DIETARY ENERGY INTAKES IN CHILDREN WITH MENTAL HEALTH CONDITIONS TREATED WITH SECOND-GENERATION ANTIPSYCHOTICS

by

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Abstract

Approximately one in six Canadian children suffer from mental health conditions (MHC), including: anxiety, bipolar disorder, and depression. Second-generation antipsychotics (SGAs) are increasingly used to treat children with MHCs. Recent evidence suggests that SGAs are implicated in rapid weight gain, increased measures of adiposity, and cardiometabolic dysfunction in the pediatric population. The mechanisms for these adverse side effects have yet to be elucidated. One postulation is that SGAs may increase dietary energy intakes; however, little is known about the diets of SGA-treated children. My thesis research explored dietary intake and its potential association with adiposity and cardiometabolic dysfunction, in SGA-treated children.

This cross-sectional study recruited SGA-treated (n=25) and SGA-naïve (n=20) children (6-19 yrs) with MHCs, from the Psychiatry Department at BC Children’s Hospital. Demographics, medical history, and anthropometrics were obtained. In a subset, fasting plasma lipids, glucose, and insulin were obtained and the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated. Three 24-hour food records were collected and analyzed for average three-day total energy (kcal), macronutrient, saturated fat, sugar, fibre, and sodium intakes.

There were no statistically significant differences between groups for energy intakes (mean ± SD; 2036.5±715.8 vs. 1725.5 ± 545.6, P = 0.352) or macronutrient, saturated fat, sugar, fibre, and sodium intakes; adjusting for sex, height, pubertal status, and psychostimulant medications. SGA-treated children had higher zBMI (p=0.001), waist circumference (p=0.019), and HOMA-IR (p=0.009), compared to SGA-naïve children. There were no associations of energy intake and measures of adiposity. There were positive associations of sodium intake and
HOMA-IR (p=0.017; 95% CI: 0.013, 0.109) and saturated fat intake and low-density lipoprotein cholesterol (LDL-c) (p=0.041; 95% CI: 0.004, 0.170), in the SGA-treated group; adjusting for sex, pubertal status, overweight/obesity, height, and psychostimulant treatment.

These data suggest that SGA-treated children do not have greater dietary energy intakes compared to SGA-naïve children, and dietary energy intakes may not be responsible for greater measures of adiposity in SGA-treated children. However, the positive associations of sodium intake with HOMA-IR, and saturated fat intake with LDL-c, in SGA-treated children, suggest that dietary intakes in SGA-treated children may contribute to cardiometabolic dysfunction in this high-risk population.
Preface

This thesis has been prepared in partial fulfillment of the requirements for the degree of Master of Science in Human Nutrition under the direction of Dr. Angela Devlin and Dr. Constadina Panagiotopoulos from September 2012 to December 2014. Dr. Angela Devlin, Dr. Constadina Panagiotopoulos, Dr. Tim Green, and Dr. Yvonne Lamers reviewed this thesis.

This study was approved by the Children and Women’s Health Centre and the University of British Columbia Clinical Research Ethics Board, certificate numbers: H10-01409 and H09-02973.

Research assistants were responsible for recruitment, consent, and demographic information collection in collaboration with myself. I performed the dietary data collection, along with the help of dietitians and staff at BC Children’s Hospital Department of Child Psychiatry, and I performed all dietary analyses. I performed anthropometric measurements for outpatient participants and nursing staff at BC Children’s Hospital performed measurements for inpatient participants. Fasting blood samples were collected and quantified by the Clinical and Pathology Laboratory at BC Children’s Hospital. I performed DNA extraction and genotyping in the Devlin lab. I performed data entry with the help of research assistants and statistical analyses with the help of Mr. Boris Kuzeljevic and Drs. Devlin, Panagiotopoulos, Cote, and Green.

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# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tr>
<td>5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Serotonin receptors</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention-deficit/hyperactivity disorder</td>
</tr>
<tr>
<td>AI</td>
<td>Adequate intake</td>
</tr>
<tr>
<td>AMDR</td>
<td>Acceptable macronutrient distribution range</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>BC</td>
<td>British Columbia</td>
</tr>
<tr>
<td>BCCH</td>
<td>BC Children’s Hospital</td>
</tr>
<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CCHS</td>
<td>Canadian community health survey</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>D&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Dopamine receptor</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>DRI</td>
<td>Dietary reference intake</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>EAR</td>
<td>Estimated average requirement</td>
</tr>
<tr>
<td>EPS</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td>HDL-c</td>
<td>High-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Homeostatic model assessment of insulin resistance</td>
</tr>
<tr>
<td>IFG</td>
<td>Impaired fasting glucose</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>LDL-c</td>
<td>Low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>MHC</td>
<td>Mental health condition</td>
</tr>
<tr>
<td>MetS</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>RDA</td>
<td>Recommended dietary allowance</td>
</tr>
<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
</tr>
<tr>
<td>SGA</td>
<td>Second-generation antipsychotic</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>TGs</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>UL</td>
<td>Tolerable upper intake level</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>zBMI</td>
<td>Body mass index z-score</td>
</tr>
</tbody>
</table>
Acknowledgements

I would first like to thank the children and their parents/guardians who participated in this research study and took the time to diligently complete their food records. I would also like to thank the Psychiatry Department staff at BC Children’s Hospital for their help and time with the data collection process.

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Chapter 1: Literature Review

1.1 Overview

Approximately one in five Canadians will experience a mental health condition (MHC) in their lifetime\(^1\). Most MHCs begin in adolescence, with approximately 70\% of adult MHCs beginning before the age of 18\(^2\). An estimated 10-20\% of Canadian children and youth are affected by MHCs each year,\(^3\) and according to the British Columbia (BC) Ministry of Child and Family Development, approximately 140,000 or 15\% of BC children suffer from MHCs\(^1,3-5\). A range of diagnoses are classified as MHCs, including but not limited to: anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), depressive disorders, bipolar disorder, and psychotic disorder\(^6\). One class of medications increasingly used to treat MHCs is second-generation antipsychotic (SGA) medications; examples include: aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Using BC Ministry of Health data, SGA prescriptions for children and adolescents were reported to have increased 18-fold between 1996/97 and 2010/11\(^7\).

Concurrent with the rise of SGA prescriptions to children and adolescents, recent evidence has revealed that severe and rapid weight gain can occur in the SGA-treated pediatric population\(^8,9\), and is potentially more severe than what is observed in adults\(^10\). Weight gain in the pediatric population is often accompanied by other surrogate measures of adiposity, such as increased body mass index (BMI) and waist circumference (WC); and cardiometabolic dysfunction\(^11\). Cardiometabolic dysfunction is defined as having risk factors for cardiovascular disease (CVD) and/or type 2 diabetes. Examples of these risk factors include: physical inactivity, smoking, dyslipidemia, elevated fasting blood glucose, insulin resistance, elevated diastolic and systolic blood pressure, and obesity\(^12,13\). The mechanisms responsible for the weight gain, excess
adiposity, and the development of cardiometabolic dysfunction in the pediatric SGA-treated population are not fully understood. One contributing factor may be the effect of SGA treatment on dietary energy intakes; however, very little research has examined SGA-treated children with MHCs. **The goal of my thesis is to explore whether SGA treatment in children affects dietary energy intakes and contributes to cardiometabolic side effects.** I will begin with a literature review covering areas relevant to my thesis research including: mental health conditions and prevalence; mechanism of action and cardiometabolic side effects of SGAs; obesity and cardiometabolic dysfunction; dietary assessment; and the role of diet in the development of obesity and cardiometabolic dysfunction. This will be followed by the rationale for my research, methodology, results, discussion, conclusion, and future directions.
1.2 Mental Health

The World Health Organization (WHO) defines health as “a complete state of physical, mental and social well-being and not merely the absence of disease or infirmity”\textsuperscript{14}. The WHO also states that mental health is an integral part of this definition, being more than just the absence of a mental disorder or disability. Mental health is defined as “a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community”\textsuperscript{14}. My thesis is focused on children and adolescents whose mental health is compromised, and in turn, have a diagnosis of a MHC.

Mental health condition is a term used to refer to a range of diagnostic disorders. The 5\textsuperscript{th} edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-V)\textsuperscript{6} provides an in depth explanation of recognizing, classifying, and diagnosing MHCs. The following provides common examples, but is not an exhaustive list, of various categories of MHCs as defined by the DSM-V: neurodevelopment disorders, schizophrenia and psychotic disorders, bipolar disorders, depressive disorders, anxiety disorders, obsessive compulsive disorders, dissociative disorders, personality disorders, substance-related and addictive disorders, disruptive disorders, impulse control and conduct disorders, and neurocognitive disorders.

Diagnosing MHCs in children and adolescents may differ when compared to diagnosing MHCs in adults\textsuperscript{15}. Children and adolescents are in a period of rapid growth and development and special consideration needs to be appropriated when recognizing and diagnosing MHCs in this
population\textsuperscript{16}. Specific MHCs that are prevalent in youth\textsuperscript{1} include: ADHD, anxiety disorders, depressive disorders, and psychosis. ADHD is defined by the DSM-V\textsuperscript{6} as, “the persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development”. Anxiety disorders are defined as, “disorders that share features of excessive fear and anxiety and related behavioural disturbances”. Depressive disorders all present with “the common feature of the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function”. Bipolar disorders require a manic episode defined as “distinct periods of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least one week and present part of the day, nearly every day” and is followed or preceded by a depressive episode. Psychotic disorders are broadly defined as “hallucinations, delusions, disorganized speech, abnormal psychomotor behavior, and negative symptoms, as well as dimensional assessments of depression and mania”\textsuperscript{6}.

1.2.1 Prevalence of Mental Health Conditions in Canada

Every year in Canada approximately one in five adults will suffer from a MHC\textsuperscript{1}. Of those adult MHCs, approximately 70\% will begin before the age of 18, either in adolescence or childhood. According to a report published in 2009\textsuperscript{2} by the BC Division of the Canadian Mental Health Association, the most common MHC in children and adolescents is anxiety disorders, with greater than 6\% of youth experiencing some form of an anxiety disorder. Anxiety disorders are followed closely by attention-deficit (hyperactivity) disorder (ADD or ADHD) affecting approximately 5\% of youth, and conduct disorder and depressive disorders affecting

\textsuperscript{1} Youth will be defined as children and adolescents (age < 19 years of age)
approximately 4% of youth. Psychotic disorders may affect approximately 3% of the population, but present more commonly in late adolescence and early adulthood. Bipolar disorder and schizophrenia may manifest later in adolescence and early into adulthood, and affect approximately 0.1% of the population.

The percentage of children with MHCs is comparable to adults and it is currently estimated that 10-20% of Canadian youth are affected by a MHC\(^3\). In BC it is estimated that 15% or 140,000 youth\(^3-5\) are currently suffering from a MHC. This is a substantial proportion of Canadian and British Columbian youth. There are various treatments to aid in relieving symptoms of MHCs and in the following section I will focus specifically on SGA medications.

### 1.3 Second-Generation Antipsychotics

Second-generation or ‘atypical’ antipsychotics are commonly prescribed to individuals diagnosed with a MHC. In the following section I will briefly review the mechanisms of action, prevalence of SGA prescriptions, and SGA side effects.

#### 1.3.1 Second-Generation Antipsychotic Mechanism of Action

Second-generation antipsychotic medications are a heterogeneous class of drugs that were developed to have improved efficacy of action and reduced extrapyramidal side effects\(^{ii}\), specifically when compared to first-generation antipsychotics\(^17\). All antipsychotics (first and second generation) are designed to block dopaminergic pathways. There are four dopaminergic pathways in the human brain, and SGAs are understood to potentially aid in blocking dopamine

\(^{ii}\)Extrapyramidal side effects are motor disorders induced by antipsychotic medications, such as; muscle contractions, restlessness, tremors, and rigidity.
in the mesolimbic\textsuperscript{iii} and mesocortical\textsuperscript{iv} pathways, which are postulated to be dysregulated in many MHCs\textsuperscript{18,19}.

Dopamine is a hormone and neurotransmitter of the catecholamine family and is derived from tyrosine and phenylalanine\textsuperscript{19}. Dopamine functions in the CNS as well in the periphery; however, it does not cross the blood brain barrier, and as such, the synthesis and functions are thought to be separate between the periphery and the brain\textsuperscript{19}. In the brain, dopamine may modulate processes such as emotion, reward, cognition, and memory. Dopamine has five classes of receptors (D\textsubscript{1}, D\textsubscript{2}, D\textsubscript{3}, D\textsubscript{4}, and D\textsubscript{5}) and SGAs work by partially antagonizing the D\textsubscript{2} class receptor\textsuperscript{19,20}. The D\textsubscript{2} class of receptors are highly expressed in the brain, both pre- and post-synaptically, and inhibit adenylyl cyclase\textsuperscript{v} activity\textsuperscript{20}.

Second-generation antipsychotics partially block or ‘occupy’ not only the D\textsubscript{2} receptor (as was the role of first-generation antipsychotics), but also serotonin receptors, on the postsynaptic neuron membrane\textsuperscript{17,21–23}. Serotonin is a ubiquitous neurotransmitter, derived from tryptophan\textsuperscript{17,19}. The highest concentrations of serotonin are found in the gastrointestinal tract, platelets and the central nervous system, and therefore serotonin plays various roles throughout the human body. Of relevance to optimal mental health, the functions in the brain in which serotonin may have a role include: cognition, sleep, temperature regulation, mood, appetite, sexual behavior, and hormone secretion. Serotonin exerts these functions through binding to various receptor types (5-HT receptors). The receptor class of interest to the action of SGAs is the 5-HT\textsubscript{2}\textsuperscript{24}.

\textsuperscript{iii} Mesolimbic pathway is a system in the brain widely recognized as the ‘reward’ pathway. It is a pathway that includes the ventral tegmental area, nucleus accumbens, amygdala, and hippocampus.
\textsuperscript{iv} Mesocorticol pathway is a pathway in the brain that connects the ventral tegmentum to the cerebral cortex and is involved in higher order cognitive functions.
\textsuperscript{v} Adenylyl cyclase is an enzyme that functions in the conversion of ATP to cAMP.
Given that SGAs affect both D₂ and 5-HT₂ receptors, they are referred to as D₂/5-HT₂ partial antagonists. Below is a simplified diagram of how an SGA may work antagonistically on D₂ and 5-HT₂ receptors.

**Figure 1-1 SGA mechanism of action in the brain**

![Diagram of SGA mechanism in the brain](image)

**Presynaptic Neuron**

- Serotonin
- Dopamine

**Postsynaptic Neuron**

- 5-HT₂ receptor
- D₂ receptor
- SGA

*Figure 1-1* depicts serotonin (grey circles) and dopamine (blue squares) being released from the presynaptic neuron into the synaptic cleft. Both neurotransmitters then cross the cleft to their postsynaptic neuron receptors. In this situation, the SGA (red circle and red square) is working as a partial antagonist by occupying a portion of the receptors creating the inability for the neurotransmitter to bind to the postsynaptic neuron, thereby inhibiting their ability to function.

While the main targets of SGAs action are the D₂ and 5-HT₂ receptors, they lack specificity, and each individual SGA may vary in its binding sites as well as the degree of affinity to that binding site. Such binding sites include the histamine and muscarinic receptors. The following table provides an overview of each SGA available in Canada and estimated receptor-binding affinity in the human brain.
Table 1-1 Summary of SGAs available in Canada and their reported binding affinity in the brain

<table>
<thead>
<tr>
<th>SGA</th>
<th>D₂</th>
<th>5-HT₂A</th>
<th>5-HT₂C</th>
<th>H-1</th>
<th>M</th>
</tr>
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<tr>
<td>Aripiprazole#</td>
<td>0.34</td>
<td>3.40</td>
<td>15</td>
<td>61</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Clozapine</td>
<td>210.00</td>
<td>2.59</td>
<td>4.80</td>
<td>3.10</td>
<td>9.00</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20.00</td>
<td>1.48</td>
<td>4.10</td>
<td>0.087</td>
<td>36.00</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>770.00</td>
<td>31.00</td>
<td>3500.00</td>
<td>19.00</td>
<td>1400.00</td>
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<td>Risperidone</td>
<td>3.77</td>
<td>0.15</td>
<td>32.00</td>
<td>5.20</td>
<td>34000.00</td>
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<tr>
<td>Ziprasidone</td>
<td>2.60</td>
<td>0.12</td>
<td>0.90</td>
<td>4.60</td>
<td>2440.00</td>
</tr>
</tbody>
</table>

Receptor classes; D₂: dopamine, 5-HT₂: serotonin, H-1: histamine, M: muscarinic
Data presented as Ki (nM); adapted from Richelson & Souder

Ki = strength of binding affinity of the drug
#Data collected from Abilify® package insert
*Ki values not available.

