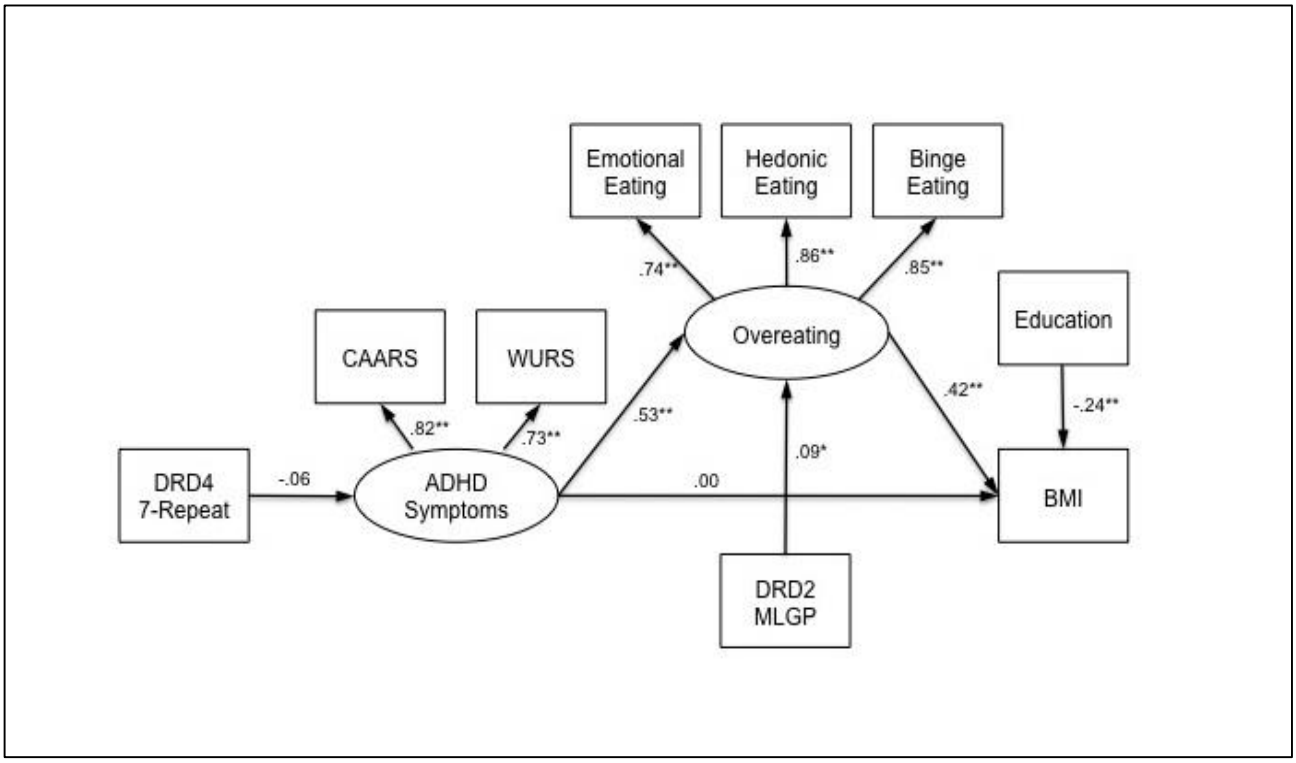
Significant parameters are bolded.

All previously significant pathways remained significant, and the MLGP effect on Overeating became significant (p=0.040). Among the variables controlled in the model, only education level had a significant effect on BMI (p<0.0001). See Table 7 for all standardized regression weights. As expected with more pathways to be estimated, and the mostly nonsignificant effects of those added, most fit indices were slightly lower with age, ethnicity, and

educational level in the model (see Table 5). The chi-square remained significant ($\chi^2$=94.722, d.f. 36; p<0.0001).

Finally, the model was re-run with only the education-level-to-BMI pathway included. Model fit indices (see Table 5) indicated an adequate to good fit. There was little to no change in the standardized regression weights (see Figure 3) from the estimates in the model without controlling for educational level.

**Figure 3. Standardized regression weights of model controlling for education level**




*p=0.05; **p<0.0001

### 4.6. Gender Analyses

Using the Multiple-Group Analysis function, there were no significant differences found between the male and female models on any of the parameter categories (see Table 8).

**Table 9. Gender comparison using multiple-group analysis**

| Model | DF | Chi-square | P |
|---|---|---|---|
| Measurement weights | 5 | 2.569 | 0.766 |
| Structural weights | 8 | 3.153 | 0.924 |
| Structural covariances | 10 | 3.944 | 0.950 |
| Structural residuals | 12 | 5.732 | 0.929 |
| Measurement residuals | 18 | 12.813 | 0.803 |

### 4.7. Individual MLGP Genetic Markers

When the model was tested with the ANKK1 Taq1A marker alone, the model fit indices very closely resembled those obtained when the model was tested with all 4 DRD2/ANKK1 markers comprising the MLGP score ($\chi^2$=45.338, df=18, p<0.0001; CMIN/DF=2.519; GFI=0.975; AGFI=0.949; CFI=0.972; TLI=0.956; NFI=0.954; RMSEA=0.060 [0.039-0.082]; Hoelter=323). The effect of the ANKK1 Taq1A on the Overeating latent variable was also significant (Standardized estimate = 0.108; p=0.022).

The DRD2 C957T (rs6277), DRD2 -141ins/del (rs1799732), and the DRD2 rs12364283 did not have significant effects on the Overeating latent variable when tested individually (p=0.062, p=0.879, and p=0.503, respectively).

## Discussion

The purpose of this dissertation was to investigate the mechanisms underlying the strong link between ADHD symptoms and obesity. Researchers have only recently moved on from prevalence studies to exploring the mechanisms underlying this connection. Despite speculation on the involvement of DA in the association, such theories have not been formally examined. The current study is the first to connect the most prominent and supported theories of ADHD with evidence-based models of hedonic eating. It is theoretically sound to imagine that symptoms of ADHD, such as impulsivity, would be particularly problematic in the context of a strong motivation for food reward. Accordingly, SEM procedures were used to test a behavioural genetics model (shown in Figure 1) in which variation in the DRD4 gene was related to ADHD symptoms, and in conjunction with the MLGP composite score, these symptoms were associated with overeating, and in turn, greater BMI. More specifically, the presence of the 7-repeat allele of the DRD4 third exon 48-bp VNTR was hypothesized to predict increased ADHD symptoms. Both greater ADHD symptoms and higher scores on the MLGP index – calculated from four functional DRD2/ANKK1 polymorphisms to represent an enhanced appetitive drive – were expected to predict higher levels of overeating. In the mediation analysis, overeating was expected to partially explain a positive association between ADHD symptoms and BMI. Further tests were conducted to look for gender differences and to control for possible confounders, such as education level, age, and ethnicity, with the theory that relationships would hold in all cases.