1.3.2 Prevalence of Second-Generation Antipsychotic Prescriptions in British Columbia to Youth and Adults

Second-generation antipsychotics are becoming increasingly prescribed in BC. According to BC PharmaCare health insurance data “No-Charge Psychiatric Medication Plan” claims rose from 380,000 in 2004/05 to 750,000 in 2012/13 showing a 97% increase in prescription claims for psychiatric drugs. Further, in 2012-2013, BC PharmaCare data for adults and children indicated that quetiapine was the fifth most reimbursed medication, with $19 million reimbursed, only behind infliximab, adalimumab, etanercept (all for Rheumatoid arthritis, Crohn's disease and Psoriasis), methadone (an opioid for pain and addiction), and atorvastatin (a cholesterol lowering medication).
In the past decade, a dramatic increase in SGA prescriptions to BC youth alone has been reported. A recent study using BC Ministry of Health administrative data by Ronsley et al (2013), found that the number of SGA prescriptions rose from 315 in 1996/7 to 5432 in 2010/11, which is an 18.1-fold increase\(^7\). Second-generation antipsychotics comprised 96.1\% of all antipsychotics prescribed to youth in 2010/11\(^7\). The breakdown of SGAs prescribed include: 48\% risperidone, 36.2\% quetiapine, 5.9\% olanzapine, 3\% aripiprazole, 1.4\% clozapine, 1.1\% ziprasidone, and 0.5\% paliperidone\(^7\). Concurrent with this rise of SGA prescriptions, emerging evidence is indicating that weight gain and cardiometabolic side effects are becoming increasingly common in SGA-treated youth\(^8-11,27-31\).

1.3.3 Second-Generation Antipsychotic Use and Associations with Weight Gain and Cardiometabolic Health

As stated previously, SGAs were originally designed to reduce extrapyramidal side effects and to improve efficacy of action. However, it has been widely observed that SGAs can cause rapid weight gain and cardiometabolic dysfunction in both the adult\(^27\) and the pediatric populations\(^8-11,27-29\). This section will highlight key findings regarding weight gain and metabolic abnormalities associated with SGA use in the pediatric population.

SGA Treatment in Youth Compared to Adults

It has been suggested that children treated with olanzapine or risperidone are more susceptible to weight gain compared to adults\(^10,30\). A 2012 meta-analysis by Kryzhanovskaya et al, analyzed the effects of olanzapine in adolescents (13-17 years) and adults (>18 years) and reported that the mean weight gain from baseline to endpoint (at least 24 weeks) was 11.2 kg (95\% CI: 10.1, 12.4) for adolescents (n=179) compared (p<0.05) with 4.8 kg (95\% CI: 4.6, 5.0) in adults (n=4,280). There were no differences between adolescents and adults regarding changes
in blood lipids and glucose; however, both groups showed an increase in mean fasting blood glucose, total cholesterol, LDL-c, and triglycerides (TGs). Similarly, a 2004 meta-analysis evaluating age-specific risperidone-induced weight gain found that percent of baseline body weight increased across all ages and weeks of treatment (4-8 weeks vs. 9-16 weeks vs. 17-56 weeks). Children aged 5-11 years (n=594) had the greatest percent body weight gain across all treatment durations (5.6% vs. 7.4% vs. 16.3%, respectively), followed by adolescents aged 12-17 years (n=292) (4.1% vs. 6.3% vs. 8.1%, respectively), after controlling for growth. Adults aged 33-44 years (n=1,528) showed a smaller percent body weight gain (2.1% vs. 2.9% vs. 3.4%, respectively), and older adults aged 71-83 years (n=252) showed the lowest percent body weight gain (0.5% vs. 0.2% vs. 0.3%, respectively). These two meta-analyses provide compelling evidence of greater and more rapid olanzapine- and risperidone-induced weight gain in the pediatric population compared to the adult population.

First Time SGA Use in Youth

First time SGA use in the pediatric population can also cause severe and rapid weight gain, which is greater than that observed in children with previous SGA exposure. A 2009 observational study of the effects of first time SGA treatment in 205 children and adolescents treated with aripiprazole, olanzapine, quetiapine, or risperidone reported significant weight gain for all medications (median treatment duration of 10.8 weeks). Children treated with olanzapine had the greatest increase in weight, with an average of 8.5 kg, followed by quetiapine (6.1 kg), risperidone (5.3 kg), and aripiprazole (4.4 kg). Additionally, all SGA-treated children had increases in fasting blood glucose, insulin, total cholesterol, LDL-c, and TGs (with the exception of aripiprazole, which was associated with a decrease in TGs). Furthermore, a meta-analysis of 21 double blind randomized controlled trials in youth (≤18 years), evaluating first time SGA
treatment versus a placebo for 4-26 week duration, reported that SGA treatment was associated (p<0.05) with weight gain. Olanzapine treatment was associated with the greatest average weight gain (3.45 kg), followed by risperidone (1.77 kg gained), and aripiprazole (0.94 kg gained).\(^{32}\)

**SGA Treatment of Children in British Columbia**

In BC, three cross-sectional studies by Panagiotopoulos et al (2009, 2012) and Devlin et al (2012) have investigated zBMI and cardiometabolic abnormalities in SGA-treated youth\(^8,11,31\). The 2009 retrospective chart review analyzed zBMI and fasting glucose and reported SGA-treated children (n=68) to have a greater zBMI compared to SGA-naïve children with MHCs (n=99) (1.06 vs. 0.25; 95% CI: 0.46, 1.16; p<0.01). Further, a greater (p=0.01) proportion of SGA-treated children had elevated fasting glucose (21.5%) compared to SGA-naïve children (7.5%). The 2012 study sought to determine the cross-sectional prevalence of Metabolic Syndrome (MetS\(^vi\)) in the SGA-treated pediatric population. The overall observed MetS prevalence was 19.0% for the SGA-treated group (n=84) and 0.8% for the SGA-naïve group (n=127) (OR 29.7; 95% CI: 3.85, 228.40; p<0.001). Using logistic regression the authors discerned that the greatest association with MetS was SGA treatment (OR 19.2; p=0.006). Moreover, Panagiotopoulos et al (2012) also observed 50.5% and 23.6% prevalence of overweight and obesity for SGA-treated and SGA-naïve participants, respectively (OR: 3.3; 95% CI: 1.97, 5.52; p<0.001) and a greater prevalence of elevated waist circumference in SGA-treated compared to SGA-naïve participants (40.7% vs. 10.1%; OR: 6.1; 95% CI: 3.09, 12.17, p<0.001). SGA-treated participants also had a greater observed prevalence (p<0.05) for

\(^{vi}\) MetS (metabolic syndrome): the pediatric clinical definition is having ≥ three of the following; WC ≥90\(^{th}\) percentile, SBP or DBP ≥90\(^{th}\) percentile, TG ≥1.24mmol/L, HDL-C ≤1.03mmol/L or fasting glucose ≥5.6mmol/L.\(^{13,52,65}\)
hypertriglyceridemia, elevated fasting glucose, and elevated blood pressure. Furthermore, Devlin et al (2012) observed a greater zBMI (1.01 vs. 0.73; p=0.038), as well as a greater prevalence of elevated waist circumference (37.1% vs. 25.0%; p=0.037) for SGA-treated participants compared to SGA-naïve, respectively. Moreover, a MetS rate of 15.6% and 2.1% was observed for SGA-treated and SGA-naïve participants, respectively (p=0.001). Individual components of MetS were reported and SGA-treated youth had higher prevalence of elevated blood pressure (25.0% vs. 14.4%; p=0.042), elevated fasting glucose, insulin, total cholesterol, and LDL-c (p<0.05). The following table summarizes the three cross-sectional studies performed in BC.

**Table 1-2 Summary of adiposity and cardiometabolic dysfunction in SGA-treated children in British Columbia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Main Findings</th>
</tr>
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| Panagiotopoulos et al (2009) | SGA-treated n=68 SGA-naïve n=99 | • 57% SGA-treated vs. 23% SGA-naïve overweight or obese  
• Elevated fasting glucose prevalence: SGA-treated (n=65) = 21.5%, SGA-naïve (n=80) = 7.5% (p=0.01) |
| Panagiotopoulos et al (2012) | SGA-treated n=104 SGA-naïve n=182 | • SGA-treated had greater prevalence of overweight and obesity as well as elevated waist circumference (p<0.001)  
• MetS prevalence: SGA-treated (n=84): 19.0% vs. SGA-naïve (n=127): 0.8% (p<0.001)  
• SGA treatment had the greatest association with MetS (OR 19.2, p=0.006). |
| Devlin et al (2012)  | SGA-treated n=105 SGA-naïve n=112 | • SGA-treated had greater zBMI (p=0.038) and greater prevalence of elevated waist circumference (p=0.037)  
• MetS prevalence: SGA-treated: 15.6% vs. SGA-naïve: 2.1% (p=0.001)  
• SGA-treated had higher prevalence of elevated blood pressure (p=0.042) and higher elevated fasting glucose, insulin, total cholesterol and LDL-c (p<0.05) |

Adapted from Panagiotopoulos et al (2009, 2012) and Devlin et al (2012)\(^{8,11,31}\)  
SGA-treated: participants with MHCs treated with SGAs; SGA-naïve: participants with MHCs not treated with SGAs
Long term SGA use

Data supporting short duration SGA-induced weight gain and cardiometabolic dysfunction in the pediatric population is convincingly clear; however, there is little long-term data (> 1 year) regarding continuous SGA use with weight gain and cardiometabolic side effects in the pediatric population. A systematic review by Martinez-Ortega et al (2013) analyzed weight gain and BMI in children and adolescents treated with SGAs. The final review included 14 literature reviews, 71 intervention trials and 42 observational studies, with very few studies examining long-term exposure to SGAs. Of those long-term studies many had very small sample sizes (n < 15), high dropout rates, or only studied one type of SGA. One study by Fleischhaker et al (2008) assessed the long-term effects of clozapine (n=15), olanzapine (n=8), and risperidone (n=10) on weight gain in children and adolescents (9 females, 24 males) over 45 weeks of treatment. They reported increases in zBMI scores over the 45 weeks of treatment, with olanzapine showing the greatest increase, followed by clozapine and risperidone. The groups treated with clozapine and olanzapine exhibited a steady increase with no plateau in zBMI over the treatment period, but risperidone plateaued between weeks 25 and 29. The lack of data regarding the long-term effects of SGAs in the pediatric population makes it difficult to elucidate the mechanisms underlying the weight gain and cardiometabolic side effect and how these progress over time.

1.4 Obesity and Cardiometabolic Dysfunction in Children and Adolescents

In the following section I will briefly define and describe the adverse health consequences of obesity and cardiometabolic dysfunction in children and adolescents.
1.4.1 Obesity

Obesity in youth is a growing problem worldwide and in Canada\textsuperscript{42,43}. In 2008, the WHO estimated that 35\% of the world’s population was overweight and 11\% was obese\textsuperscript{42}. Furthermore, a 2011 report using data from the 2009 Canadian Community Health Measures Survey estimated that 8.6\% of Canadian children (6-17 years) were obese\textsuperscript{43}. In their 2014 article on global, regional, and national prevalence, Ng \textit{et al} reported an estimated 23.5\% rate of overweight and obesity in Canadian children\textsuperscript{44}. Since 1980, there has been a surge in the obesity epidemic and it is difficult to elucidate the exact reason for this occurrence. Likely it is due to a variety of factors that vary among individuals. Factors that may contribute to the development of overweight and obesity include: physiological, environmental, social, cultural, genetic, medical illnesses, and medication-induced contributions\textsuperscript{43}. The focus of this thesis is on medication-induced overweight or obesity, which may also be paired with environmental, physiological, genetic, and/or medical illness contributions.

\textit{Obesity Classification}

The classification of overweight and obesity in youth is different than in adults due to normal growth of children and adolescents. Body mass index (BMI) is a common method of classifying obesity and is calculated by dividing an individual’s weight in kilograms by their height in metres squared (kg/m\textsuperscript{2}). In adults, the WHO defines overweight as a BMI of 25.0 kg/m\textsuperscript{2} to 29.9 kg/m\textsuperscript{2} and obese as a BMI $\geq$ 30.0 kg/m\textsuperscript{2}; however, due to normal growth these numerical cut-offs cannot be universally applied to define overweight and obesity in the pediatric population\textsuperscript{12,42}. Therefore BMI percentiles and BMI z-scores (zBMI) are specified based on WHO or Center for Disease Control (CDC) growth charts for age and sex\textsuperscript{12,45}. The child’s BMI is calculated and then compared to growth charts for age and sex and given a score or a deviation
from what is healthy for their age group and sex. In youth, overweight is between the 85th and 94.9th percentile or a z-score between 1.04 and 1.64, and obese is defined as greater than or equal to the 95th percentile or greater than or equal to a z-score of 1.64. 

While BMI is a quick and relatively effective measure to assess weight as a function of height, it does not capture an individual’s body composition. Body mass index does not take into account the type of tissue that is contributing to the weight. Lean tissue, such as muscle, weighs more than fat tissue due to higher density; yet it is a metabolically active and healthy tissue. An individual with a large amount of lean tissue may have a BMI greater than 25 kg/m² but still be healthy, whereas an individual with a similar BMI may have limited lean tissue with more fat tissue and therefore be more at risk. There are many other ways to determine adiposity and body fat distribution such as skin-fold measurements, bioelectrical impedance analysis (BIA), and dual-energy x-ray absorptiometry (DEXA). These methods are often costly and time consuming, therefore waist circumference is often used as a validated and simple method of measuring adiposity. Waist circumference measures ‘abdominal’ or central adiposity, which can be used to help determine the more pathological distribution of adiposity. Specific cutoffs have been determined for age, sex, and ethnicity groups. Moreover, waist circumference is a better predictor than BMI of cardiovascular and cardiometabolic disturbances. Furthermore, there have been many reports of central adiposity being more of a risk than subcutaneous or gynoid adiposity.

Health Risks of Obesity

Excess adiposity alone, confers a risk of further complications such as musculoskeletal disorders, high blood pressure, insulin resistance, type 2 diabetes, and CVD. Having excess
adiposity in childhood may confer risks later in life such as obesity as an adult, increased risk of CVD, and premature death\textsuperscript{42,64}.

1.4.2 Cardiometabolic Dysfunction

Cardiometabolic dysfunction is defined as risk factors that may lead to CVD and/or type 2 diabetes. Examples of markers of cardiometabolic dysfunction in youth include: obesity; elevated plasma TGs, total cholesterol and LDL-c; low HDL-c; elevated fasting glucose; insulin resistance; and diastolic and systolic blood pressure $\geq 90^{th}$ percentile for age, sex and height\textsuperscript{13}. Another common term used for cardiometabolic complications is metabolic syndrome (MetS), which is a clinical classification of a constellation of clinical measures. In children, classification of MetS is based on the presence of any three of the following components: waist circumference $\geq 90$th percentile for age and sex; fasting glucose $\geq 5.6$ mmol/L; plasma TGs $\geq 1.24$ mmol/L; plasma HDL-c $\leq 1.03$ mmol/L; and systolic or diastolic blood pressure $\geq 90$th percentile for age, sex and height\textsuperscript{13,52,65}. However, any one of the components of cardiometabolic dysfunction may confer risk for CVD\textsuperscript{66}, especially if developed in childhood.

Elevated fasting plasma glucose is associated with an increased risk of CVD and mortality\textsuperscript{67,68}. Fasting blood lipids include TGs and total cholesterol as well as its components: LDL-c and HDL-c, all of which have been implicated in the development of CVD\textsuperscript{69,70}. Due to the role of TGs in lipid metabolism, increased TG levels have been implicated in the development of atherosclerosis and CVD\textsuperscript{71–74}. Elevated LDL-c may confer a risk for CVD, myocardial infarction, and even death\textsuperscript{75}. Conversely, a low HDL-c may increase the risk of CVD\textsuperscript{76,77}. In adults, healthy blood pressure is $<120/80$ mm Hg, elevated blood pressure or ‘prehypertension’ is between 120-139/80-89 mm Hg and hypertension is defined as $\geq140/90$ mm Hg\textsuperscript{78}. In children, blood pressure $z$-scores (zSBP and zDBP) standardized for age, sex, and height
percentiles are calculated. Elevated blood pressure is defined as ≥90th percentile and hypertension is defined as ≥95th percentile\textsuperscript{79}. Prehypertension and hypertension are both well established as risk factors for CVD and all-cause mortality\textsuperscript{78,80,81}.