Results indicated that the model was a good fit to the data. In support of the measurement model, the two ADHD measures and the three hedonic eating scales contributed significantly to their respective latent variables. All predicted pathways were significant and in the expected direction, except for the relationship between the DRD4 48-bp VNTR and ADHD symptoms,

and between the MLGP score and the overeating latent variable, although the latter showed a trend (p=0.058). The model was retested controlling for the highest level of education achieved based on this variable's significant correlation with BMI. When education level was added to the model, the fit remained acceptable, and the pathway from the MLGP score to overeating was positive and significant. Age and ethnicity did not have a significant impact on any of the variables, and there were no differences when the model was tested in males and females separately. As anticipated, overeating mediated the association between ADHD symptoms and BMI. When the model was retested with each of the four DRD2/ANKK1 polymorphisms that comprised the MLGP score independently, the Taq1A SNP significantly predicted overeating in the positive direction, while the other markers did not. The effect of the Taq1A SNP on overeating was only slightly stronger than the effect of the MLGP score. Overall, results indicate that individuals who have more ADHD symptoms and carry genetic profiles associated with greater DA activation in the brain reward areas, are more likely to engage in forms of hedonic eating, and as result, have a higher BMI.

**1. ADHD Symptoms and Overeating**

The mediation analysis confirms previous reports that overeating accounts, in part, for the connection between ADHD symptoms and BMI (e.g., Davis et al., 2006; Strimas et al., 2008). Past research testing mediation models has typically focused on binge eating. For instance, Ivan et al. (2009) and Pagoto et al. (2009) found support for binge eating partially mediating the ADHD symptom and weight status association. While a formal mediation analysis was not conducted, results of a pediatric chart review by Reinblatt et al. (2014) also suggested that binge eating partly explained the ADHD-BMI connection. Likewise, in a large community-based sample of adults, adjustment for binge eating weakened the association between ADHD and

obesity, although the relationship remained significant, indicating that other factors are also involved in this relationship (de Zwaan et al., 2011). Correlational studies further support a link between binge eating and ADHD symptoms (Bleck et al., 2014; Erhart et al., 2012), especially those characterized by impulsive responding (Nasser et al., 2004; Schag, Schonleber, Teufel, Zipfel & Giel., 2013). The link between binge eating, weight gain, and obesity is also well established (e.g., Masheb et al., 2015; Mussell et al., 2006).

The current model builds on previous findings by including additional forms of eating behaviour. Along with binge eating, both hedonic (i.e., eating in response the palatability and appearance of food) and emotional eating (i.e., eating to soothe negative emotions, rather than in response to homeostatic hunger cues) significantly contributed to the latent overeating variable, indicating they too play an important role in the ADHD symptom-BMI association. Earlier research by Davis et al. (2006) and Strimas et al. (2008) also tested a mediation model where the ADHD symptom-BMI connection was accounted for by emotional and binge eating, along with external eating – defined as eating in response to environmental stimuli, such as the sight or smell of food cues, rather than physical hunger. This construct overlaps conceptually with hedonic eating, as measured in the current study.

Some evidence suggests that ADHD symptoms also predict greater intake of high sugar, fat, and ultraprocessed "snack" or "fast" foods (Azadbakht & Essmaillzadeh, 2012; Hartman, Rief, & Hilbert, 2012), which tend to be those consumed most frequently during binge or emotional eating episodes. Kim et al. (2013) used SEM procedures to demonstrate an indirect effect of ADHD symptoms on BMI through dietary behaviours, such as speed of eating and unhealthy food intake (i.e., soft drinks, fast food, and instant noodles) in a general population sample of Korean children and youth. Conversely, however, a cross-sectional study of preschool

children in Switzerland found no relationship between ADHD symptoms and intake of fatty and sweet foods, but snacking in front of the television was related to hyperactivity and inattention (Ebenegger et al., 2012). However, these samples have been restricted to children, and parents typically control most food choices at these early ages, making comparisons to adult studies problematic.

It appears that ADHD-related difficulties interfere with individual's abilities to withhold urges to binge or comfort eat, or to pass up high sugar/fat food options, and consequently, can lead to weight gain overtime. From an evolutionary perspective, impulsivity was likely advantageous in fostering high-calorie eating when food was available; however, these tendencies have become maladaptive in today's environment where food is relatively inexpensive, vastly available, and a highly convenient commodity (Scully, 2014; Swinburn et al., 2011). Considerable behavioural control and foresight is required to regularly prepare healthy meals, and to resist consumption of more easily accessible and hyperpalatable options, particularly with their persuasive and omnipresent marketing (Swinburn et al., 2011; Yale Rudd Centre for Food Policy & Obesity, 2013). Davis (2010) suggests that the ADHD-obesity link was not recognized until the past decade or so as it only emerged with noticeable clinical frequency in response to our recent obesogenic environment. Past ADHD co-morbidity research has extensively documented the correlation between ADHD symptoms and drug use or abuse (e.g., Lee, Humphreys, Flory, Liu & Glass, 2011; Wilens et al., 2011) – substances that have been readily available for decades. Notably, ultraprocessed foods available today possess many addictive properties, and bear little resemblance to those grown naturally (Davis, 2014; Gearhardt, Davis, Kuschner & Brownell, 2011). Compulsive overeating may represent a more modern form of reward-seeking behaviour among those with ADHD symptoms.

However, not all of those who have ADHD or related symptoms are obese, and despite this "toxic" food environment, a large variation of adiposity exists in the population. Moreover, the literature is inconsistent when looking at ADHD, eating behaviour, and weight status (Dubnov-Raz et al., 2011; Cortese et al., 2014; Lingineni et al., 2012; Pauli-Pott et al., 2013). While past studies were typically limited by small sample sizes, reliance on report of a past ADHD diagnosis, or a lack of control for confounding factors such as medication status, socio-economic level, or common co-morbidities such as depression, there still appeared to be a missing factor in the ADHD symptom-obesity connection. Consequently, it is important to determine what differentiates those with ADHD symptoms who are prone to overeating and obesity, from those who have been able to maintain a healthy weight despite the symptoms of this disorder.

The model indicates that a heightened responsivity to rewarding stimuli plays a central role in the tendency to overeat among those with ADHD symptoms. These results correspond with evidence from previous studies that have independently found increased hedonic eating and obesity among individuals with poor impulse control (e.g., Dawe & Loxton, 2004; Nasser et al., 2004) or elevated reward sensitivity (e.g., Davis et al., 2004, 2007; Franken & Muris, 2005; Temple et al., 2008). To date, two other studies that have included both of these factors in one analysis. Specifically, higher reward sensitivity was predictive of greater palatable food intake and weight gain over a one-year period, but only among participants with diminished inhibitory control – a symptom of ADHD (Applehans et al., 2011; Nederkoorn et al., 2010).

The joint involvement of these two forces – impulsiveness and higher reward sensitivity – relates to the "reinforcement pathology" theory of obesity. According to this perspective, overeating and weight gain are fostered by an imbalance between the drive to consume food and

the diminished ability to delay gratification (Carr, Daniel, Lin & Epstein, 2011; Epstein, Salvy, Carr, Dearing, Bickel, 2010). Epstein et al. (2013) used the analogy of a "brake and an accelerator", where individuals susceptible to obesity are too heavy on the gas, which promotes eating, and possess insufficient brakes to cease or avoid eating. Testing this theory, Epstein et al. (2013) found that while both delay discounting and food reinforcement independently predicted BMI, greater variance was accounted for by their interaction. Similarly, the interaction between the inability to delay gratification and high food reinforcement increased caloric intake (Rollins, Dearing & Epstein, 2010) and inhibited weight loss (Best et al., 2012) to a greater extent than either factor alone.

Corresponding to the "reinforcement pathology" theory, the combined effect of two independent but interacting neural systems has been proposed to contribute to addictive behaviours: a motivational network, in which the striatum is chiefly responsible for promoting reward-driven behaviours, and a system dependent on prefrontal cortical function, involved in decision making, projecting future consequences, and inhibitory control (Volkow, Wang, Fowler, & Telang, 2008; Bickel et al., 2007; Goldstein & Volkow, 2011; Grant, Contoreggi & London, 2000; Jentsch & Taylor, 1999). Koritzky et al. (2014) have argued that overeating could result from malfunctioning of either of these two systems. The current research represents the first study to include genetic measures reflecting the neurobiology of both reward sensitivity and ADHD symptoms in the analysis of hedonic eating and obesity.

**2. Sex/Gender Analyses**

No significant model differences were found when comparing males and females using the multi-group analysis function on any of the included parameters. Testing the effect of sex/gender on the link between ADHD symptoms and obesity was imperative based on suggested variances

in ADHD symptoms. The large majority of previous studies have not done so due to insufficient power or samples consisting of only males or females, and the limited number of reports that have included sex/gender as a variable were conducted among youth. For instance, one study found ADHD symptoms to predict later overweight status in males, whereas females with such symptoms were more likely to engage in compensatory behaviours (i.e., dysfunctional eating habits; Petrone et al., 2013), that may have prevented an impact on adiposity. Participants in the current study were screened such compensatory eating disordered-related behaviours. A different study found an age-dependent effect of ADHD symptoms on weight status among girls only, with puberty appearing to have a protective effect on weight gain (Fliers et al., 2013); however, there was no control for medication status and being a clinical sample, many participants had potentially been exposed to stimulant drugs. Therefore, the findings may reflect an increased sensitivity to the appetite suppressant effects of stimulation drugs among post-pubertal females as a result of estrogen's interaction with dopamine (Pal et al., 2007).

There were also no sex/gender significant differences on the two ADHD scales, although, there was a trend ($p= 0.059$) of males having higher scores on the retroactive assessment of childhood symptoms. These findings are somewhat in line with previous work. Some sex differences in ADHD phenotypes, prevalence, and average age at diagnosis have been suggested among children and adolescents. The disorder tends to be identified later in girls than boys, likely due to the greater frequency of externalizing symptoms, such as hyperactivity and behavioural impulsivity (e.g., physical aggression) among males (Quinn, 2008; Rucklidge, 2008, 2010), that can be disruptive in school, and therefore, more likely to get noticed. In contrast, girls exhibit more inattention and internalizing symptoms (Efron et al., 2014; Quinn, 2008; Rucklidge, 2010; Skogli et al., 2013), such as anxiety, depression, poor coping skills, and low self-efficacy

(Quinn 2008; Rucklidge, 2008, 2010; Skogli et al., 2013). However, many nonreferred samples fail to replicate these findings, and symptom dissimilarities are less apparent by adulthood (Rucklidge, 2008). Several reports suggest differences dissipate with age, with few male or female adults meeting the purely hyperactive/impulsive subtype criteria (Quinn, 2008), although, ADHD research among adults is lagging behind childhood studies. Some recent evidence indicates females with ADHD continue to have greater inattention symptoms, and males with the disorder remain more impulsive and hyperactive in adulthood (Rucklidge, 2010). The literature is consistent in demonstrating the sex discrepancy in the prevalence of ADHD are no longer evident among adults (Vingilis et al., 2015).

In terms of eating behaviour, females are more likely to emotionally eat in response to negative mood states (van Strien et al., 1986). Females also have higher rates of binge eating (Kelly-Weeder, Jennings, & Wolfe, 2012; Presnell, Pells, Stout, & Musante, 2008). In line with these past reports, females in the current sample had significantly higher scores than males on all three eating variables: binge, hedonic, and emotional eating.

Theoretically, the greater behavioural impulsivity symptoms among males could predispose them to binge eat or indulge in cravings when they see food-related cues as a result of difficulty suppressing urges; whereas, the internalizing symptoms of anxiety and depression may place females at risk for both emotional overeating and binge eating. Some evidence suggests that women with ADHD are more prone to co-morbid substance use disorders relative to men (Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2002, 2014). The same may apply to compulsive eating behaviours, in which case, the model could be expected to fit better among females. However, a recent study found no sex/gender effect on the relationship between addictive behaviours and ADHD symptoms (Davis, Cohen, Davids, & Rabindranath, 2015).

Similarly, in the current study, the modeled relationships among ADHD symptoms, reward sensitivity, hedonic overeating, and BMI were equivalent in males and females.

**3. The MLGP Score and the DRD2/ANKK1 Polymorphisms**

Results of this study suggest that a strong DA signal in the brain reward pathways contributes to a proneness to overeating among those with ADHD symptoms. This finding is reflected by the positive and significant pathway from the MLGP index to the overeating latent variable, after controlling for education level. That is, higher MLGP scores – indicative of enhanced signaling in the ventral striatum – were associated with higher levels of overeating.

The MLGP score is a quantitative genetic measure reflecting variation, in this case, in DA reactivity in the midbrain reward-related areas of the brain (Nikolova et al., 2011). Individual candidate genes typically only explain a small portion of phenotypic variance, since multiple genes contribute to complex human traits and behaviours. Independently, the effect sizes often fail to reach significance statistically, which is why the composite MLGP measure, which allows for stronger powered analyses, is advantageous (Nikolova et al., 2011; Plomin, 2013). Four functional DRD2/ANKK1 polymorphisms were included in the summative score. When tested individually, the ANKK1 Taq1A SNP predicted overeating in the model, while the DRD2 C957T (rs6277), rs12364283, and -141 Ins/Del (rs17999732) markers did not have significant effects.

Carrying the C (A2) allele of the ANKK1 Taq1A C/T SNP predicted increased overeating. This variant has been associated with greater D2 receptor binding affinity and higher striatal receptor density (Jonsson et al., 1999), and therefore, is believed to result in a relatively stronger DA signal (Noble et al., 1991), in comparison to the alternate T (A1) allele. The model fit statistics were nearly equivalent when testing the model with the full MLGP score or with the

ANKK1 Taq1A polymorphism alone. The variance accounted for by the single marker was also roughly equal to, or very slightly greater, than that of the composite index. The effect of the composite index on overeating only reached significance when the model was retested controlling for education level.