1.5 Dietary Intake

1.5.1 Dietary Intake and Obesity and Cardiometabolic Dysfunction

\textit{Dietary Intake and Obesity}

Energy homeostasis is the balance of energy intake versus energy output. Dietary energy intake plays a significant role in the balance of this homeostasis and the management of body weight. An increased energy intake with no change in energy output may cause an increase in weight, as excess energy is stored as adipose tissue, which in turn may lead to obesity\textsuperscript{82,83}. Obesity is an independent risk factor for cardiometabolic dysfunction and CVD\textsuperscript{63}, but individual dietary components, apart from total energy intake, may also play a role in the development of cardiometabolic dysfunction and CVD.

\textit{Dietary Intake and Cardiometabolic Dysfunction}

As diet can impact weight and adiposity, it can also impact our cardiovascular and metabolic systems. This is a complicated and vast area and I will touch briefly on key nutrients and their associations with cardiometabolic dysfunction.

There have been many reports of positive associations between total dietary intakes of saturated fat and serum total cholesterol and LDL-c concentrations\textsuperscript{84,85}. Furthermore, it has been reported that reducing total dietary fat and saturated fat intakes lowers plasma total cholesterol and LDL-c\textsuperscript{86,87}. Dietary fibre (specifically viscous soluble fibre) has been indicated to have a protective effect in the development of CVD as it reduces total and LDL cholesterol, as well as
reduces fasting blood glucose\textsuperscript{88-91}. Furthermore, high dietary fibre intake has also been associated with a lower HOMA-IR\textsuperscript{92,93}. The association of high sodium intake and high blood pressure, as well as its association with CVD events, is well documented\textsuperscript{94-96}. Reducing dietary sodium intake may aid in lowering blood pressure, but other components of the diet may also have a role in blood pressure reduction. Studies have reported reducing carbohydrate intake by replacing it with protein\textsuperscript{97-99} as well as implementing the Dietary Approaches to Stop Hypertension (DASH) diet\textsuperscript{100} as successful approaches in lowering blood pressure.

### 1.5.2 Dietary Intake and SGA treatment

There are anecdotal suggestions that SGAs may lead to increased dietary energy consumption; however, there is very little scientific evidence regarding dietary intakes in individuals with MHCs treated with SGAs, especially in the pediatric population. SGAs are D\textsubscript{2} and 5-HT\textsubscript{2} receptor antagonists; however, they lack specificity, and therefore, may also have varying affinities to numerous neurotransmitter receptors, including histamine and muscarinic receptors (Table 1-1)\textsuperscript{22,101}. Serotonin, dopamine, and histamine have been implicated in the regulation of food intake. The serotoninergic system is involved in the neural and peripheral regulation of food intake and satiety\textsuperscript{102,103}, and dopamine has been implicated in the motivation and reward system of food intake\textsuperscript{104}. Furthermore, the histamine system exerts its effects on various receptors\textsuperscript{105}, the H\textsubscript{1} receptor being of interest to SGA antagonism\textsuperscript{106}. The H\textsubscript{1} receptors in the central nervous system are expressed throughout the brain\textsuperscript{105} and have been implicated in appetite regulation\textsuperscript{107}. Additionally, the muscarinic receptor may be involved in glucose homeostasis\textsuperscript{108}. There are many subclasses of the muscarinic receptor and the M\textsubscript{3} receptor subclass has been indicated to be involved in insulin release and blood glucose homeostasis, due to its binding of the neurotransmitter acetylcholine in the peripheral parasympathetic nervous
system. At the onset of food ingestion, acetylcholine is released by intra-pancreatic vagal nerve endings and binds to the M₃ receptor. This binding of acetylcholine to M₃ receptors in pancreatic β-cells elicits an insulin releasing response. Given that SGAs have an affinity for M₃ receptors, one postulation is that peripheral binding of SGAs to M₃ receptors may cause an increase in insulin secretion.

Cuerda et al (2014) reviewed the literature for studies regarding SGAs and their effects on food intake, resting energy expenditure, and physical activity. The authors located ten studies that evaluated food intake and/or appetite; of which only one assessed adolescents. This study only involved 10 inpatient male adolescents with schizophrenia (mean age = 17 years) at baseline and after four weeks of olanzapine treatment. Body mass index and waist circumference both increased significantly (p<0.05) over four weeks. Total energy intake also increased by an average of 27.7% (p=0.03) or 589kcal/day from baseline to four weeks; however, macronutrient composition did not change. No changes in resting energy expenditure (REE) (measured by indirect calorimeter) and energy expenditure (measured by mobile accelerometers and heart rate monitors) were observed.

Studies in the adults have reported conflicting results on the effects of SGAs on dietary energy intakes. Several studies used volunteers with no MHCs, hospitalized them for two weeks, and treated them with an SGA or a placebo. Two of these studies in subjects without MHCs, reported increased energy intakes with SGA treatment compared to a placebo, but no differences in macronutrient composition. One study observed no difference in energy intakes or hunger rating scales with SGA treatment. However, the duration of these studies may not be long enough for SGA-related cardiometabolic side effects to develop and SGA treatment in healthy individuals may differ from individuals with a MHC. Of the studies in adults...
with MHCs, only one collected 24-hour dietary records\textsuperscript{114}. This study collected four 24-hour dietary records from adults treated for at least one year with clozapine (n=31) or risperidone (n=15). Although results indicated no differences in overall energy intake between drug treatment groups, macronutrient intake differed; specifically, the clozapine treated group had a greater percent fat and saturated fat intake (p=0.007) and a lower percent of carbohydrate (p=0.009) and protein (p=0.036) intake compared to the risperidone group.

1.5.3 Dietary Data Collection

There is no gold standard for assessing dietary intakes. Diet is an ever changing, diverse, and fluid part of daily lives that makes it difficult to assess. This section will touch on estimated dietary records and their limitations.

1.5.3.1 Dietary Data Collection from Individuals

There are various methods of dietary data collection, including: food frequency questionnaires, 24-hour recalls, diet history, and estimated and weighed food records\textsuperscript{115}. A seven-day weighed food record is often considered the most appropriate way to capture an individual’s usual intake by reducing the day to day within-subject variability\textsuperscript{115}. This technique requires the individual to weigh all food and beverages over a 24-hour period on seven different days. The seven-day weighed food record is clearly labour-intensive and has a high respondent burden. Therefore, fewer days are commonly collected or other methods are employed. Another method to capture individual intake is the 24-hour estimated food record method, whereby the individual records all food and beverages consumed in a 24-hour period, usually from the time of waking until the following morning\textsuperscript{115,116}. While similar to the weighed food record, intake is estimated based on household measurements, rather than weighed, and it can also be repeated.
over multiple days in order to capture within-subject variability\textsuperscript{117}. The estimated food record is less burdensome on the individual and doesn’t rely on memory like the 24-hour recall method\textsuperscript{118}. All of these dietary data collection methods have limitations. In the following section I will address the potential limitations of the estimated food record method.

1.5.3.2 Limitations of Estimated Food Records

Respondent Bias

Respondent bias such as underreporting, over reporting, misreporting, or alteration of diet, whether intentional or unintentional, are all issues regarding estimated food records\textsuperscript{115,119,120}. Underreporting is the failure to record all foods eaten in the period being recorded and can be influenced by weight, specific foods and beverages, age, and sex. Over reporting, while a lesser concern, is a potential limitation and often occurs in the context of social desirability bias\textsuperscript{vii}. Alteration of diet during recording of estimated food records is a major concern, such that the individual changes their eating habits during the days they are recording\textsuperscript{118}.

Interviewer Bias

Different interviewers may employ different approaches to collecting and filling in missing data and information for estimated food records. The degree of probing, rapport with the individual being interviewed, and recording of responses may all be part of interviewer bias. This inter-interviewer variability may affect the dietary data collected. In order to reduce this bias, using one interviewer for all participants is preferred. Further, using a standardized interviewing protocol also aids in reducing this bias.

\textsuperscript{vii} Social desirability bias is the inclination of individuals to alter answers to appear more favourable, often by over reporting ‘good’ behaviour and underreporting ‘bad’ behaviour.
**Incorrect Estimation of Portions**

Estimating sizes, weights, and portions is inherently difficult even for trained individuals. Incorrect estimation of food eaten, as well as incorrect estimation of weights and measures used in recipes and mixed dishes, are limitations of estimated food records. Food models, measuring instruments, as well as pictures of common food items and sizes, can all be used to aid in reducing the error in estimating food portions.

**Children and Dietary Records**

While assessing diet in children and adolescents is possible, many challenges may arise\(^{121–123}\). Often children have trouble estimating weights and measures, lack knowledge of food preparation and components of mixed dishes, and may lack interest in recording in general. It is suggested that from the age of 8 and beyond, children and youth have the ability to record their food intake\(^{124}\). Before the age of 8 (or even after) a proxy such as a parent or guardian is a good alternative to complete the food records in lieu of or along with the child\(^{124,125}\).

Crawford *et al* (1994) determined the three-day weighed food record to be the most accurate recording method, in 9 and 10 year old females, for the degree of correlation between the observed and reported intake at one specific meal, when compared to the 24-hour recall method and the five-day food frequency questionnaire\(^{126}\). However, there have been various validation studies done in children using doubly labeled water\(^{\text{viii}}\) in comparison with estimated food records that have indicate consistent underreporting\(^{127–129}\).

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\(^{\text{viii}}\) Doubly labeled water is a method to measure an individual’s total energy expenditure over multiple days or weeks.
1.6 Genetic Variants and Obesity

Due to the varying degree of weight gain, adiposity, and development of cardiometabolic dysfunction among individuals treated with SGAs, one conjecture is that underlying individual factors, such as genetic variants, may play a role in weight gain.

Single gene variants can cause rare heritable forms of obesity. However, the majority of obesity most likely involves multiple genetic factors and their interaction with environment. Several genetic variants have been identified that may place an individual at risk for obesity. The two gene variants that I will focus on are the fat mass and obesity gene (FTO) rs9939609 variant and the melanocortin 4 receptor gene (MC4R) rs17782313 variant.

1.6.1 FTO rs9939609 Variant

Genome wide association studies (GWAs) have identified FTO variants that are associated with BMI in adults and children. The AA genotype of the FTO rs9939609 variant was reported to be associated with a 1.38 odds of being overweight and a 1.67 odds of being obese compared to individuals with the TT genotype. This was conducted in 13 cohorts of adults (28-74 years) and children (7-14 years) with European ethnicity, totaling 38,759 participants. Furthermore, it has also been demonstrated that children with the AT and AA genotype had greater fat mass but not greater lean mass when evaluating body composition using skin fold measurements and DEXA. Perez-Iglesias et al (2010) sought to determine any association that may be present between the FTO rs9939609 variant and SGA-induced weight gain. From baseline to one year follow up, in 165 adult participants experiencing first episode psychosis, no differences in weight gain were observed between FTO rs9939609 genotypes.
**FTO** is expressed ubiquitously, with its highest expression in the hypothalamus\(^\text{136}\). Given its expression in the hypothalamus, current theories suggest that it may play a role in the regulation of food intake and as such, may affect energy homeostasis. Studies in children and adults have reported significantly greater energy intake and reduced satiety for those with the **FTO** rs9939609 AT and AA genotypes compared to individuals with the TT genotype, but reported no differences in energy expenditure\(^\text{130,133,135–141}\).

### 1.6.2 **MC4R** rs17782313 Variant

The **MC4R** gene is expressed in the hypothalamus of the human brain and it functions to bind the \(\alpha\)-melanocyte stimulating hormone (\(\alpha\)-MSH)\(^\text{142,143}\). When \(\alpha\)-MSH is bound to its receptor, an anorexigenic\(^\text{ix}\) signal is induced. Deletions in **MC4R** gene underlie the most common forms of monogenic obesity\(^\text{144,145}\). Genome wide association studies have revealed that after the **FTO** rs9939609 variant, the **MC4R** rs17782313 variant is reported to have the next strongest association with obesity in 16,785 European individuals\(^\text{132,136}\). In order to replicate these findings, a meta-analysis across 77,228 European adults and 10,583 children (7-11 years) was performed\(^\text{132}\). This analyses observed that adults with the CT or CC genotype of **MC4R** rs17782313 had a 0.05 increase in \(\log_{10}\) BMI units per C allele when compared to individuals with the TT genotype\(^\text{132}\). In children, it was observed that there was a 1.30 (per C allele) increased odds of being obese compared to healthy weight\(^\text{132}\). This same variant has also been implicated in SGA-induced weight gain in adults. Czerwensky *et al* (2013) demonstrated that SGA-induced weight gain was significantly greater after four weeks of treatment in individuals

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\(^\text{ix}\) anorexigenic: causing the loss of appetite.
with the CT and CC \textit{MC4R} rs17782313 genotypes compared to individuals with the TT genotype\textsuperscript{131}.

Due to the mechanism of action of \textit{MC4R} and \(\alpha\)-MSH, one postulation is that obesity may result from increased energy intake. Studies have reported that individuals with CT and CC genotypes for \textit{MC4R} rs17782313 have greater self-reported snacking, overeating, and food cravings\textsuperscript{146–148}. One study observed significant trends towards increased snacking in obese European children (n=1004; p=0.01), adults (n=1274; p=0.04), and adolescents (n=5612; p=0.04)\textsuperscript{147}. Furthermore, one study in 323 adults observed significantly (p<0.05) higher emotional eating scores and higher food craving questionnaire scores in individuals with CT and CC genotype compared to individuals with the TT genotype for \textit{MC4R} rs17782313\textsuperscript{146}. Moreover, one study in 5724 adult females (85.9\% postmenopausal) observed that those with the CC genotype for \textit{MC4R} rs17782313 had a greater total energy intake (p=0.028) as well as greater fat (p=0.008) and protein (p=0.003) intakes when compared to women with the TT genotype\textsuperscript{148}.

Based on this background, the \textit{FTO} rs9939609 and \textit{MC4R} rs17782313 variants may place an individual at risk for SGA-related weight gain and cardiometabolic side effects.
Chapter 2: Study Rationale

Recent evidence suggests that SGA use causes severe and rapid weight gain, increased measures of adiposity, as well as cardiometabolic dysfunction in the pediatric population. Interestingly, these side effects are not observed in all SGA-treated children, and the mechanisms predisposing certain individuals have yet to be elucidated. Second-generation antipsychotics antagonize D₂ and 5-HT₂ receptors and have a potential affinity for antagonism to histamine and muscarinic receptors. These neurotransmitters are implicated in the regulation of dietary intake and satiety, and therefore, it is postulated that SGA-treatment may cause an increase in dietary energy intakes. This increased energy intake may in part be responsible for the weight gain and cardiometabolic dysfunction observed in the SGA-treated population; however, little is known regarding dietary energy intakes in children with mental health conditions. Therefore, I hypothesize that SGA-treated children with mental health conditions have greater dietary energy intakes, and that this is associated with greater adiposity and cardiometabolic dysfunction compared to SGA-naïve children with mental health conditions.

My hypothesis will be addressed by three Specific Aims: [1] to determine total dietary energy and macronutrient intakes in SGA-treated and SGA naïve children; [2] to determine the association of dietary energy intake with adiposity and cardiometabolic dysfunction in SGA-treated and SGA-naïve children; and [3] to determine if FTO rs9939609 and MC4R rs17782313 variants are associated with differences in dietary energy and macronutrient intakes in SGA-naïve and SGA-treated children.

**Specific Aim 1:** To determine total dietary energy and macronutrient intakes in SGA-treated and SGA naïve children
**Specific Aim 1A:**
To determine differences in total dietary energy and macronutrient intakes between SGA-treated and SGA-naïve children.

**Specific Aim 1B:**
To assess sodium, saturated fat, fibre, and simple sugar intakes in SGA-treated and SGA-naïve children and to determine differences between groups.

**Specific Aim 2:** To determine the association of dietary energy intake with adiposity and cardiometabolic dysfunction in SGA-treated and SGA-naïve children.

**Specific Aim 2A:**
To assess and compare adiposity and cardiometabolic dysfunction in SGA-treated and SGA-naïve children.