The Taq1A has received the most research attention of the DRD2-related markers, especially in relation to addictive behaviours. Generally, possession of Taq1A T (A1) variant – predictive of diminished DA signaling capacity – has been alleged to increase susceptibility for substance use and abuse, including alcohol, nicotine, opioid, and cocaine dependency (Noble, 2000; Smith, Watson, Gates, Ball, & Foxcroft, 2008). These findings lead to the theory of a "Reward Deficiency Syndrome" (Blum et al., 1996), which proposes that due to a dysfunction in the brain reward cascade, or miscommunication in the cross-talk amongst various neurotransmitters, some individuals have a lowered capacity for DA release in response to rewarding stimuli, and therefore, are more likely to seek out drugs of abuse as a means of self-medication. Based on the many parallels with substance-use dependence, some researchers have extended this theory to obesity and the overconsumption of high sugar and/or fat foods (Wang et al., 2001; Wang, Volkow, Thanos & Fowler, 2004).

Contrary to the current study results, and in line with the "Reward Deficiency Syndrome" theory (Blum et al., 1996) of addictive behaviours, the ANKK1 Taq1A T (A1) allele – associated with lower DA signaling capability – has been linked to disinhibited eating (defined as overconsumption of foods associated with a loss of control over food intake; Ariza et al., 2012), higher BMI (Carpenter, Wong, Li, Noble & Heber, 2013), and future weight gain (Muller et al., 2012; Winkler et al., 2012), compared to the alternate C (A2) variant. However, there has been a number of inconsistent findings and debate regarding the DA D2 receptors, particularly in terms

of which allelic variants of the gene represent a putative risk for weight gain. Several null reports also exist. For instance, Col Araz et al. (2012) found no significant differences in frequency of DRD2 Taq1A genotypes or alleles between children with obesity and normal-weight controls. Similarly, a large population-based sample of children and their mothers reported a lack of association between the DRD2 Taq1A and adiposity (Hardman, Rogers, Timpson & Munafo, 2014). Interestingly, Davis et al. (2012) found the Taq1A C (A2) allele to be more prevalent among individuals with both obesity and binge eating disorder, while obese participants who did not binge eat were more likely to carry the T (A1) variant.

More recent research suggests that both ends of the DA-distribution continuum may confer risk for various addictive behaviours, obesity, and compulsive overeating (e.g., Davis et al., 2012; Davis, 2013). Results of the current study lend support to the "Reward Surfeit Theory" of obesity (Davis et al., 2004; Stice et al., 2008; Yokum et al., 2015) – that is, individuals who experience greater DA responsivity to palatable food consumption are more prone to overeating and weight gain. Further evidence comes from certain neuroimaging reports that future weight gain is predicted by elevated activation in the brain reward pathways in response to food intake (Geha et al., 2013), or food-related images (Demos et al., 2012) and food commercials (Yokum et al., 2015).

Brain imaging research has revealed a decreased availability of DA D2 receptors in the striatum among those with obesity (Stice, Spoor, Bohon & Small, 2008; Volkow et al., 2008; Wang, et al., 2001). However, as mentioned, case-control designs using neuroimaging methods must be interpreted with caution. While valuable, they only reveal the current state of neuronal functioning and structure, and therefore, consequences of behavioural or environmental factors

may be misconstrued as causal or innate attributes. For this reason, genetic approaches, as applied in the present study, allow for better predictions of predisposing factors.

There is accumulating evidence that the link between DA-activation potential and eating behaviour and obesity varies according to the type of overeating. Davis (2013) proposed a continuum of overeating behaviours, from those of a more passive nature and increasing in severity to the most compulsive forms. Obesity itself is not a homogeneous condition, and certain subgroups likely exist with differing risk factors. Among individuals with ADHD symptoms, the current study supports a relationship between greater DA responsivity and more compulsive forms of hedonic eating behaviours including binge eating and emotional eating. Likewise, other research has linked ANKK1 Taq1A and DRD2 C957T (rs6277) genotypes predictive of enhanced DA transmission with food cravings, and binge, hedonic, and emotional eating (Davis et al., 2013), while the Taq1A variant associated with diminished DA activation (i.e., the T [A1] allele) shows connections to non-bingeing subtypes of obesity (Davis, Levitan, Yilmaz, Kaplan, Carter & Kennedy, 2012).

Of relevance, some evidence indicates that individuals with ADHD symptoms who are homozygous for the C (A2) variant of the ANKK1 Taq1A polymorphism have an increased likelihood of being smokers (McClernon et al., 2008), and report more pleasurable responses upon initial cigarette use (Bidwell et al., 2012). Furthermore, smokers with ADHD have greater difficulty quitting (Covey et al., 2008; Humfleet et al., 2005; Pomerleau et al., 1995), work harder for cigarettes, have more severe withdrawal symptoms (McClernon et al., 2008, 2011), and experience stronger reinforcement effects from smoking after a 24-hour period of abstinence (Kollins et al, 2013). This research lends support to the current model suggesting that among

those with ADHD symptoms, a greater reward response places some individuals at risk of engaging in DA-boosting behaviours, in this case, excessive intake of palatable foods.

Davis et al. (2013) have also employed an aggregate genetic score to reflect DA signaling capacity in their study of "food addiction" and related sub-phenotypes among participants with obesity. Results indicated that MLGP scores were higher among individuals meeting food addiction criteria than their weight and age-matched counterparts. Also, MLGP values positively correlated with binge eating, food cravings, and emotional overeating, but not with hedonic eating and snacking on sweets. Overall, these results suggest that reward responsiveness may selectively influence more compulsive forms overeating, rather than passive consumption. Moreover, Davis et al. (2013) found support for a multiple-mediation model in which reward-driven overeating facilitated the relationship between the MLGP index and food addiction. Considering the overlap in these results and the current analyses, along with the robust links between ADHD and substance abuse (Lee et al., 2011; Wilens et al., 2011), and parallels between drug addictions and compulsive eating (Curtis & Davis, 2014; Davis, 2014; Davis & Carter, 2009), an intriguing area for future research would be to examine food addiction in relation to ADHD symptoms.

Another recent and similar study by Yokum et al. (2015) applied the MLGP technique to testing the association between elevated DA signaling in the reward circuitry and future weight gain. Using multiple study populations, varying in average age and BMI, they found their MLGP risk score – which included the Taq1A C (A2) allele, DRD2 -141C Ins/Del and Del/Del genotypes, DRD4 48-bp VNTR short allele, DAT1 VNTR short allele, and COMT Val/Val genotype – predicted future increases in BMI in all three study groups, as well as in the overall sample (Yokum et al., 2015). That is, individuals carrying a higher number of genetic variants

representative of stronger DA signaling capacity gained more weight than those with fewer of these alleles or genotypes. Moreover, the MLGP index moderated the effectiveness of a weight loss treatment, where higher MLGP scores were associated with less weight loss two years following the intervention (Yokum et al., 2015).