**Specific Aim 2B:**
To examine the association of dietary energy intake with zBMI, waist circumference, and cardiometabolic dysfunction in both groups.

**Specific Aim 2C:**
To examine the association of dietary components and cardiometabolic dysfunction in both groups.

**Specific Aim 3:** To determine if FTO rs9939609 and MC4R rs17782313 variants are associated with differences in dietary energy and macronutrient intakes in SGA-treated and SGA-naïve children.
Chapter 3: Methods

3.1 Study Design

This was a cross-sectional study designed to assess dietary energy intakes in children with MHCs. This study took place at the inpatient and outpatient psychiatric units at BC Children’s Hospital (BCCH) and at the Child & Family Research Institute in Vancouver, BC, Canada.

3.2 Study Participants

The study sample size was chosen based on Specific Aim 1. The following equation was used to determine an adequate sample size based on a clinically relevant difference in energy intake (kcal) between the SGA-treated and SGA-naïve groups.

\[
\text{Sample size: } n = \left[ \frac{(Z_{\alpha/2} + Z_\beta)(\bar{\sigma})}{(\mu_1 - \mu_0)} \right]^2
\]

In order to determine a difference in total energy (kcal) of 400 kcal between groups, with a standard deviation of 500 kcal and an alpha of 0.05 with a power of 80%, a sample size of 50 participants, 25 SGA-treated and 25 SGA-naïve, was required.

Participants were actively recruited by a research assistant at the inpatient and outpatient psychiatric units at BCCH between August 1, 2012 and August 31, 2014. Hospital medical charts were accessed prior to approaching the participant to deem if they were eligible for the study (eligibility is defined in section 3.4.1). If eligible, participants’ legal guardians were approached by a research assistant about their interest in participating in the research study.
3.2.1 Inclusion and Exclusion Criteria

Males and females between the ages of 6 and 18 years, diagnosed with one or more MHCs (by a board certified psychiatrist) at the time of consent were eligible to participate. Participants were eligible for the study if they were treated with an SGA for equal to or greater than four weeks (SGA-treated) or were not currently treated with an SGA (SGA-naïve).

Exclusion criteria for both groups included: previous treatment with an SGA greater than one week followed by discontinuation of the SGA for greater than one week, a genetic disorder (eg Prader-Willi syndrome), a pre-existing endocrine disorder (eg type 1 or type 2 diabetes), a current or previously diagnosed eating disorder, and current or previous use of medications identified to induce weight gain (eg glucocorticoids).

3.3 Demographic Characteristics

At the time of consent and assent (Appendix A), participants’ self-reported demographic information was collected (Appendix B) and included: sex, ethnicity, family medical history, smoking status, approximate daily hours of screen time, and physical activity (Appendix C). Pubertal status was assessed using the self-reported Assessment of Adolescent’s Puberty Development (Tanner Staging) Form (Appendix D).

After informed consent and assent (where applicable) were obtained, medical charts were reviewed to obtain participants’ date of birth, medication history, including dose and duration of medication use (Appendix B). Medical charts were also accessed to obtain MHC diagnosis and severity. A BCCH board certified psychiatrist using the Multiaxial DSM-IV-TR\textsuperscript{149} and the DSM-V\textsuperscript{6} completed the MHC diagnoses.
3.4 Anthropometric Assessments

Nursing staff in the inpatient psychiatry unit at BCCH collected anthropometric data for all inpatient participants. I measured height, weight, and waist circumference for outpatient participants, and a trained echocardiography technician measured outpatient diastolic and systolic blood pressure (Appendix B).

Height was taken to the nearest 0.1 cm using a Seca 240 Stadiometer (Hamburg, Germany); weight to the nearest 0.1 kg using a Tronix Scale, model 5002 (White Plains, NY, USA); and waist circumference was taken to the nearest 0.5 cm using a non-elastic flexible tape measure at the umbilicus\textsuperscript{150,151}; all of which were an average of two readings.

BMI was calculated and standardized based on the United States CDC growth chart data for age and sex\textsuperscript{45} giving each participant a zBMI. For children, the following classifications are used to define weight categories:

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentile</th>
<th>zBMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy weight</td>
<td>&lt; 85\textsuperscript{th}</td>
<td>&lt; 1.04</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥ 85\textsuperscript{th} and &lt; 95\textsuperscript{th}</td>
<td>≥ 1.04 and &lt; 1.64</td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 95\textsuperscript{th}</td>
<td>≥ 1.64</td>
</tr>
</tbody>
</table>

Based on the CDC growth charts\textsuperscript{45}

Systolic and diastolic blood pressure was taken after the child had been in the supine or seated position for five minutes and accomplished using a Dinamap automated monitor (PRO 100–400, GE Medical Systems, Waukesha, WI, USA) and an appropriately sized cuff for the child. The average of three readings was recorded in mm Hg. Systolic and diastolic blood pressure z-scores (zDBP and zSBP) and percentiles were calculated (standardized for age, sex,
and height percentile) using the National High Blood Pressure Education Program Working
Group data for the Detection, Evaluation and Treatment of High Blood Pressure in Children and
Adolescents\textsuperscript{79}. The following table defines blood pressure categories for children (1-17 years):

Table 3-2 Blood pressure categories for children

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 90\textsuperscript{th} for systolic or diastolic</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>$\geq 90\textsuperscript{th}$ and &lt; 95\textsuperscript{th} for systolic or diastolic</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$\geq 95\textsuperscript{th}$ for systolic or diastolic</td>
</tr>
</tbody>
</table>

Based on the guidelines set by the National Blood Pressure Education Program Working Group\textsuperscript{79}

3.5 Dietary Assessments

3.5.1 Dietary Data Collection

To assess dietary intakes, three 24-hour estimated food records were collected on three
separate days (Appendix E). Inpatient participants recorded their intake themselves if they had
the ability to do so, if not, a trained staff recorded as a proxy. Hospital menus were used to aid in
recording. Outpatient participants also recorded their intake themselves if they had the ability to
do so, if not, their parent/guardian recorded as a proxy. The following day I spoke to the
participant or the proxy to confirm all items consumed. Kitchen recipes, measures, portion sizes,
and brands (where applicable) were recorded to be used for analyses.

3.5.2 Dietary Analysis

Participants’ three 24-hour estimated food records were analyzed using the Food
Processor Nutrition Software by ESHA Research\textsuperscript{TM} (Salem, OR, USA). When possible the
Canadian Nutrient File was selected, and if an item was not available in the Canadian Nutrient
File, the United States Department of Agriculture Nutrient Database was selected. If the item
was not searchable, the recipe was entered or nutritional information was obtained from the
package and input into the database. Each individual day as well as the three-day average of the
following dietary components was analyzed.

Table 3-3 Nutritional information and measures extracted from food records

<table>
<thead>
<tr>
<th>Dietary Component</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Energy Intake</td>
<td>kcal</td>
</tr>
<tr>
<td>Fat</td>
<td>g, % kcal</td>
</tr>
<tr>
<td>Protein</td>
<td>g, % kcal</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>g, % kcal</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>g</td>
</tr>
<tr>
<td>Sugar</td>
<td>g</td>
</tr>
<tr>
<td>Fibre</td>
<td>g</td>
</tr>
<tr>
<td>Sodium</td>
<td>mg</td>
</tr>
</tbody>
</table>

The final analysis included the three-day average of all of the above components.
Differences between groups were analyzed for all of the above components and the results
compared to the Dietary Reference Intakes (DRIs)\textsuperscript{152}. The DRIs are evidence-based
recommendations for dietary intakes set for the healthy population, and have specific terms to
aid describing intake values. The acceptable macronutrient distribution range (AMDR) defines
the percent each macronutrient should contribute to total energy intake. The estimated average
requirement (EAR) is the median intake value set to meet the needs of half the healthy
individuals at specific age and sex groups. The recommended dietary allowance (RDA) is set
from the EAR plus 2 standard deviations, and is set to meet the needs of 97.5% of healthy
individuals in specific age and sex groups. The adequate intake (AI) is used when no RDA is
available and is set to meet or exceed the needs of individuals in specific age and sex groups.
The tolerable upper intake level (UL) is the level at which it is acceptable to consume a nutrient before it is likely to pose a risk of adverse health effects. The following tables outline the DRI recommendations for each age group.

**Acceptable macronutrient distribution ranges**

**Table 3-4 Acceptable macronutrient distribution ranges for males and females (4-18 years)**

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>Percent of kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>25 – 35 %</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>45 – 65 %</td>
</tr>
<tr>
<td>Protein</td>
<td>10 – 30 %</td>
</tr>
</tbody>
</table>

Source: Dietary Reference Intakes

**Sodium**

**Table 3-5 Dietary reference intakes for sodium**

<table>
<thead>
<tr>
<th>Age</th>
<th>AI (mg/day)</th>
<th>UL (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 – 8 years</td>
<td>1200</td>
<td>1900</td>
</tr>
<tr>
<td>9 – 13 years</td>
<td>1500</td>
<td>2200</td>
</tr>
<tr>
<td>14 – 18 years</td>
<td>1500</td>
<td>2300</td>
</tr>
</tbody>
</table>

Source: Dietary Reference Intakes

**Fibre**

**Table 3-6 Dietary reference intakes for fibre**

<table>
<thead>
<tr>
<th>Age</th>
<th>AI (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>4 – 8 years</td>
<td>25</td>
</tr>
<tr>
<td>9 – 13 years</td>
<td>31</td>
</tr>
<tr>
<td>14 – 18 years</td>
<td>38</td>
</tr>
</tbody>
</table>

Source: Dietary Reference Intakes
**Saturated fat**

While no AI or UL has been set for the intake of saturated fat, it has been suggested that the lower the intake, within a nutritionally adequate diet, the better\textsuperscript{90}. The American Heart Association indicates that 5-6\% of daily energy intake should come from saturated fat\textsuperscript{153}.

**Sugar**

No AI or UL has been set for the intake of sugar\textsuperscript{90}; however, the American Heart Association recommends no more than 10\% of total energy intake per day should come from added sugars\textsuperscript{154}. Further, the 2002 WHO recommendation also proposed that less than 10\% of daily energy intake come from added sugars. In a recent 2014 draft guideline the WHO confirms its recommendation of less than 10\% of daily energy intake to come from added sugars; however, it further suggests that reducing sugar intakes to less than 5\% of daily energy intake would be more beneficial\textsuperscript{155}. The final WHO guideline has yet to be published.

**Physical activity**

Physical activity was self-reported in minutes per day. Each child was classified as over or under the recommendation of 60 minutes per day of physical activity, which is the guideline set by the Canadian Society for Exercise Physiology\textsuperscript{156}.

### 3.6 Fasting Blood Sample Collections

In a subset of the sample (n=37), biochemical assessments were conducted in plasma collected after a minimum eight-hour overnight fast (Appendix B). Fasting plasma glucose, insulin, total cholesterol, HDL-c, LDL-c, and TG concentrations were quantified by routine clinical laboratory methods in the Pathology Laboratory at BCCH. Insulin resistance was calculated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
calculated by the following equation\textsuperscript{157,158}:

\[
\text{HOMA-IR} = [(\text{glucose (mmol/L)} \times \text{insulin (µU/L)})/22.5]
\]

The following table outlines the clinical cutoffs for each biochemical measure:

**Table 3-7 Clinical ranges for biochemical measures**

<table>
<thead>
<tr>
<th>Fasting Measure</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>3.9 – 5.9</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>13 – 100</td>
</tr>
<tr>
<td>TGs (mmol/L)</td>
<td>0.4 – 1.5</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>2.6 – 5.2</td>
</tr>
<tr>
<td>HDL-c (mmol/L)</td>
<td>1.0 – 1.9</td>
</tr>
<tr>
<td>LDL-c (mmol/L)</td>
<td>1.3 – 3.4</td>
</tr>
<tr>
<td>HOMA-IR* M F</td>
<td></td>
</tr>
<tr>
<td>Prepubertal</td>
<td>&lt; 2.67 &lt; 2.22</td>
</tr>
<tr>
<td>Pubertal</td>
<td>&lt; 5.22 &lt; 3.82</td>
</tr>
</tbody>
</table>

For ages 1 - <19 years. Values are abnormal if outside this range.
*Based on cutoffs proposed by Kurtoglu \textit{et al}\textsuperscript{159}

### 3.7 Genotyping

A subset of participants (n=33) consented to participate in the genetic aspect of the study (Appendix F). Genomic DNA was isolated from buccal epithelial cells using the QIAamp DNA micro kit from Qiagen Inc® (Mississauga, ON, Canada) and quantified using a NanoDrop Nanovue™ Spectrophotometer (GE Healthcare, Montreal, QC). Genotyping of the \textit{FTO} rs9939609 and \textit{MC4R} rs17782313 variants was accomplished using Taqman genotyping reagents and a 7500 Real-Time PCR system (Applied Biosystems, Foster City, CA).
3.8 Statistical Analyses

All analyses were performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL). The following table (3-10) indicates the variables included in the analysis along with their unit or ‘coding’ as well as their distribution.
Table 3-8 Variables included in analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type</th>
<th>Unit/Coding</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA status</td>
<td>Categorical</td>
<td>0=no, 1=yes</td>
<td></td>
</tr>
<tr>
<td>SGA duration</td>
<td>Continuous</td>
<td>months</td>
<td>Right skew</td>
</tr>
<tr>
<td>SGA type</td>
<td>Categorical</td>
<td>1=risperidone, 2=quetiapine, 3=olanzapine, 4=clozapine, 5=ziprasidone, 6=aripiprazole, 7=paliperidone</td>
<td></td>
</tr>
<tr>
<td>Antidepressant status</td>
<td>Categorical</td>
<td>0=no, 1=yes</td>
<td></td>
</tr>
<tr>
<td>Psychostimulant status</td>
<td>Categorical</td>
<td>0=no, 1=yes</td>
<td></td>
</tr>
<tr>
<td>Inpatient status</td>
<td>Categorical</td>
<td>0=no, 1=yes</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>years, months</td>
<td>Normal</td>
</tr>
<tr>
<td>Sex</td>
<td>Categorical</td>
<td>0=male, 1=female</td>
<td></td>
</tr>
<tr>
<td>Tanner stage</td>
<td>Categorical</td>
<td>Stage; 1=I, 2=II or III, 3=IV or V</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Categorical</td>
<td>0=European, 1=other</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>Categorical</td>
<td>0=no, 1=yes</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>Continuous</td>
<td>cm</td>
<td>Normal</td>
</tr>
<tr>
<td>Weight</td>
<td>Continuous</td>
<td>kg</td>
<td>Normal</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>Continuous</td>
<td>cm</td>
<td>Normal</td>
</tr>
<tr>
<td>zBMI</td>
<td>Continuous</td>
<td>kg/m²; standardized</td>
<td>Polymodal</td>
</tr>
<tr>
<td>Obesity</td>
<td>Categorical</td>
<td>0=healthy, 1=overweight/obese</td>
<td></td>
</tr>
<tr>
<td>zSBP</td>
<td>Continuous</td>
<td>mm Hg; standardized</td>
<td>Normal</td>
</tr>
<tr>
<td>zDBP</td>
<td>Continuous</td>
<td>mm Hg; standardized</td>
<td>Right skew</td>
</tr>
<tr>
<td>Screen time per day</td>
<td>Continuous</td>
<td>hours</td>
<td>Right skew</td>
</tr>
<tr>
<td>Physical activity per day</td>
<td>Continuous</td>
<td>mins</td>
<td>Right skew</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>Continuous</td>
<td>mmol/L</td>
<td>Left skew</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>Continuous</td>
<td>pmol/L or µIU/mL</td>
<td>Right skew</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Continuous</td>
<td>[glucose X insulin (µIU/mL)]/22.5</td>
<td>Right skew</td>
</tr>
<tr>
<td>Fasting Total cholesterol</td>
<td>Continuous</td>
<td>mmol/L</td>
<td>Normal</td>
</tr>
<tr>
<td>Fasting HDL-c</td>
<td>Continuous</td>
<td>mmol/L</td>
<td>Normal</td>
</tr>
<tr>
<td>Fasting LDL-c</td>
<td>Continuous</td>
<td>mmol/L</td>
<td>Normal</td>
</tr>
<tr>
<td>Fasting TGs</td>
<td>Continuous</td>
<td>mmol/L</td>
<td>Right skew</td>
</tr>
<tr>
<td>Total energy intake</td>
<td>Continuous</td>
<td>kcal; 3-day average</td>
<td>Normal</td>
</tr>
<tr>
<td>Fat intake</td>
<td>Continuous</td>
<td>g. %kcal; 3-day average</td>
<td>Normal</td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td>Continuous</td>
<td>g. %kcal; 3-day average</td>
<td>Normal</td>
</tr>
<tr>
<td>Protein intake</td>
<td>Continuous</td>
<td>g. %kcal; 3-day average</td>
<td>Normal</td>
</tr>
<tr>
<td>Sodium intake</td>
<td>Continuous</td>
<td>mg; 3-day average</td>
<td>Normal</td>
</tr>
<tr>
<td>Saturated fat intake</td>
<td>Continuous</td>
<td>g. %kcal; 3-day average</td>
<td>Normal</td>
</tr>
<tr>
<td>Total sugar intake</td>
<td>Continuous</td>
<td>g. %kcal; 3-day average</td>
<td>Right skew</td>
</tr>
<tr>
<td>Total fibre intake</td>
<td>Continuous</td>
<td>g. 3-day average</td>
<td>Right skew</td>
</tr>
<tr>
<td>FTO rs9939609</td>
<td>Categorical</td>
<td>0=TT, 1=AT/AA</td>
<td></td>
</tr>
<tr>
<td>MC4R rs17782313</td>
<td>Categorical</td>
<td>0=TT, 1=CT/CC</td>
<td></td>
</tr>
</tbody>
</table>
Normality was assessed for continuous variables via the Shapiro-Wilks test\textsuperscript{160} and visually via histograms. Non-normally distributed variables were transformed using the natural log (ln) (Table 3.5). The only variable that was not successfully transformed using the natural log was fasting plasma glucose, and therefore, non-parametric testing was performed. The variables that had already been standardized that were not normally distributed, were zBMI and zDBP, which both consist of negative values and as such, require a constant to be added before transformation. To normalize zDBP, a constant of 2 was added and then natural log transformed. However, due to zBMI having a polymodal distribution (see Figure 3-1), no transformation could be performed and therefore non-parametric testing was used regarding between group comparisons for zBMI. In aim 2B I sought to determine the relationship between dietary energy intake and measures of adiposity (zBMI and waist circumference), which requires a parametric test. As such, I did not use zBMI as a dependent variable; instead I used weight and adjusted for height, age, and pubertal status in the analyses.

**Figure 3-1 The distribution of zBMI for all participants**

![Histogram of zBMI](image)

*Figure 3-1* depicts the histogram of zBMI, which has a polymodal distribution.
Each statistical model used, as well as dependent variables, independent variables, and covariates are indicated in Table 3-9. I will briefly explain the analyses used for each aim.

**Participant Characteristics**

Between group comparisons for participant characteristics was analyzed by Chi-square ($\chi^2$) for categorical variables and t-tests for continuous variables.

**Aim 1: To determine total dietary energy and macronutrient intakes in SGA-treated and SGA naïve children**

Differences between SGA-treated and SGA-naïve children for total energy, macronutrient, saturated fat, fibre, sugar, and sodium intakes were assessed by ANCOVA (analysis of covariance) models and adjusted for covariates.

**Aim 2: To determine the association of dietary energy intake with adiposity and cardiometabolic dysfunction in SGA-treated and SGA-naïve children**

**Aim 2A:** ANCOVA was used to determine potential differences between SGA-treated and SGA-naïve participants for weight, waist circumference, insulin, HOMA-IR, LDL-c, HDL-c, total cholesterol, and TGs; all adjusted for covariates. ANOVA (analysis of variance) was used to determine potential differences between SGA-treated and SGA-naïve participants for zSBP and zDBP. To determine differences between groups for zBMI and glucose, the Mann-Whitney U non-parametric test for independent samples was used.

**Aim 2B and 2C:** ANCOVA was also used to determine any associations of total energy intake with measures of adiposity and cardiometabolic dysfunction as well as to determine any interaction of energy intake and SGA treatment on those outcomes. If an interaction was observed, the SGA-treated and SGA-naïve groups were analyzed separately. The dependent
variables included weight, waist circumference, HOMA-IR, zSBP, zDBP, and lipid profile; all adjusted for covariates. ANCOVA was also used to determine any association of saturated fat intake with LDL-c and any association of sodium intake with zSBP, zDBP, and HOMA-IR; adjusted for covariates.

In order to visually represent any potential adjusted association of energy intake or dietary components with adiposity or cardiometabolic parameters, it was necessary to depict a partial regression plot. Therefore, I used multiple linear regression to make this plot. I checked the assumptions of multiple linear regression: linearity between the dependent and independent variables visually via residual plots, multicollinearity using the variance inflation factor, normal distribution of residuals visually by the P-P plot, and homoscedasticity visually using the Q-Q plot.

Aim 3: To determine if FTO rs9939609 and MC4R rs17782313 variants are associated with differences in dietary energy and macronutrient intakes in SGA-treated and SGA-naïve children.

The effect of the FTO rs9939609 and MC4R rs17782313 variants on total energy and macronutrient intakes as well as any interaction with genotype and SGA treatment was assessed by ANCOVA and adjusted for covariates.
<table>
<thead>
<tr>
<th>Aim 1</th>
<th>Analysis</th>
<th><strong>Dependent Variables</strong></th>
<th><strong>Independent Variables</strong></th>
<th><strong>Covariates</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim 1A</td>
<td>ANCOVA</td>
<td>Energy intake Macronutrient intake</td>
<td>SGA treatment</td>
<td>Psychostimulant treatment, height, weight, physical activity and antidepressant treatment</td>
</tr>
<tr>
<td>Aim 1B</td>
<td>ANCOVA</td>
<td>Saturated fat, fibre, sodium, and sugar intakes</td>
<td>SGA treatment</td>
<td>Psychostimulant treatment and height</td>
</tr>
<tr>
<td>Aim 2</td>
<td>ANCOVA</td>
<td>Weight, waist circumference Insulin, HOMA-IR, TGs, total cholesterol, LDL-c and HDL-c</td>
<td>SGA treatment</td>
<td>Height</td>
</tr>
<tr>
<td></td>
<td>ANOVA</td>
<td>zSBP and zDBP</td>
<td>SGA treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mann-Whitney U test</td>
<td>Glucose and zBMI</td>
<td>SGA treatment</td>
<td></td>
</tr>
<tr>
<td>Aim 2B</td>
<td>ANCOVA</td>
<td>Weight and waist circumference</td>
<td>SGA treatment, energy intake</td>
<td>Height, psychostimulant treatment</td>
</tr>
<tr>
<td>&amp; 2C</td>
<td></td>
<td>HOMA-IR</td>
<td>SGA treatment, energy intake, and sodium intake</td>
<td>Height, obese/overweight, psychostimulant treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>zDBP and zSBP</td>
<td>SGA treatment and sodium intake</td>
<td>Height, psychostimulant treatment, energy intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDL cholesterol</td>
<td>SGA treatment and saturated fat intake</td>
<td>Height, weight, psychostimulant treatment</td>
</tr>
<tr>
<td>Aim 3</td>
<td>ANCOVA</td>
<td>Energy intake and macronutrient intakes</td>
<td>SGA treatment FTO and MC4R genotypes</td>
<td>Psychostimulant treatment and height</td>
</tr>
</tbody>
</table>

All ANCOVA models are adjusted for sex and Tanner stage
Chapter 4: Results

The results are presented in subsections based on the main aims. The sections are as follows: 4.1 Participant Characteristic, 4.2 Aim 1: Dietary intakes in SGA-treated and SGA naïve Children, 4.3 Aim 2: Dietary Intakes and Adiposity and Cardiometabolic Dysfunction, 4.4 Aim 3: FTO rs9939609 and MC4R rs17782313 Genotypes and Dietary Intakes.

4.1 Participant Characteristics

A total of 60 participants were recruited; however, due to dropout, loss to follow up or ineligibility, the final sample included 45 participants; 25 SGA-treated and 20 SGA-naïve. Below is Figure 4-1, outlining the sample size for each group as well as various measures obtained for each group.
Figure 4-1 Flowchart of participant recruitment

Figure 4-1 depicts the flow of participant recruitment with final sample sizes for each measure. Exclusions were based on loss of follow up, medication changes mid food records or dropout from study.

Participant characteristics are summarized in Table 4-1. The SGA-treated group was slightly older than the SGA-naïve group (13.3 vs. 11.6 years), but this did not reach statistical significance (p=0.070). Ages ranged from 7 – 18 years for the SGA-treated group and 6 – 16 years for the SGA-naïve group. Tanner stage of the SGA-treated group was higher (p=0.031) compared to the SGA-naïve group, with 64% of SGA-treated participants at stage IV or V of pubertal assessments (Tanner stage). For all study subjects, approximately half were European
(53.3%) followed by mixed First Nations and European (8.9%), Asian (6.7%), Hispanic/Mexican (6.7%), mixed Asian and European (6.7%), mixed Black/African/Caribbean and European (4.4%), South Asian (2.2%), First Nations (2.2%), Southeast Asian (2.2%), mixed South Asian and European (2.2%), mixed Hispanic/Mexican and European (2.2%), and mixed Hispanic/Mexican, First Nations, and European (2.2%). There were no significant differences between groups for sex, height, inpatient vs. outpatient status, screen time, or physical activity. Participants' family medical history is reported in Table 4-2 and includes history of diabetes (type 1, 2 and gestational), hyperlipidemia, CVD, and MHCs. There were no significant differences between groups regarding family medical history.
Table 4-1 Participant characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>12.6 (3.12)</td>
<td>13.3 (3.08)</td>
<td>11.6 (2.98)</td>
<td>0.070</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>25 (55.6)</td>
<td>14 (56.0)</td>
<td>11 (55.0)</td>
<td>0.947</td>
</tr>
<tr>
<td>Inpatient, n (%)</td>
<td>20 (44.4)</td>
<td>12 (48.0)</td>
<td>8 (40.0)</td>
<td>0.592</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>1 (2.2)</td>
<td>1 (4.0)</td>
<td>0 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Height, cm (SD)</td>
<td>153.47 (17.68)</td>
<td>157.96 (18.09)</td>
<td>147.85 (15.84)</td>
<td>0.055</td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>55.81 (22.42)</td>
<td>65.57 (21.11)</td>
<td>43.61 (17.86)</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist circumference, cm (SD)</td>
<td>76.0 (17.40)</td>
<td>83.5 (15.44)</td>
<td>66.5 (15.20)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tanner stage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td>I</td>
<td>12 (26.7)</td>
<td>5 (20.0)</td>
<td>7 (35.0)</td>
<td></td>
</tr>
<tr>
<td>II or III</td>
<td>12 (26.7)</td>
<td>4 (16.0)</td>
<td>8 (40.0)</td>
<td></td>
</tr>
<tr>
<td>IV or V</td>
<td>21 (46.7)</td>
<td>16 (64.0)</td>
<td>5 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.423</td>
</tr>
<tr>
<td>European</td>
<td>24 (53.3)</td>
<td>12 (48.0)</td>
<td>12 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21 (46.7)</td>
<td>13 (52.0)</td>
<td>8 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Screen time, hrs/day (SD)</td>
<td>2.67 (1.90)</td>
<td>2.95 (2.06)</td>
<td>2.32 (1.65)</td>
<td>0.277</td>
</tr>
<tr>
<td>Physical activity, mins/day (SD)</td>
<td>85.1 (68.07)</td>
<td>70.0 (59.52)</td>
<td>93.1 (79.15)</td>
<td>0.516</td>
</tr>
</tbody>
</table>

*p-value represents between group comparisons using t-tests for continuous variables and chi-square (χ²) for categorical variables
Other ethnicity = an ethnicity, whether mixed or not, other than European.
Note for physical activity: n=23 for SGA-treated and n=19 for SGA-naïve.
Table 4-2 Participants’ family medical history

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history (yes), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>5 (11.1)</td>
<td>2 (8.0)</td>
<td>3 (15.0)</td>
<td>0.360</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>21 (46.7)</td>
<td>13 (52.0)</td>
<td>8 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5 (11.1)</td>
<td>2 (8.0)</td>
<td>3 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (11.1)</td>
<td>4 (16.0)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (40.0)</td>
<td>9 (36.0)</td>
<td>9 (45.0)</td>
<td>0.761</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (13.3)</td>
<td>4 (16.0)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>19 (42.2)</td>
<td>10 (40.0)</td>
<td>9 (45.0)</td>
<td>0.170</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (8.9)</td>
<td>4 (16.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Mental health conditions</td>
<td>15 (33.3)</td>
<td>9 (36.0)</td>
<td>6 (30.0)</td>
<td>0.698</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (13.3)</td>
<td>4 (16.0)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
</tbody>
</table>

*p-value represents between group comparisons using chi-square ($\chi^2$) for categorical variables

Participants’ diagnoses and medications are summarized in Table 4-3. A wide range of primary diagnoses was observed in both groups, with no significant differences between groups. Anxiety was the most common primary diagnosis for the total sample (37.8%) as well as for the SGA-treated (32.0%) and SGA-naïve (45.0%) groups. In the SGA-treated group, psychotic disorders (24%) and ADHD (16%) were the second and third most common diagnoses. In the SGA-naïve group, ADHD (20%) and depressive disorder (15%) were the most common primary diagnoses after anxiety disorder. Aripiprazole (36%), risperidone (40%), and quetiapine (24%) were the SGAs used by SGA-treated group. The median duration of treatment was 11 months and ranged from 1 to 64 months. Both groups were prescribed other medications, including antidepressants and psyhostimulants: SGA-treated; antidepressants (44%), psyhostimulants (24%) vs. SGA-naïve; antidepressants (55%), psyhostimulants (25%). The type of antidepressant medication predominantly prescribed was fluoxetine hydrochloride.
Table 4-3 Participants’ diagnoses and medications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>17 (37.8)</td>
<td>8 (32.0)</td>
<td>9 (45.0)</td>
<td>0.163</td>
</tr>
<tr>
<td>ADHD</td>
<td>8 (17.8)</td>
<td>4 (16.0)</td>
<td>4 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Adjustment disorder</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>3 (6.7)</td>
<td>0 (0.0)</td>
<td>3 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Disruptive behaviour disorder</td>
<td>4 (8.9)</td>
<td>2 (8.0)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Mood disorder</td>
<td>3 (6.7)</td>
<td>2 (8.0)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>6 (13.3)</td>
<td>6 (24.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Pervasive development disorder</td>
<td>1 (2.2)</td>
<td>1 (4.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>1 (2.2)</td>
<td>1 (4.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Tic disorder</td>
<td>1 (2.2)</td>
<td>1 (4.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>SGA duration, median months (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;)</td>
<td>11.00 (2.13,16.4)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>9 (36.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>10 (40.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6 (24.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychostimulants</td>
<td>11 (24.4)</td>
<td>6 (24.0)</td>
<td>5 (25.0)</td>
<td>0.938</td>
</tr>
<tr>
<td>Antidepressants, n (%)</td>
<td>22 (48.9)</td>
<td>11 (44.0)</td>
<td>11 (55.0)</td>
<td>0.463</td>
</tr>
<tr>
<td>Fluoxetine hydrochloride</td>
<td>11 (24.4)</td>
<td>4 (16.0)</td>
<td>7 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>3 (6.7)</td>
<td>2 (8.0)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>5 (11.1)</td>
<td>3 (12.0)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>1 (2.2)</td>
<td>1 (4.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine hydrochloride</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>4 (8.9)</td>
<td>4 (16.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

p-value represents between group comparisons using t-tests for continuous variables and chi-square ($\chi^2$) for categorical variables
4.2 Aim 1: Dietary Intakes in SGA-treated and SGA-naïve Children