Interestingly, the effect sizes were greater in the two samples comprising subjects who were overweight or obese compared to the sample with BMIs under 25 $kg/m^2$ (Yokum et al., 2015). Past inconsistencies studying DA-related genes in obesity may have arisen due to restriction in the body weights and sizes represented by the sample. The current study is advantageous in reflecting a wide range of BMIs, up to a maximum of 75.19 $kg/m^2$. Also, analyzed independently, only the DRD4 48-bp VNTR short allele and DAT1 had significant effects in certain samples in Yokum et al.'s (2015) report, while the ANKK1 Taq1A, COMT, and DRD2 -141C markers did not predict weight change over the two-year follow-up period. While the effects of the DRD4 and DAT1 were slightly stronger than that of overall MLGP score, as was also the case in the current study for the ANKK1 Taq1A, the authors proposed that the MLGP index represents a more reproducible predictor as it emerged in multiple samples. Given the results of the present model and those of Davis et al. (2013), the effect of the MLGP score found in Yokum et al.'s analyses (2015) on weight gain and loss may have been mediated by overeating. However, unlike Davis et al. (2013), Yokum et al. (2015) report that no relationship was found between the MLGP score and food cravings in *post hoc* analyses, but other forms of eating behaviours were not mentioned. Also, their sample may not have reflected comparatively severe levels compulsive eating. These results suggest that additional genetic polymorphisms are worthwhile including in MLGP indices, and that such genetic composite

measures may be useful in predicting and preventing future weight gain, and tailoring intervention strategies.

**4. The DRD4 Gene**

The DRD4 gene was included in the model based on neuroimaging evidence of the D4 receptor's predominance in the prefrontal cortex regions of the brain (Ariza et al., 2012; Meador-Woodruff et al., 1996; Gizer et al., 2009; Li et al., 2014; Thapar et al., 2013; Wu et al, 2012) – areas regulating some of the attentional and decision-making functions that are impaired in ADHD. The 7-repeat variant of the DRD4 third exon 48-bp VNTR has been associated with cortical thinning in these same regions (Shaw et al., 2007). A number of meta-analyses support a role of the 48-bp VNTR in clinical cases of ADHD (Langley et al., 2005; Li et al., 2014; Thapar et al., 2013; Wu et al., 2012). In addition, this polymorphism has been implicated in specific symptoms of the disorder. For instance, possession of the 7-repeat allele of the 48-bp VNTR predicted inattention (Albrecht et al., 2014; Gizer & Waldman, 2012) and high trait impulsivity (Varga et al., 2012) as measured by behavioural tasks and psychometric scales, respectively. Likewise, in animal models, reduced DRD4 expression results in response disinhibition and poor attentional performance (Young, Powell, Scott, Zhou & Geyer, 2011).

In comparison to the alternate variants, the 7-repeat allele of the polymorphism likely leads to diminished DA availability, based on neuroimaging reports of reduced receptor densities and decreased binding affinity for DA among individuals carrying this variant (Asghari et al., 1995; Schoots & Van Tol, 2003; Swanson et al., 2000). In line with this evidence, and the hypo-dopaminergic theory of ADHD, the presence of the 7-repeat was hypothesized to predict greater ADHD symptomatology in the current model. The results did not support this theory; although, when examining the residuals, considerable shared variance was apparent between both of the

individual ADHD symptom measures (i.e., the WURS and the CAARS, independently) and the DRD4 7-repeat, that was not explained by the pathway from the DRD4 to the ADHD symptoms latent variable. In other words, the ADHD scales have separate associations with the DRD4 that are not captured by the relationship between their combined variance and the gene. The former scale is a retroactive assessment of childhood ADHD symptoms and possessed a positive residual covariance with the DRD4, while the latter measures current adulthood symptoms and had a negative residual value with the genetic marker. It is not immediately clear what these relatively larger residual covariances represent.

While the 7-repeat variant of the DRD4 is widely cited as the risk allele for ADHD and its symptoms, several inconsistencies exist in the research literature, with many reports of null or opposite effects (e.g., Ariza et al., 2012; Paterson, Sunohara & Kennedy, 1999; Langley et al., 2004; Manor et al., 2002; Swanson et al., 2000). For instance, numerous studies reveal significant associations between the 7-repeat and impaired executive functioning in both children with ADHD (Froehlich et al., 2007; Langley et al., 2004; Waldman, 2005) and those without (Froehlich et al., 2007); however, others have failed to replicate a relationship of this allele with executive functioning (Ariza et al., 2012), or a preferential transmission in family-based ADHD studies (Eisenberg et al., 2000). Likewise, various null reports exist on the proposed link between the 7-repeat and attentional processes in ADHD patients (Langley et al., 2004; Manor et al., 2002; Swanson et al., 2000), along with conflicting results of improved attention (Manor et al., 2002; Thissen et al., 2015) or lower trait impulsivity (Schiling, Kuhn, Sander & Gallinat, 2014) among individuals carrying long repeat variants. In adult samples, the 7-repeat has been associated with both worse (Muglia et al., 2000; Congdon et al., 2008) and better (Boonstra et al., 2008) performance on neurocognitive tests. Other research indicates that the DRD4 7-repeat

may have specificity for certain ADHD symptoms only (Albrecht et al., 2014), although a lack of agreement is present concerning with which symptoms the genetic variant is associated.

Considering that the majority of DRD4 studies have used clinical populations, it is plausible that the 7-repeat allele is distinctly associated with more severe ADHD symptoms, increasing the likelihood of being diagnosed with the disorder. The expected effect of the DRD4 may be less consistent and strong among participants in the current sample, who had not been formally diagnosed with ADHD. Moreover, even among those who have an ADHD diagnosis, variation in the DA system is apparent in the differing efficacy of methylphenidate in ameliorating symptoms (McGough et al., 2009)

In addition, much of the research on the DRD4 has been done in samples of children or youth. Thissen et al. (2015) recently found support for a moderating effect of age for the DRD4 48-bp VNTR and ADHD symptoms. Contradictory to most reports, the 7-repeat carriers had *fewer* ADHD inattention symptoms, but only among adults. Similarly, other adult studies have found the longer repeat alleles to predict improved attention (Manor et al., 2002) and lower impulsivity scores (Schilling et al., 2014). The authors propose differential genotype-phenotype associations at various stages of life for the 7-repeat due to changes in the DA system, as DA transporter densities decrease with age (Spencer et al., 2005) and ADHD symptoms tend to decrease in adolescence (Biederman et al, 2000). Interestingly, the cortical thinning seen in childhood among those carrying the DRD4 7-repeat allele is largely normalized by adolescence (Shaw et al., 2007). Thissen et al. (2015) theorize a possible protective effect of the 7-repeat allele in adult ADHD that emerges during or after middle-to-late adulthood, and therefore, is not consistently found among samples of adolescents and young adults. If this notion is correct, age may account for the null pathway from the DRD4 to ADHD symptoms in the current model, as

the sample consisted of participants aged 25 to 50 years, falling into this period of alleged inconsistency. These age-related findings are particularly interesting in light of the large residuals found in the current analyses between the DRD4 and each of the two ADHD scales, which assessed retroactive childhood symptoms and current adulthood symptoms.