**Aim 1A**: To determine total dietary energy and macronutrient intakes in SGA-treated and SGA naïve children.

The primary objective of this thesis was to determine if SGA-treated children have greater dietary energy intakes compared to SGA-naïve children. The unadjusted mean three-day average energy intake for the SGA-treated group was 2037±715.8 kcal/day and 1726±545.6 kcal/day for the SGA-naïve group (p=0.116; 95% CI: -701.6, 79.9) (Table 4-4). Energy intake varies based on a number of factors specific to an individual, such as age (or maturity), sex, height, weight, and physical activity level. To adjust for various cofactors and covariates, ANCOVA was used and three-day average energy intake was compared between the SGA-treated and SGA-naïve group. Multiple models are presented to depict adjustments for various cofactors and covariates that may impact energy intake. In model 1 (Table 4-5) the adjusted estimated marginal means for average dietary energy intake adjusted for sex, Tanner stage, height, and psychostimulant treatment was [mean (SE)], SGA-treated: 1845 (158.87) and SGA-naïve: 1657 (153.17). In model 1 (Table 4-5), when using pairwise comparisons, psychostimulant treatment had the second largest effect on energy intake (B=396.98; p=0.082), with individuals receiving psychostimulant treatment reporting lower total dietary energy intakes than individuals not receiving psychostimulant treatment. The largest influence on dietary energy intake was sex (B=407.66; p=0.053); males had a greater intake than females. Model 2 (Table 4-5) is Model 1 further adjusted for weight (kg), which had no influence on dietary energy intakes between the SGA-treated and SGA-naïve groups. Adding physical activity and antidepressant treatment, each separately to model 1, also did not have a significant influence on between group three-day average energy intakes (p=0.405 and p=0.361, respectively).
### Table 4-4 Unadjusted three-day average energy intake

<table>
<thead>
<tr>
<th></th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>Beta</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy intake (kcal)</td>
<td>1898 (657.6)</td>
<td>2037 (715.8)</td>
<td>1726 (545.6)</td>
<td>-311.01</td>
<td>0.116</td>
<td>(-701.9, 79.9)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)  
*p-value, beta, and 95% CI determined by one way ANOVA for between group comparisons*

### Table 4-5 Adjusted three-day average energy intake

<table>
<thead>
<tr>
<th>Model 1</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>Beta</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy intake (kcal)</td>
<td>1845 (158.87)</td>
<td>1657 (153.17)</td>
<td>-187.94</td>
<td>0.352</td>
<td>(-591.7, 215.9)</td>
</tr>
</tbody>
</table>

Data presented as mean (SE)  
Total energy intake based on the estimated marginal means and *p*-value, beta, and 95% CI determined by general linear models; adjusted for sex, Tanner stage, height, and psychostimulant treatment

<table>
<thead>
<tr>
<th>Model 2</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>Beta</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy intake (kcal)</td>
<td>1828 (162.4)</td>
<td>1694 (165.5)</td>
<td>-134.31</td>
<td>0.543</td>
<td>(-577.7, 309.1)</td>
</tr>
</tbody>
</table>

Data presented as mean (SE)  
Total energy intake is the estimated marginal means and *p*-value, beta, and 95% CI determined by general linear models; model 1 + weight
The standard deviation in both the SGA-treated group and SGA-naïve group was large, indicating how variable energy intakes may be between individuals. The minimum and maximum for three-day average energy intake was (634 – 3920 kcal) for the SGA-treated group and (748 – 2618 kcal) for the SGA-naïve group. The unadjusted average three-day energy intake is depicted visually using boxplots stratified by SGA treatment in Figure 4-2.

**Figure 4-2 Unadjusted three-day average energy intake**

![Boxplot of unadjusted three-day average energy intake](image)

*Figure 4-2* Boxplots of unadjusted three-day average energy intake for SGA-treated and SGA-naïve groups; boxes represent the median, 25th and 75th quartiles, whiskers represent the range, and circles represent outliers.
The second part of Aim 1A was to determine if energy intake differed by macronutrient intake. Using ANCOVA to compare groups for fat, protein, and carbohydrate intakes (grams), and adjusting for sex, Tanner stage, height, and psychostimulant treatment, there were no significant differences between groups.

**Table 4-6 Three-day average macronutrient intake**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat intake (g)</td>
<td>63 (29.4)</td>
<td>68 (29.2)</td>
<td>57 (29.3)</td>
<td>0.485</td>
</tr>
<tr>
<td>Carbohydrate intake (g)</td>
<td>260 (94.4)</td>
<td>280 (108.7)</td>
<td>235 (67.2)</td>
<td>0.392</td>
</tr>
<tr>
<td>Protein intake (g)</td>
<td>73 (26.4)</td>
<td>79 (28.1)</td>
<td>66 (22.8)</td>
<td>0.389</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)  
*p*-value determined by general linear models; adjusted for sex, Tanner stage, height and psychostimulant treatment

Figure 4-3 depicts the percent of energy intake from each macronutrient. The groups had almost identical means for three-day average percent of energy intake from macronutrients; protein [SGA-treated: 16±2.9, SGA-naïve: 15±2.2], carbohydrate [SGA-treated: 55±6.3, SGA-naïve: 55±7.1, and fat [SGA-treated: 30±6.4, SGA-naïve: 30±6.4]. As a group, the Acceptable Macronutrient Distribution Ranges (AMDR) were met; however, not all individuals met the AMDR for each macronutrient. Table 4-7 indicates that the AMDR for fat intake for both groups was poorly met with 16% of SGA-treated and 30% of SGA-naïve below the recommended intake and 16% SGA-treated and 25% SGA-naïve above the recommended intake. Regarding carbohydrate intake; 88% of SGA-treated and 85% of SGA-naïve met the AMDR. Only one SGA-treated participant was below the AMDR for protein.
Figure 4-3 Three-day average macronutrient intake as percent of energy intake

![Graph showing average macronutrient intake as a percent of energy intake for SGA-treated and SGA-naïve groups. There were no statistically significant differences between groups.](image)

Table 4-7 Acceptable macronutrient distribution ranges

<table>
<thead>
<tr>
<th>AMDR</th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td>26 (57.8)</td>
<td>17 (68.0)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>Below</td>
<td>10 (22.2)</td>
<td>4 (16.0)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Above</td>
<td>9 (20.0)</td>
<td>4 (16.0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td>30 (86.7)</td>
<td>22 (88.0)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Below</td>
<td>3 (6.7)</td>
<td>1 (4.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Above</td>
<td>3 (6.7)</td>
<td>2 (8.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Protein intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td>44 (97.8)</td>
<td>24 (96.0)</td>
<td>20 (100.0)</td>
</tr>
<tr>
<td>Below</td>
<td>1 (2.2)</td>
<td>1 (4.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Above</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Data presented as n (%)  
AMDR = acceptable macronutrient distribution range (recommendations stated in section 3.5.1)
**Aim 1B**: To assess sodium, saturated fat, fibre, and simple sugar intakes in SGA-treated and SGA-naïve children and to determine differences between groups.

Table 4-8 depicts the means of the three-day average dietary intakes of saturated fat, sugar, sodium, and fibre stratified by SGA treatment. No significant differences were observed between groups.

**Table 4-8 Three-day average dietary intakes of saturated fat, sugar, sodium and fibre**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat</td>
<td>g (SD)</td>
<td>g (SD)</td>
<td>g (SD)</td>
<td></td>
</tr>
<tr>
<td>% kcal</td>
<td>23 (11.34)</td>
<td>24 (11.31)</td>
<td>22 (11.56)</td>
<td>0.819</td>
</tr>
<tr>
<td></td>
<td>11 (3.25)</td>
<td>10 (2.83)</td>
<td>11 (3.77)</td>
<td>0.691</td>
</tr>
<tr>
<td>Sugar</td>
<td>g (1st, 3rd)</td>
<td>g (1st, 3rd)</td>
<td>g (1st, 3rd)</td>
<td></td>
</tr>
<tr>
<td>% kcal</td>
<td>100 (65.83, 124.83)</td>
<td>105 (74.9, 131.7)</td>
<td>88 (56.3, 120.8)</td>
<td>0.183†</td>
</tr>
<tr>
<td></td>
<td>21 (6.28)</td>
<td>21 (2.94)</td>
<td>20 (7.74)</td>
<td>0.379</td>
</tr>
<tr>
<td>Sodium, mg</td>
<td>2515 (909.32)</td>
<td>2726 (814.13)</td>
<td>2250 (972.29)</td>
<td>0.306</td>
</tr>
<tr>
<td>Fibre, g</td>
<td>15 (11.6, 21.11)</td>
<td>19 (11.6, 25.2)</td>
<td>15 (10.1, 18.4)</td>
<td>0.338†</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) for normally distributed variables and median (25th, 75th) for non-normally distributed variables. Sugar = monosaccharides & disaccharides; fibre = insoluble & soluble. p-value determined by general linear models; adjusted for sex, Tanner stage, height, and psychostimulant treatment. Significance determined by natural log (ln) transformed value.
**Saturated fat**

The mean dietary intakes of saturated fat as a percent of energy (Table 4-8) were 10±2.83 and 11±3.77 for the SGA-treated and SGA-naïve groups, respectively. Saturated fat intake ranged from 2% to 16% energy intake, for the total sample. Figure 4-4 depicts saturated fat as a percent of energy intake in different categories, stratified by SGA-treated and SGA-naïve groups. No UL is set for saturated fat, but it is recommended that no more than 7% of daily energy intake come from saturated fat\textsuperscript{153}. Only 8% of SGA-treated individuals and 20% of SGA-naïve individuals met this recommendation.

**Figure 4-4 Three-day average saturated fat intake in categories**

![Saturated fat intake categories diagram](image)

**Figure 4-4** Saturated fat intake (percent of energy) in categories stratified by SGA treatment.
Sugar

Sugar intake includes monosaccharides and disaccharides from all sources in the diet. In Table 4-8 the median (25th, 75th) of three-day average sugar intake was 105 grams (75, 132) for the SGA-treated group and 88 grams (56, 121) for the SGA-naïve group. As a percent contributing to total energy intake, the total sample ranged from 7% to 34%. Sugar is depicted in Figure 4-5 in categories as a percent of energy intake.

Figure 4-5 Three-day average sugar intake in categories

![Bar Chart]

Figure 4-5 Total sugar intake (percent of energy) as a categorical variable stratified by SGA treatment.
Sodium intake refers to sodium from food sources only, not salt added to food from the ‘salt shaker’. The mean three-day average sodium intakes (mg) were 2726±814.13 for the SGA-treated group and 2250±972.29 for the SGA-naïve group (Table 4-4). Figure 4-6 shows sodium as a categorical variable stratified as < 1500mg, 1500 – 2300 mg, 2300 – 3500 mg and >3500mg per day. Participants were also categorized as above the UL\(^{152}\) for their age. For the total sample, 68.9% were above the UL: 80% of SGA-treated and 55% of SGA-naïve.

Figure 4-6 Three-day average sodium intakes in categories

![Figure 4-4](image)

**Figure 4-4** Sodium intake (milligrams) as a categorical variable stratified by SGA treatment.
Fibre

The median (25\textsuperscript{th}, 75\textsuperscript{th}) fibre intake (Table 4-8) was 19 grams (11.6, 25.2) for the SGA-treated group and 15 grams (10.1, 18.4) for the SGA-naïve group. Only 20\% of the SGA-treated group and 5\% of the SGA-naïve group met their AI for fibre as defined in section 3.7.1. Figure 4-7 shows the categorical distribution of three-day average intake of fibre in grams.

Figure 4-7 Three-day average fibre intake in categories

![Figure 4-7 Fibre intake (grams) as a categorical variable stratified by SGA treatment.](image-url)
4.3 Aim 2: Dietary Intakes and Adiposity and Cardiometabolic Dysfunction

**Aim 2A:** To assess and compare adiposity and cardiometabolic dysfunction in SGA-treated and SGA-naïve children.

Table 4-9 represents mean and median values for weight, zBMI, waist circumference, zSBP, and zDBP as well as between group comparisons. Significant differences were observed for weight (p=0.011) and waist circumference (p=0.019) after adjusting for sex, Tanner stage, and height. A significant difference was also observed for zBMI (p=0.001) using the Mann-Whitney U non-parametric test for independent samples. For all three measures the SGA-treated group had higher scores compared to the SGA-naïve group. Interestingly, SGA-treated participants had greater zSBP scores and lower zDBP scores compared to SGA-naïve participants, but the differences were not statistically significant. Using the cutoffs for elevated BP as defined in section 3.6, 15.8% of SGA-naïve participants and 20% of SGA-treated participants had elevated BP scores.
### Table 4-9 Anthropometric characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=45)</th>
<th>SGA-treated (n=25)</th>
<th>SGA-naïve (n=20)</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>55.8 (22.4)</td>
<td>65.6 (21.1)</td>
<td>43.6 (17.9)</td>
<td>0.011*</td>
<td>(-17.17, -2.34)</td>
</tr>
<tr>
<td>zBMI</td>
<td>0.74 (-0.26, 1.84)</td>
<td>1.55 (0.37, 2.03)</td>
<td>-0.15 (-0.74, 1.03)</td>
<td>0.001‡</td>
<td>N/A</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>76.0 (17.4)</td>
<td>83.5 (15.4)</td>
<td>66.5 (15.2)</td>
<td>0.019*</td>
<td>(-20.34, -1.97)</td>
</tr>
<tr>
<td>zSBP</td>
<td>0.18 (1.01)</td>
<td>0.38 (1.08)</td>
<td>-0.08 (0.87)</td>
<td>0.133</td>
<td>(-1.07, 0.15)</td>
</tr>
<tr>
<td>zDBP</td>
<td>-0.16 (-0.57, 0.33)</td>
<td>-0.03 (-0.57, 0.42)</td>
<td>-0.28 (-0.70, 0.17)</td>
<td>0.396</td>
<td>(-0.23, 0.091)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) for normally distributed variables and median (25th, 75th) for non-normally distributed variables.

* p-value and 95% CI; adjusted for sex, Tanner stage, and height.
‡ p-value determined by Mann-Whitney U non-parametric test for independent samples.

zSBP and zDBP: n=19 for SGA-naïve group.
In the SGA-treated group, 48% were classified with obesity and a 16% were classified as overweight, for a combined prevalence of 64% overweight or obese. In the SGA-naïve group, 20% were classified with obesity and 10% were classified as overweight, for a combined prevalence of 30% overweight or obese. The SGA-treated group had a 4.15 greater odds of being overweight or obese when compared to the SGA-naïve group (p=0.023).

**Figure 4-8 Categorization of body mass index standardized for age and sex**

![Chart showing body mass index categories](image)

---

**Figure 4-8** zBMI grouped in categories based on definitions outlined by the CDC for overweight and obesity in youth. When combining the overweight and obese groups, Pearson’s chi-square indicated a 4.15 greater odds of being overweight or obese for SGA-treated participants compared to the SGA-naïve participants (p=0.023).
In a subset (n=37) of the sample, fasting plasma blood samples were obtained. ANCOVA was used to compare SGA-treated and SGA-naïve groups and to adjust for sex and Tanner stage (Table 4-10). No statistical differences were observed between groups regarding; total cholesterol, LDL-c, HDL-c, and TGs. Significant differences were observed between groups for glucose (p=0.015), insulin (p=0.010), and HOMA-IR (p=0.009); all were higher in the SGA-treated group compared to the SGA-naïve group.

### Table 4-10 Fasting blood parameters

<table>
<thead>
<tr>
<th>Characteristic (mmol/L)</th>
<th>All (n=37)</th>
<th>SGA-treated (n=21)</th>
<th>SGA-naïve (n=16)</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>5.0 (4.75, 5.20)</td>
<td>5.2 (4.90, 5.30)</td>
<td>4.8 (4.63, 5.00)</td>
<td><strong>0.015</strong>†</td>
<td>N/A (-1.01, -0.148)</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>54.0 (30.0, 77.5)</td>
<td>62.0 (42.5, 89.5)</td>
<td>35.0 (26.0, 52.8)</td>
<td><strong>0.010</strong> †</td>
<td>(-1.09, -0.167)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.72 (0.99, 2.52)</td>
<td>2.06 (1.39, 2.81)</td>
<td>1.05 (0.66, 1.71)</td>
<td><strong>0.009</strong> †</td>
<td>(-0.257, 0.669)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>4.12 (0.61)</td>
<td>4.06 (0.56)</td>
<td>4.20 (0.67)</td>
<td>0.372</td>
<td>(-0.25, 0.61)</td>
</tr>
<tr>
<td>LDL-c</td>
<td>2.38 (0.58)</td>
<td>2.35 (0.49)</td>
<td>2.41 (0.69)</td>
<td>0.400</td>
<td>(-0.07, 0.31)</td>
</tr>
<tr>
<td>HDL-c</td>
<td>1.27 (0.27)</td>
<td>1.19 (0.24)</td>
<td>1.37 (0.29)</td>
<td>0.210</td>
<td>(-0.49, 0.12)</td>
</tr>
<tr>
<td>TGs</td>
<td>0.91 (0.68, 1.30)</td>
<td>0.92 (0.73, 1.39)</td>
<td>0.87 (0.54, 1.25)</td>
<td>0.218 ‡</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean (SD) for normally distributed variables and median (25th, 75th) for non-normally distributed variables

† p-value and 95% CI determined by general linear models; adjusted for sex and Tanner stage

‡ p-value and 95% CI determined by natural log (ln) transformed value

†† p-value determined by Mann-Whitney U non-parametric test for independent samples

HOMA-IR = (glucose x insulin (µU/L))/22.5
**Aim 2B**: To examine the association of dietary energy intake with zBMI, waist circumference, and cardiometabolic dysfunction in both groups.

As was stated in section 3.10, zBMI was not normally distributed and therefore was not used in parametric testing. As such, weight was used and adjusted for height, sex, and Tanner stage. Table 4-11 represents weight, waist circumference, and HOMA-IR and the association of energy intake as well as the interaction of SGA treatment and energy intake. No associations were observed between energy intake and zSBP, zDBP, or lipid profile. Plasma insulin and glucose concentrations were not included in the analysis as those measures would have been repetitive to the use of HOMA-IR. There were no associations between energy intake and measures of adiposity. The interaction between SGA treatment and energy intake had a significant association with HOMA-IR (p=0.007; 95% CI: 0.016, 0.084). As such, I did not analyze both groups together; rather, the SGA-treated and SGA-naïve groups were analyzed separately. The association between energy intake and HOMA-IR was not significant in SGA-treated group (p=0.093; B=0.042); however, it was significant in the SGA-naïve group (p=0.015; B=0.058).
Table 4-11 Association of energy intake with measures of adiposity and cardiometabolic dysfunction

<table>
<thead>
<tr>
<th>Characteristic (n=45)</th>
<th>SGA*kcal p-value</th>
<th>kcal p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.776</td>
<td>0.538</td>
<td>(-0.30, 0.526)</td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>0.627</td>
<td>0.355</td>
<td>(-0.27, 0.79)</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td><strong>0.007</strong></td>
<td><strong>0.015</strong></td>
<td>(-0.008,0.093) to (0.015,0.101)</td>
</tr>
</tbody>
</table>

SGA\*kcal p-value = the interaction of SGA treatment and three-day average energy intake (kcal)

kcal p-value = the association of three-day energy intake and each characteristic

*p-value determined by general linear models; adjusted for SGA treatment, sex, Tanner stage, height, and psychostimulant treatment

SGA\*treated, SGA-naïve

95% CI based per 100 kcal

Figure 4-9 shows the adjusted relationship between three-day average energy intake and the natural log of HOMA-IR ($R^2=0.544$; $p=0.015$) in the SGA-naïve group. After adjusting for sex, Tanner stage, height, psychostimulant treatment, and overweight/obese, 54.4% of the variation in HOMA-IR was explained by energy intake in the SGA-naïve group.
Figure 4-9 Adjusted relationship between energy intake and HOMA-IR for SGA-naïve participants

The dark line represents the regression line and the dotted line represents the 95% CI around the line.

Average energy intake

$R^2 = 0.544$

$p = 0.015$

Figure 4-9 Linear relationship between three-day average energy intake and HOMA-IR for SGA-naïve participants; adjusted for sex, Tanner stage, height, psychostimulant treatment, and overweight/obese. The dark line represents the regression line and the dotted line represents the 95% CI around the line.
Figure 4-10 depicts the adjusted relationship between three-day average energy intake and the natural log of HOMA-IR ($R^2=0.201; \ p=0.093$) in the SGA-treated group. After adjusting for sex, Tanner stage, height, SGA treatment, psychostimulant treatment, and overweight/obese, 20.1% of the variation in HOMA-IR was explained by energy intake in the SGA-treated group.

Figure 4-10 Adjusted relationship between energy intake and HOMA-IR for SGA-treated participants

![Graph showing adjusted relationship between energy intake and HOMA-IR](image)

Figure 4-10 Linear relationship between three-day average energy intake and HOMA-IR for SGA-treated participants; adjusted for sex, Tanner stage, height, SGA treatment, psychostimulant treatment, and overweight/obese. The dark line represents the regression line and the dotted line represents the 95% CI around the line.
**Aim 2C:** To examine the association of dietary components and cardiometabolic dysfunction in both groups.

The association of dietary sodium intake with blood pressure and HOMA-IR and the association of dietary saturated fat intake and LDL-c were examined. There was a significant relationship between $z$DBP (natural log transformed) and sodium intake ($p=0.043$) in an unadjusted model; however, after adjusting for SGA treatment, sex, Tanner stage, height, psychostimulant treatment, overweight/obese, and average energy intake the relationship was no longer significant. Table 4-12 indicates no associations of sodium intake (mg) with $z$SBP and $z$DBP and no interaction of SGA treatment and sodium intake with $z$SBP and $z$DBP.

There was an interaction between SGA treatment and sodium intake with HOMA-IR ($p=0.032$). As such, the SGA-treated and SGA-naïve groups were analyzed separately. The association of sodium intake with HOMA-IR was significant in the SGA-treated group ($p=0.017$; $B=0.061$); and it was not significant in the SGA-naïve group ($p=0.676$; $B=-0.007$).

There was a significant interaction between saturated fat intake as a percent of energy intake and SGA treatment with LDL-c ($p=0.010$) (Table 4-13). The association of saturated fat intake with LDL-c was significant in the SGA-treated group ($p=0.041$; $B=0.087$); and it was not significant in the SGA-naïve group ($p=0.352$; $B=0.066$).
Table 4-12 Adjusted association of sodium intake with blood pressure and HOMA-IR

<table>
<thead>
<tr>
<th>Characteristic (n=44)</th>
<th>SGA*sodium p-value</th>
<th>sodium p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>zSBP</td>
<td>0.474</td>
<td>0.807</td>
<td>(-0.053, 0.067)</td>
</tr>
<tr>
<td>zDBP#</td>
<td>0.347</td>
<td>0.144</td>
<td>(-0.012, 0.082)</td>
</tr>
<tr>
<td>HOMA-IR#</td>
<td>0.032</td>
<td>0.017</td>
<td>0.676</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SGA-treated</th>
<th>SGA-naïve</th>
<th>95% CI</th>
<th>SGA-treated</th>
<th>SGA-naïve</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA*sodium p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| p-value determined by general linear models; adjusted for SGA treatment, sex, Tanner stage, height, psychostimulant treatment, overweight/obese, and average energy intake
#p-value and 95% CI determined by natural log (ln) transformed value
95% CI based per 100mg sodium
Note: HOMA-IR n=37

Table 4-13 Adjusted association between saturated fat intake and LDL-c

<table>
<thead>
<tr>
<th>Characteristic (n=37)</th>
<th>SGA*saturated fat p-value</th>
<th>Saturated fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SGA-treated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-value (95% CI)</td>
</tr>
<tr>
<td>LDL-c</td>
<td>0.010</td>
<td>0.041 (0.004, 0.170)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SGA*saturated fat p-value</th>
<th>Saturated fat p-value (95% CI)</th>
<th>Saturated fat p-value (95% CI)</th>
</tr>
</thead>
</table>
| SGA*treatment and three-day average saturated fat intake as a percent of energy
Saturated fat p-value = the association of three-day average saturated fat intake and LDL-c
p-value determined by general linear models; adjusted for SGA treatment, sex, Tanner stage, height, psychostimulant treatment, and overweight/obese
Figure 4-11 depicts the adjusted relationship between three-day average sodium intake and HOMA-IR in the SGA-treated group ($R^2=0.391; p=0.017$). After adjusting for sex, Tanner stage, height, psychostimulant treatment, and overweight/obese, 39.1% of the variation in HOMA-IR was explained by sodium intake in the SGA-treated group.

**Figure 4-11 Adjusted relationship between sodium intake and HOMA-IR for SGA-treated participants**

![Graph showing adjusted relationship between sodium intake and HOMA-IR](image)

**Figure 4-11 Linear relationship between dietary sodium intake and HOMA-IR for the SGA-treated group; adjusted for sex, Tanner stage, height, psychostimulant treatment, overweight/obese, and average energy intake. The dark line represents the regression line and the dotted line represents the 95% CI around the line.**
Figure 4-12 depicts the adjusted relationship between three-day average sodium intake and HOMA-IR in the SGA-naïve group ($R^2=0.026$; $p=0.676$). No relationship was observed between sodium intake and HOMA-IR in the SGA-naïve group.

Figure 4-12 Adjusted relationship between sodium intake and HOMA-IR for SGA-naïve participants

![Graph showing the adjusted relationship between sodium intake and HOMA-IR](image)

$R^2=0.026$

$p=0.676$

Figure 4-12 Relationship between dietary sodium intake and HOMA-IR for the SGA-naïve group; adjusted for sex, Tanner stage, height, psychostimulant treatment, overweight/obese, and average energy intake. The dark line represents the regression line and the dotted line represents the 95% CI around the line.
Figure 4-13 depicts the adjusted relationship between three-day average saturated fat intake and LDL-c in the SGA-treated group ($R^2=0.281; p=0.041$). After adjusting for sex, Tanner stage, height, psychostimulant treatment, and overweight/obese, 28.1% of the variation in LDL-c was explained by saturated fat intake in the SGA-treated group.

**Figure 4-13** Adjusted relationship between saturated fat intake and LDL-c for SGA-treated participants

![Graph showing the linear relationship between dietary saturated fat intake and LDL-c for the SGA-treated group. The graph includes a regression line and a 95% confidence interval.](image)

**Figure 4-13** Linear relationship between dietary saturated fat intake and LDL-c for the SGA-treated group; adjusted for sex, Tanner stage, height, psychostimulant treatment, overweight/obese, and average energy intake. The dark line represents the regression line and the dotted line represents the 95% CI around the line.
Figure 4-14 shows the adjusted relationship between three-day average saturated fat intake and LDL-c in the SGA-naïve group ($R^2=0.109; p=0.352$). There was no significant relationship between saturated fat intake and LDL-c in the SGA-treated group.

**Figure 4-14 Adjusted relationship between saturated fat intake and LDL-c for SGA-naïve participants**

Figure 4-14 Relationship of saturated fat intake and LDL-c in the SGA-naïve group; adjusted for sex, Tanner stage, height, psychostimulant treatment, and overweight/obese. The dark line represents the regression line and the dotted line represents the 95% CI around the line.
4.4 Aim 3: FTO rs9939609 and MC4R rs17782313 Genotypes and Dietary Intakes

A subset of the study participants (n=33) consented to provide DNA samples and were genotyped for FTO rs9939609 and MC4R rs17782313 variants. Due to such small sample sizes, the risk alleles were combined such that for the FTO rs9939609 variant, individuals with AT and AA genotypes were compared to individuals with the TT genotype and for MC4R rs17782313 variant, individuals with the CT and CC genotypes were compared to individuals with the TT genotype.

Table 4-14 depicts the unadjusted three-day average energy intake (kcal) and three-day average macronutrient intakes (percent of energy) by the FTO rs9939609 variant. Table 4-15 depicts the unadjusted three-day average energy intake (kcal) and three-day average macronutrient intakes (percent of energy) by the MC4R rs17782313 variant.

Table 4-16 presents adjusted models for the effect of the FTO rs9939609 variant on total and macronutrient energy intakes and interactions with SGA treatment. The models were adjusted for SGA treatment, sex, Tanner stage, height, and psychostimulant treatment. There was no effect of the FTO rs9939609 variant and no interaction of SGA treatment and the FTO rs9939609 variant on three-day average energy intake. There were significant interactions of SGA treatment and the FTO rs9939609 variant observed for percent of energy from both fat and carbohydrate intakes, but no interaction for protein intakes (Table 4-16). In the SGA-treated group there was a significant difference between genotypes for fat intake (p=0.031; B=6.8) and carbohydrate intake (p=0.037; B= -6.3); and these were not significant in the SGA-naïve group. Interestingly, individuals with the TT genotype had a greater fat intake and a lower carbohydrate intake compared to individuals with the AT/AA genotypes.
Table 4-17 depicts the findings of the adjusted models investigating the effect of the $MC4R$ rs17782313 variant and the interaction of SGA treatment and $MC4R$ rs17782313 variant on total dietary energy and macronutrient intakes. Models were adjusted for SGA treatment, sex, Tanner stage, height, and psychostimulant treatment. No effect of the $MC4R$ rs17782313 variant and no interaction of SGA treatment and the $MC4R$ rs17782313 variant were observed for dietary energy intakes. No interactions between SGA treatment and the $MC4R$ rs17782313 variant were observed for macronutrient intakes; however, there was a significant relationship between the $MC4R$ rs17782313 genotype and dietary protein intakes. Individuals with the TT genotype had lower protein intakes ($p=0.031$; CI: -3.76, -0.197) compared to individuals with the CT/CC genotype (Table 4-17), independent of SGA treatment.
Table 4-14 Unadjusted three-day average energy and macronutrient intakes by SGA treatment and *FTO* rs9939609 genotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SGA-treated</th>
<th>SGA-naïve</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT (n=7)</td>
<td>AT/AA (n=12)</td>
<td>TT (n=6)</td>
</tr>
<tr>
<td>Energy intake</td>
<td>1918 (666.25)</td>
<td>2080 (795.79)</td>
<td>1600 (584.10)</td>
</tr>
<tr>
<td>Macronutrients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>33 (4.05)</td>
<td>27 (4.97)</td>
<td>32 (5.69)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>52 (2.09)</td>
<td>58 (5.36)</td>
<td>52 (6.21)</td>
</tr>
<tr>
<td>Protein</td>
<td>15 (3.12)</td>
<td>15 (1.90)</td>
<td>16 (2.10)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)
Energy intake (kcal); macronutrient intake (% kcal)

Table 4-15 Unadjusted three-day average energy and macronutrient intakes by SGA treatment and *MC4R* rs17782313 genotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SGA-treated</th>
<th>SGA-naïve</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT (n=12)</td>
<td>CT/CC (n=6)</td>
<td>TT (n=10)</td>
</tr>
<tr>
<td>Energy intake</td>
<td>1925 (564.2)</td>
<td>2148 (1085.7)</td>
<td>1595 (558.4)</td>
</tr>
<tr>
<td>Macronutrients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>29 (5.84)</td>
<td>28 (4.73)</td>
<td>29 (6.83)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>56 (5.96)</td>
<td>56 (3.74)</td>
<td>57 (7.51)</td>
</tr>
<tr>
<td>Protein</td>
<td>15 (2.55)</td>
<td>16 (1.86)</td>
<td>14 (2.12)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)
Energy intake (kcal); macronutrient intake (% kcal)
Note: one SGA-treated DNA sample was unable to be genotyped for MC4R
Table 4-16 Association of SGA treatment and FTO rs9939609 genotype with energy and macronutrient intakes

<table>
<thead>
<tr>
<th>Characteristic (%) kcal</th>
<th>SGA*FTO p-value</th>
<th>FTO p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kcal)</td>
<td>0.981</td>
<td>0.925</td>
<td>(-534.6, 487.1)</td>
</tr>
<tr>
<td>Protein intake</td>
<td>0.650</td>
<td>0.539</td>
<td>(-1.24, 2.31)</td>
</tr>
<tr>
<td>Fat intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGA*FTO p-value = the interaction of SGA treatment and FTO rs9939609 genotype
FTO p-value = the association of FTO rs9939609 genotype with each characteristic
p-value determined by general linear models; adjusted for SGA treatment, sex, Tanner stage, height, and psychostimulant treatment
95% CI for the FTO p-value

Table 4-17 Association of SGA treatment and MC4R rs17782313 genotype with energy and macronutrient intakes

<table>
<thead>
<tr>
<th>Characteristic (%) kcal</th>
<th>SGA*MC4R p-value</th>
<th>MC4R p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kcal)</td>
<td>0.885</td>
<td>0.832</td>
<td>(-606.5, 492.0)</td>
</tr>
<tr>
<td>Protein intake</td>
<td>0.055</td>
<td>0.031</td>
<td>(-3.76, -0.197)</td>
</tr>
<tr>
<td>Fat intake</td>
<td>0.664</td>
<td>0.642</td>
<td>(-6.45, 4.05)</td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td>0.272</td>
<td>0.241</td>
<td>(-2.27, 8.61)</td>
</tr>
</tbody>
</table>

SGA*MC4R p-value = the interaction of SGA treatment and MC4R rs17782313 genotype
MC4R p-value = the association of MC4R rs17782313 genotype with each characteristic
p-value determined by general linear models; adjusted for SGA treatment, sex, Tanner stage, height, and psychostimulant treatment
95% CI for the MC4R p-value