It is also possible that other DA-related genes that have been linked to the ADHD could contribute to obesity risk – such as the DA transporter gene (DAT1), DA D5 receptor gene (DRD5), or DA D3 receptor genes (Bobb et al., 206; Davis et al., 2009; Li et al., 2006; Thapar et al., 2013; Wu et al., 2012). A single polymorphism of the DRD4 was analyzed in the study, and as discussed in the case of the DRD2/ANKK1 MLGP score, individual genetic markers typically explain little of the phenotypic variance of complex human behaviours and disorders. Additional markers on the DRD4 gene were not included due to the lack of consistent evidence of an association with ADHD symptoms according to a recent meta-analysis (Wu et al., 2012).

While extensive ADHD research has focused on the DRD4, negligible work has been done on the gene in relation to obesity. One study reported a positive relationship between the 7-repeat allele and maximal lifetime BMI and obesity among overeating women with Seasonal Affective Disorder (Levitan et al., 2004). In contrast, another report found that the DRD4 VNTR short variants (2-5 repeats) predicted increased BMI over a two-year period in populations with overweight or obesity, but not among normal-weight participants (Yokum et al., 2015). In terms of eating behaviour, the 7-repeat allele was linked to greater food cravings in a single study (Sobik, Hutchinson & Craighead, 2005), and patients treated with DA D4 receptor antagonist medications exhibit increased food intake (Theisen et al., 2003). Otherwise, a direct effect of the gene on adiposity or overeating has not been supported (Ariza et al., 2012; Fuemmeler et al., 2012; Stice et al., 2010; Yilmaz et al., 2012); although, the 7-repeat risk allele was more

prevalent in patients with a greater severity of ADHD symptoms among those with eating disorders or obesity (Ariza et al., 2012; Yilmaz et al., 2012). This evidence contributed to the hypothesis tested in the current model that the lower cortical DA activity associated with the 7-repeat variant would have an indirect effect on overeating through increasing ADHD symptoms, when combined with high DA reactivity in the reward neurocircuitry. As mentioned, the DRD4 portion of this prediction was not supported in the current sample with a wide range of BMIs.

**5. Prenatal Influences in Obesity and ADHD**

Recent investigations suggest that ADHD symptomatology is not necessarily produced by innate genetic factors, but could also arise as a consequence of engaging in certain behaviours or due to exposure to environmental factors. For instance, accumulating evidence indicates that prenatal and early life factors such as maternal smoking, alcohol use, and excessive consumption of high sugar and/or fat foods during pregnancy may increase the risk for ADHD symptoms (Greenbaum et al., 2009; Rodriguez et al., 2008, 2010). Individuals with fetal alcohol spectrum disorders (FASDs), or what have also been called alcohol-related neurodevelopmental disorders, exhibit symptoms remarkably similar to those of ADHD, including inattention, restlessness, impulsivity, and antisocial behaviours (Greenbaum et al., 2009). In fact, up to 70% of children with prenatal exposure to alcohol also receive a diagnosis of ADHD (Greenbaum et al., 2009), and as many as 30% of U.S. women are estimated to have consumed alcohol during pregnancy in the late-1980s (Golden, 1999). Akin to ADHD symptoms, indicators of alcohol exposure exist on a continuum with a dose-response relationship. Therefore, it is imaginable that many offspring were impacted and are now adults. Similar to the cross-sensitization seen with addictive substances, Davis (2010) proposed that prenatal exposure to tobacco or alcohol may sensitize the developing fetus, which may account for the elevated rates of substance abuse among those with

ADHD. The same logic may apply to the increased risk of obesity as a result of a greater prevalence of hyperpalatable food consumption in our current society.

Relevant is research revealing that maternal-obesity status may have an effect analogous to mothers drinking alcohol during pregnancy. For instance, a prospective study found mothers who were overweight or obese during pregnancy were more likely to give birth to children with symptoms of inattentiveness as rated by kindergarten teachers, when compared to mothers who had normal weights at the time of conception (Rodriguez et al., 2008). The relationship held even after controlling for offspring birth weight, and maternal age and smoking status. In a follow-up project, the researchers controlled for parental ADHD symptoms, and again found that maternal prepregnancy obesity predicted offspring ADHD-related symptoms of inattention and negative emotionality (Rodriguez, 2010). Based on this evidence, along with the addictive-like behaviours seen in response to high sugar intakes, Davis (2010) proposed that a "fetal sugar spectrum disorder" may occur if these mothers consumed large and frequent quantities of highly palatable foods, similar to that seen in the offspring of mothers who drank alcohol during pregnancy.

As evidenced in these studies, and the current model, the relationships among ADHD symptoms, eating behaviour, and dopaminergic state are more complex than initially assumed. While a genetic predisposition in the brain reward pathways contributing to overeating is supported, the current study found no evidence that the DRD4 48-bp VNTR polymorphism plays a role in ADHD symptoms.

**6. Implications for Treatment and Prevention**

Raising awareness of the connection between ADHD symptoms and obesity will assist in the diagnosis of ADHD among obese individuals in whom the disorder may have otherwise been overlooked. Agranat-Meged et al. (2005) recommend screening all obese children after finding

the disorder was missed in 60% of their sample prior to participating in the study. Similarly, a new report found that only 17% of children who were identified by the researchers as having ADHD had been previously diagnosed (Efron et al., 2014). In particular, girls tend to be underidentified because of differences in symptom expression (Skogli et al., 2013). However, the current model demonstrated that equivalent relationships exist among symptoms, overeating, and BMI in both males and females.

Screening adults who engage in binge eating and obese patients attending weight loss clinics for ADHD is also warranted based on the high prevalence of the disorder reported among these individuals (Alfas, 2002; Fleming & Levy, 2002). Adults with ADHD attending a weight management program had more clinic visits and longer treatment duration than their non-ADHD counterparts – indicating that weight loss is particularly difficult for adults with inattention and impulsivity symptoms (Alfas, 2002). Individuals with elevated ADHD symptoms appear to require additional support in health-related compliance (Alfonsson et al., 2012). These implications extend beyond those meeting full diagnostic criteria, as established in the well-fitting model tested in the current study, using a nonclinical sample. Recognizing the ADHD symptom-obesity connection is imperative in assisting all affected populations in achieving weight loss and maintenance goals, if symptoms have hindered past efforts.

In terms of prevention, identifying individuals with signs of impulsivity and inattention is advisable as they represent a high-risk group for obesity. Considering that many children with ADHD symptoms begin to gain weight at a young age (Anderson et al., 2006) and engage in overeating (Erhart et al., 2012), prevention would need to start early in life – perhaps as young as the prenatal stage, in light of evidence discussed above. The current model provides support for

incorporating eating strategies into ADHD treatment plans, and regularly monitoring weight and dietary patterns in assessments among those with symptoms.

In view of the ADHD-obesity association, developing joint intervention programs would be worthwhile as many similarities exist in behavioural treatments commonly used for these conditions. In support, ADHD treatments show some evidence of success in treating obesity (Shaw et al., 2012). For instance, behavioural contingency approaches that incorporate reinforcement principles may prove useful. These management plans involve setting specific goals, tracking behaviours, and rewarding improvements. Similar interventions show some efficacy for cigarette smoking among individuals with ADHD symptoms (McClernon et al, 2011). In addition, interventions aiming to enhance mindfulness (Lillis, Hayes, Bunting & Masuda, 2009; Papies, Barsalou & Custers, 2012), awareness of hunger (Boutelle et al., 2011), and recollection of past eating (Higgs, 2002) appear to improve control over eating, and may prove effective for those with ADHD symptoms. Epstein et al. (2013) suggest that working memory training may assist impulsive individuals in focusing on long-term benefits over short-term rewards, and this approach has been used as a complement to obesity treatment (Verbeken, Braet, Goossens, van der Oord, 2013). Based on the current study results, along with ADHD symptoms, interventions would need to account for an enhanced responsiveness to reward cues, which may take the form of environmental modifications, such as keeping high sugar and/or fat foods and related cues out of the home and school.

In addition to behavioural treatments, the study results have direct implications for the development of pharmaceutical obesity interventions. A number of reports suggest stimulant medications improve ADHD symptoms and abnormal eating patterns in patients exhibiting both conditions (Cortese et al., 2007). Likewise, some evidence suggests that ADHD pharmacological

treatment has a protective influence on adiposity (Ptacek et al., 2009; Waring & Lapane, 2008). For instance, two separate studies found medication-naïve children with ADHD were at greater risk of being overweight or having higher body fat percentage, compared to their medicated counterparts and to population norms (Ptacek et al., 2009; Waring & Lapane, 2008). In fact, the medicated youth with ADHD actually had higher odds of being underweight in one of these reports (Waring & Lapane, 2008). As these studies had correlational designs, it remains unclear whether the differences resulted from the medication's appetite-suppressive effect, or if treated individuals had more control over their eating behaviours due to improved ADHD symptoms. Also, individual variation exists in the effect methylphenidate has on both appetite and food cravings (Davis, Fattore, Kaplan, Carter, Levitan & Kennedy, 2012; Davis et al., 2007) and ADHD symptom response (McGough et al., 2009).

More recent studies have raised the question of whether an adiposity rebound effect occurs once these stimulant medications are ceased (Bernard et al., 2014; Schwartz et al., 2014), and approximately half of childhood methylphenidate prescriptions are stopped before adulthood (Goodman, 2013). In comparison to nonmedicated youth with or without ADHD, a large longitudinal study found children who began stimulant use at younger ages, and who continued for longer durations, had a slower BMI growth in early childhood, followed by a more rapid BMI rebound in late childhood, resulting in higher BMIs when they reached late adolescence (Schwartz et al., 2014). Clearly, more work is important to understand the long-term risks and benefits of these medications on both eating behaviours and adiposity. Interestingly, based on evidence of the cross-sensitization process that occurs between intermittent sugar intake and illicit drugs, similar to that seen from one drug to another (Avena, Rada & Hoebel, 2008), Davis (2010) proposes that ADHD medications may predispose individuals to the reinforcing

properties of high sugar foods and later obesity, which may explain this possible weight-rebound effect. On the other hand, it may simply reflect the resurgence of ADHD symptoms, putting them at risk for overeating again (Bernard et al., 2014).

Current research efforts are evaluating the potential use of ADHD pharmaceuticals for the treatment of binge eating disorder. A newly available paper on a randomized clinical trial provides evidence in support of the efficacy of stimulant medication lisdexamfetamine dimesylate – a dextroamphetamine prodrug with the brand name Vyvanse – in decreasing binge eating days, cessation of binge eating, and global improvement in comparison to a placebo group (McElroy et al., 2015). In fact, Vyvanse recently gained FDA approval for the treatment of binge eating. Similarly, ongoing research by Murati and colleagues (2015) is testing the use of an ADHD medication with the brand name Concerta – a slow-release, long-lasting form of methylphenidate – in the treatment of binge eating disorder.

Continued study of ADHD medications is promising in adding to the currently limited available options for effectively treating binge eating and obesity. In most cases, a combination of psychotherapy, dietary support, and pharmaceutical treatments will be necessary in order to ameliorate such a complex condition. These interventions are critical to treat the substantial number of people who already have obesity, and combat the trend of increasing adiposity and growing morbid obesity levels; however, prevention is ideal when it comes to future populations. As we have seen, obesity and binge eating behaviours appear to have emerged in response to changes in the food environment. This trend is particularly obvious in morbid obesity rates, and the prevalence of ADHD symptoms appears to be especially high among this group (Alfas, 2002; Gruss et al., 2012). As Davis (2010) proposed, the ADHD-obesity link was likely not recognized until recently because it only arose in a clinically relevant prevalence coinciding with changing

in our food landscape. Therefore, the most effective strategy will involve changes to our food environment, and recognizing subgroups that are particularly vulnerable to these factors.

**7. Study Limitations**

The current study had many strengths, including the use of strong statistical procedures, psychometrically-validated ADHD assessment scales, and a large non-medicated, nonclinical, and well-screened sample of both male and female participants, in order to avoid confounding co-morbidities and treatment effects. However, it is imperative to address some potential limitations.

First, the use of BMI has been criticized (e.g., Burkhauser & Cawley, 2008; Rothman, 2008) as it is a proxy rather than a direct measure of adiposity, does not differentiate between body fat and lean mass, and its correlation with body fat can vary depending on factors such as ethnicity, sex, and exercise level. As participants were recruited from the general population, discrepancies due to body composition related to high activity or exercise profiles were considered minimal because the inclusion of a significant portion of elite athletes was unlikely. Participants from certain ethnic backgrounds (e.g. South East Asian), for whom different BMI cut-offs have been discussed (Barba et al., 2004), were excluded from the sample. Regardless, utilizing BMI on a continuum avoids some of the issues related to differing views on the appropriateness of weight class categories.

Other studies have found significant links between ADHD symptoms and excess adiposity using waist circumference or body fat assessments (Erhart et al., 2012; Jeoung, 2014; Nigg, 2013). Unfortunately, calculating body fat percentages through more sophisticated and expensive methods such as underwater weighing, dual energy x-ray absorptiometry, or computerized tomography was not practical based on the budget of this project. While waist

circumference has become a popular measure, it is not without its own failings. For instance, the validity of waist circumference in predicting abdominal obesity varies considerably based on measurement site and this inaccuracy is particularly prevalent among females, larger individuals, and certain age groups (Berker et al., 2010; Mason & Katzmarzyk, 2009; Pettit et al., 2012; Pinter et al., 2013). Also, the inter- and intra-observer variability is higher for the measure than BMI (Nadas, Putz, Nagy, & Jermendy, 2008), largely due to the lack of standardized measurement procedure. Similarly, the use of calipers to determine skinfold thickness is known to have poor reliability, particularly among heavier individuals (Hu, 2008). Bioelectric impedance can be a relatively inexpensive and convenient method; however its accuracy depends on the ratio of body water to fat, which can vary in cases of illness, dehydration, or weight loss (Hu, 2008). These other forms of measurement are also more invasive than BMI, which was a concern since the protocol addresses potentially sensitive issues, and participants were already required to provide blood work for genetic testing. Therefore, BMI was considered an appropriate gauge of obesity for this sample and the purposes of the current study.

Second, educational level was the only assessment associated with socio-economic status included in the study protocol. When controlling for educational achievement, the model remained a good fit to the data and the MLGP pathway to overeating reached significance, suggesting further control of other variables indicative of socio-economic status would strengthen results rather than invalidate them.

Third, the MLGP score assumes that the four DRD2 polymorphisms have an additive effect. While the function of each of the four loci is known, and their aggregate was found to account to more variability in striatal reactivity (Nikolova et al., 2011), their relative impact has

not been determined, and only the ANKK1 Taq1A marker predicted overeating in the current model when tested independently.

## 8. Summary and Conclusions

This dissertation provides an analysis of mechanisms that may underlie the association between ADHD symptoms and obesity incorporating data from multiple disciplines – genetic, behavioural, and psychological. Despite research on the role of reward sensitivity and impulse control in relation to obesity, their joint involvement has not been tested in a singular model including their neurobiological markers. The proposed model was a good fit to the data. When controlling for educational achievement, the composite MLGP score positively predicted overeating, which mediated the association between ADHD symptoms and BMI. However, the DRD4 48-bp VNTR did not demonstrate the expected relationship with ADHD symptoms.

Overall, it can be concluded that individuals who have more ADHD symptoms and carry a genetic profile associated with greater DA activation in the brain reward areas are more likely to overeat, and as a result, have a greater risk of obesity. The current findings confirm, and expand on, previous evidence that hedonic eating partially explains the ADHD symptom-obesity link (Davis et al., 2006; Ivan et al., 2009; Pagoto et al., 2009; Strimas et al., 2008). They also mesh with reports that compulsive overeating is more likely to occur among those carrying DRD2/ANKK1 Taq1A variants predictive of greater DA responsivity (Davis et al., 2012), and brain imaging data showing heightened activation in the ventral striatum in response to food cues among individuals prone to weight gain (Demos et al., 2012; Geha et al., 2013; Yokum et al., 2015). In summary, these results support the “reward surfeit” view of obesity, and challenge hypotheses that diminished DA levels account for association between ADHD symptoms and adiposity.

While ADHD symptoms were likely once adaptive, they now appear problematic in the modern obesogenic environment, particularly among individuals who also possess a strong appetitive motivation. In fact, it has been suggested that the overconsumption of hyperpalatable foods may have partially replaced substance use as a contemporary mode of the reward-seeking behaviour among those with ADHD symptoms (Davis, 2010). Accordingly, ideal obesity prevention methods would involve environmental modifications and ADHD symptom-screening in order discourage susceptible individuals from overeating. Further research should test the effectiveness of ADHD interventions in weight loss management. Early evidence indicates ADHD pharmaceuticals hold promise for the treatment of binge eating, and contingency management approaches have been utilized in obesity programs.

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## Appendix A: Sample of Items on the Binge Eating Questionnaire (BEQ)

1. Do you ever get uncontrollable urges to eat and eat until you feel physically ill? Yes or No

2. Are there times when you are afraid that you cannot voluntarily stop eating? Yes or No

3. Have you ever had an episode of eating an enormous amount of food in a short space of time (an eating binge)? Yes or No

## Appendix B: Sample of Items on the DEBQ Emotional Eating Subscale

| | Never 1 | Seldom 2 | Sometimes 3 | Often 4 | Very Often 5 |
|---|---|---|---|---|---|
| 3. Do you have the desire to eat when you are lonely? | | | | | |
| 7. Do you get the desire to eat when you are anxious, worried or tense? | | | | | |
| 10. Do you have the desire to eat when you are disappointed? | | | | | |
| 11. Do you have the desire to eat when you are emotionally upset? | | | | | |
| 12. Do you have the desire to eat when you are bored or restless? | | | | | |

## Appendix C: Sample of Items on the Power of Food Scale (PFS)

Please indicate the extent to which you agree that the following items describe you.

Use the following 1-5 scale for your responses.

**1 don't agree at all**

**2 agree a little**

**3 agree somewhat**

**4 agree**

**5 strongly agree**

---

1. I find myself thinking about food even when I'm not physically hungry.

5. If I see or smell a food I like, I get a powerful urge to have some.

7. I often think about what foods I might eat later in the day.

12. When I see delicious foods in advertisements or commercials, it makes me want to eat.

14. Just before I taste a favorite food, I feel intense anticipation.

17. I think I enjoy eating a lot more than most other people.

18. Hearing someone describe a great meal makes me really want to have something to eat.

19. It seems like I have food on my mind a lot.

## Appendix D: Sample of Items on the CAARS

| | Not at all, never | Just a little, once in a while | Pretty much, often | Very much |
|---|---|---|---|---|
| 8. I have trouble waiting in line or taking turns with others. | 0 | 1 | 2 | 3 |
| 9. I have trouble keeping my attention focused when working. | 0 | 1 | 2 | 3 |
| 18. I fidget (with my hands or feet) or squirm in my seat. | 0 | 1 | 2 | 3 |
| 19. I make careless mistakes or have trouble paying close attention to detail. | 0 | 1 | 2 | 3 |
| 26. I have trouble finishing job tasks or school work. | 0 | 1 | 2 | 3 |
| 27. I interrupt others when they are working or playing. | 0 | 1 | 2 | 3 |
| 29. I am distracted when things are going on around me. | 0 | 1 | 2 | 3 |
| 30. I have problems organizing my tasks and activities. | 0 | 1 | 2 | 3 |

## Appendix E: Sample of Items on the WURS

| **<u>AS A CHILD</u> I WAS (OR HAD):** | **Not at all Or very slightly** | **Mildly** | **Moder-ately** | **Quite A Bit** | **Very Much** |
|---|---|---|---|---|---|
| 1. Concentration problems, easily distracted | | | | | |
| 3. Nervous, fidgety | | | | | |
| 4. Inattentive, daydreaming | | | | | |
| 7. Trouble with stick-to-it-tiveness, not following through, failing to finish things started | | | | | |
| 16. Acting without thinking, impulsive | | | | | |
| 19. Lose control of myself | | | | | |
| 20. Tend to be or act irrational | | | | | |