Figure 4-15 depicts the unadjusted boxplots of fat and carbohydrate intakes by SGA treatment and FTO rs9939609 genotype and Figure 4-16 depicts the unadjusted protein intake by MC4R rs17782313 genotype.
Figure 4-15 Unadjusted fat and carbohydrate intakes by SGA treatment and \textit{FTO} rs9939609 genotype

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4-15.png}
\caption{Boxplots of unadjusted three-day fat intake (A) and three-day carbohydrate intake (B) by SGA treatment for the \textit{FTO} rs9939609 TT and AT/AA genotypes; boxes represent the median, 25\textsuperscript{th} and 75\textsuperscript{th} quartiles, and whiskers represent the range. Note: Graph A’s y-axis begins at 10.00\% and Graph B’s y-axis begins at 30.00\%.}
\end{figure}
Figure 4-16 Unadjusted protein intake by *MC4R* rs17782313 genotype

**MC4R rs17782313 genotype**

Figure 4-16 Boxplots of unadjusted three-day protein intake for *MC4R* rs17782313 TT and CT/CC genotypes; boxes represent the median, 25th and 75th quartiles, and whiskers represent the range, circles represent outliers. Note: the y-axis begins at 5.00%.
Chapter 5: Discussion

It is widely understood that behaviours in childhood are maintained into adulthood; such behaviours may include smoking, drug abuse, physical activity, sedentary behavior, and of importance to this thesis: dietary practices. Youth suffering from MHCs may be at an increased risk for various adverse health outcomes, such as CVD, due to poor lifestyle and/or risky behaviours that may persist into adulthood\textsuperscript{161,162}. Furthermore, individuals with MHCs are reported to have a reduced life expectancy, and outside of suicide, this is mainly due to CVD implications\textsuperscript{163}. Second-generation antipsychotic treatment has been widely indicated to cause weight gain, adiposity, and cardiometabolic dysfunction in the pediatric population\textsuperscript{8–11,27–29}, adding further health risks upon an individual already bestowed potential health risks from a MHC diagnosis. Dietary intake plays a large role in human health and is also highly modifiable. The argument that increased adiposity and cardiometabolic dysfunction development during SGA treatment may be caused by an increase in dietary energy intake and an overall poor diet is convincing. The neurotransmitter regulation of food intake theory does provide an appropriate explanation for this increase in dietary energy intake, but little research has been done to confirm this in practice. Furthermore, it is difficult to discern to what degree dietary intake may influence this increased adiposity and cardiometabolic dysfunction, especially due to little research done on actual dietary intake in the pediatric population. Therefore, I sought to explore dietary intakes in children with MHCs, both SGA-treated and SGA-naïve. My novel findings include: 1) SGA-treated children may not have greater dietary energy or macronutrient intakes compared to SGA-naïve children; 2) Children with MHCs, independent of SGA treatment, may not be adequately meeting the recommendations for intakes of total fat, saturated fat, sugar, sodium, and fibre; and 3) Dietary sodium intake may be positively associated with HOMA-IR, and dietary saturated fat
intake may be positively associated with LDL-c, both in SGA-treated children.

5.1 Dietary Intakes

In this study I used three-day estimated food records to estimate total, macronutrient, and dietary components in children with MHCs. Dietary data collection in itself has several limitations of which many were addressed in section 1.5.1.2. I will briefly address the limitation of underreporting, specifically in the overweight and obese population, due to my SGA-treated sample having a high rate of overweight and obesity.

There have been various reports of overweight and obese individuals significantly underreporting their energy intake. In obese and overweight as well as non overweight adults it has been widely observed that there is a tendency to underreport\textsuperscript{119,164–166}. Doubly labeled water studies comparing estimated food records and energy expenditure in youth have found that overweight or obese youth have the highest degree of underreporting, but that non overweight youth also underreport\textsuperscript{127,129,167}. Potentially, using parents as proxies for dietary intakes may also cause underreporting. Sometimes, parents of overweight or obese youth, that are overweight or obese themselves, underreport\textsuperscript{124}. This effect of underreporting may have contributed to the lack of detectable differences in energy intake between SGA-treated and SGA-naïve participants. Furthermore, MHCs regardless of SGA treatment may already confer a poor diet\textsuperscript{168–170}, which may also be why no detectable differences in diet were observed between groups, as I did not have a group of healthy control children. These challenges make it difficult to understand and elucidate why those treated with SGAs are at a greater risk for the development of adiposity and cardiometabolic dysfunction.
5.1.1 Diet Compared to the Canadian Population

I used the 2004 Canadian Community health survey (CCHS), cycle 2.2\textsuperscript{171} to compare dietary intake in my sample to dietary intake in a representative sample of Canadian children. The CCHS nutrition survey was conducted in approximately 35,000 adults, adolescents, and children. The CCHS performed a single computer assisted 24-hour recall on each individual as well as a repeat 24-hour recall in a subset of the sample. This methodology does differ slightly when compared to the three-day estimated food record method that I used.

*Macronutrients*

In my sample, recommended dietary fat intakes were not met with 22% below and 20% above the AMDR. The CCHS reported: children 5-8 year had 5.5% below and 6.8% above the AMDR; children 9-13 years had 10.8% of males and 12.1% of females above and <3% and 6.5% of males and females, respectively, below the AMDR; and children 14-18 year had approximately 13% above and <3% below the AMDR for both males and females. My sample showed a much poorer rate of meeting the dietary fat intake requirements compared to youth across Canada. In my sample, 7% were above and 7% were below the AMDR for carbohydrate intake. The CCHS reported <3% above and below for all age groups. Only one participant in my sample was below the AMDR for protein with the rest meeting the recommendation. The CCHS reported similar results with <3% for all age groups not meeting the AMDR and none above the AMDR with the exception of <3% of males aged 14-18 years.

*Saturated fat*

I observed a mean saturated fat intake of ~10% of total energy in my sample. However, when broken down into categories, a high proportion of the SGA-treated individuals (92%) and SGA-naïve individuals (80%) were above the recommended <7% intake. The CCHS indicated a
mean saturated fat intake of approximately 12% of total energy for children aged 1-8 years and 10% of total energy for children aged 9-18 years. This is similar to my sample; however, it would be interesting to see the breakdown of saturated fat intake in categories across Canada, in order to determine how many were above the American Heart Association recommendation of <7% saturated fat intake.

Sugar

Sugar intake, monosaccharides and disaccharides from all sources, in my sample is similar to findings in the CCHS. The mean intake as a percent of energy for both males and females aged 4-8 years was 26.1%, and males and females aged 8-18 years ranged from 24-26%. In my sample, the mean intake of both groups was 20.1%, which is slightly lower than what was observed in the CCHS. However, 70% of the SGA-treated group and 40% of the SGA-naïve group had greater than 20% of energy coming from sugar.

Sodium

Without a biomarker, such as urinary sodium excretion, it is difficult to interpret whether dietary sodium intakes are accurate. There is a high variability of sodium in different food products and brands, making it difficult to understand if the food processor software is up to date and accurate. Furthermore, the reported sodium only includes that already found in foods, not added salt to food from the ‘salt shaker’. However, the observations from the total sample indicate a rate of approximately 70% above the UL for age and sex. The CCHS observed rates above the UL of: ~93% of children aged 4-8 years and ~97% and ~82-83% of males and females aged 8-18, respectively.
**Fibre**

The Canadian Nutrient File only contains naturally occurring fibres and therefore makes it difficult to interpret the CCHS data; however, estimated medians observed were: 14.8 grams per day (g/d) for children aged 4-8 years; 14.0 g/d for females aged 9-18 years; 16.3 g/d for males aged 9-13 years; and 18.2 g/d for 14-18 years. I observed median intakes of 18.8 g/d for the SGA-treated group and 14.5 g/d for the SGA-naïve group, with only 20% of the SGA-treated group and 5% of the SGA-naïve meeting their AI.

Overall, similar rates are seen in my sample to that observed in the Canadian population. Total fat, saturated fat, and fibre intakes may be of some concern in my sample with a large proportion of participants either above or below the recommended intakes.

5.2 **Adiposity and Cardiometabolic Dysfunction**

5.2.1 **Adiposity**

Prior work by my thesis supervisors has reported greater surrogate markers of adiposity (zBMI and waist circumference) and cardiometabolic dysfunction in British Columbian SGA-treated children\(^8,11,31\), which was also observed in my sample. I did not observe differences in energy or macronutrient intakes between the SGA-treated and SGA-naïve groups, nor did I observe any association of energy intake and surrogate measures of adiposity. As was stated in section 5.1, underreporting was a big concern and may be part of the reason no between group differences were observed, and why no associations of energy intake and measures of adiposity were observed. If energy intake is not associated with the development of adiposity in SGA treatment, or at least not to the degree of adiposity being observed, other mechanisms may aid in deciphering what is occurring. One potential mechanism is resting REE and physical activity.
Resting energy expenditure and physical activity

Self-reported physical activity did not differ significantly between treatment groups, suggesting that more sedentary behaviour may not be a significant cause of increased adiposity in the SGA-treated group. One cross-sectional study in adult males with schizophrenia, prescribed clozapine, found an overall low physical activity level (1.39) as determined by doubly labeled water\textsuperscript{172}. The WHO classifies a physical activity level as of < 1.5 as sedentary\textsuperscript{173}. Furthermore, a study in adolescent males with MHCs treated with olanzapine found an overall physical activity level of 2.6\% of time (\~37 minutes) doing moderate to vigorous physical activity (measured by heart rate monitor), and no change in physical activity after four weeks of treatment; however, they were inpatient participants\textsuperscript{110}. Unfortunately, we were unable to obtain REE in my study. There is conflicting evidence regarding SGA medications and REE in the adult population\textsuperscript{172,174–178}. Two longitudinal studies have reported measuring REE in adolescents with MHCs treated with SGAs\textsuperscript{110,179}. The same study in 10 adolescent inpatient males treated for four weeks with olanzapine that found no change in physical activity also measured REE. They also found no changes in REE from baseline to follow up\textsuperscript{110}. Cuerda \textit{et al} reported on 46 adolescents treated with risperidone, olanzapine, and quetiapine at baseline, 1, 3, 6, and 12 months after treatment. The study measured anthropometrics, BIA, and indirect calorimetry. The main observations included an increase in weight, as well as BMI, and no significant change in REE during treatment. However, a decrease in REE adjusting for body weight was observed, and an increase in REE expressed as REE per fat free mass ratio was observed. This hypometabolism showed a significant correlation to the increase in weight.

The effect of SGAs on REE may be a partial explanation for the observed weight gain in children with MHCs; however, evidence is controversial and needs further exploration. This
potential decrease in REE paired with a low habitual physical activity level observed in a majority of individuals with MHCs may, in part, contribute to the observed weight gain.

5.2.2 Diet and Cardiometabolic Dysfunction

*Glucose, insulin, and HOMA-IR*

Carbohydrate intake and composition, and the glycemic index of foods, have well-established effects on glucose and insulin metabolism. The relationship of glucose and insulin metabolism and other dietary components is somewhat more perplexing and often conflicting\(^{180}\). In this study I observed a positive association of dietary total energy intake and HOMA-IR, in the SGA-naïve group and a trend towards significance in the SGA-treated group. I also observed a positive linear relationship between dietary sodium intake and HOMA-IR, in the SGA-treated group. Austin *et al* reported no association of energy intake with HOMA-IR in healthy adult participants, rather overweight and obesity was the most significant association of a greater HOMA-IR\(^{181}\). Austin and colleagues did report a significant positive association of greater saturated fat intake with a greater HOMA-IR in women, but no association was observed in men and no other associations were observed for protein, sugar, monounsaturated or polyunsaturated fat with HOMA-IR.

In my sample, the SGA-treated group had a significantly higher HOMA-IR compared to the SGA-naïve group. The association of HOMA-IR with energy was significant in the SGA-naïve group and trending towards significance in the SGA-treated group; therefore, it is difficult to determine if the SGAs are causing an increase in HOMA-IR greater than what can be explained by the dietary energy intakes. The association of sodium intake with HOMA-IR was significant in the SGA-treated group. Potentially, both the energy and sodium intakes are exacerbating the effect of the SGA on HOMA-IR. The affinity of many SGAs for the muscarinic
receptor may be a potential explanation for a greater HOMA-IR\textsuperscript{25,101}. Teff et al (2011) have postulated that this affinity for the muscarinic receptors may elicit a peripheral blockade in the receptors and in turn impair the post-prandial insulin release during the cephalic phase\textsuperscript{101}. Teff et al (2013) investigated insulin sensitivity and post-prandial metabolism after a mixed meal challenge in 30 healthy individuals treated with olanzapine and aripiprazole for nine days in a controlled environment. They demonstrated that both olanzapine and aripiprazole induced insulin sensitivity, but only olanzapine impaired the post-prandial insulin response\textsuperscript{113}. These associations were demonstrated independent of weight gain, hunger, and dietary intake. This muscarinic receptor mechanism could, in part, be an explanation for a greater HOMA-IR in my SGA-treated group and may be intensified by greater energy and sodium intakes.

\textit{Saturated fat and LDL-c}

I found a significant positive linear association of saturated fat intake as a percent of energy and LDL-c, in the SGA treated group. Interestingly, the SGA-treated group had a lower mean LDL-c compared to the SGA-naïve group; however, there was no significant association of dietary saturated fat intake and LDL-c in the SGA-naïve group. Henderson et al reported total and saturated fat intake using four-day dietary records in clozapine and risperidone treated adults\textsuperscript{114}. They found a higher saturated fat intake (as a percent of total energy) in the clozapine group compared to the risperidone group (mean: 13.7\% vs. 10.6\%); however, they did not have a control group for comparison. To my knowledge, there have been no other studies reporting on saturated fat intake in the SGA-treated population. As a total sample for my study, dietary saturated fat intake was high, and this positive association of saturated fat intake and LDL-c is a cause for concern. This association may be implicated in the development of cardiometabolic dysfunction in an already vulnerable population.
5.3 Genetics

An important factor in the development of adiposity and cardiometabolic dysfunction observed in SGA-treated individuals is that not all treated individuals are susceptible to developing these side effects. As such, underlying biological factors may predispose an individual to weight gain and increased cardiometabolic abnormalities observed during SGA treatment\textsuperscript{22,101,182}. This high inter-individual variability may in part be due to the effect of a medication-gene interaction on dietary intakes. Previous work by my research supervisors has sought to elucidate potential underlying genetic effects. In SGA-treated children, they reported a positive association of the T allele of the methylene-tetrahydrofolate reductase (\textit{MTHFR}) C677T variant with zDBP and fasting plasma glucose concentrations\textsuperscript{31}. Furthermore, they recently reported that SGA-treated children with the Met allele of the catechol-O-methyltransferase gene (\textit{COMT}) rs4680 variant had significantly higher zDBP, zSBP, and fasting plasma glucose when compared to SGA-treated children with no Met allele\textsuperscript{183}. These studies provide a strong reason to believe a similar medication-gene interaction may be occurring with regard to energy intake and diet.

I sought to determine if two genetic variants, \textit{FTO} rs9939609 and \textit{MC4R} rs17782313, both previously associated with obesity\textsuperscript{130–136}, had any effect on dietary energy intake in my sample. I also sought to determine if there was a medication-gene interaction on dietary intakes. The small sample size of my third aim makes it challenging to determine whether my data will hold true at larger sample sizes, or whether it was purely due to chance. I observed no effect of the \textit{FTO} rs9939609 and \textit{MC4R} rs17782313 variants and no interaction with SGAs on dietary energy intake. I did observe a medication-gene interaction for dietary fat and carbohydrate intakes with the \textit{FTO} rs9939609 variant. In SGA-treated group, individuals with the TT
genotype had a greater fat intake but a lower carbohydrate intake compared to individuals with the AT/AA genotypes. Cecil et al (2009) reported on eating behaviours at test meals in children genotyped for the FTO rs9939609 variant\textsuperscript{130}. They observed that children with the AT and AA genotypes had significantly greater energy intake compared to children with the TT genotype. They also observed that children with the AT and AA genotype ingested more energy dense food, determined by kilojoules per gram of food\textsuperscript{130}. There were no differences observed for macronutrient intakes after controlling for energy intake, age, and body weight\textsuperscript{130}. The interaction of the SGA and FTO rs9939609 genotype on fat and carbohydrate intakes is interesting and requires further investigation in larger samples.

Due to issues of methodology, sample size, and rigour for measuring energy intake regarding the MC4R rs17782313 variant, it is hard to compare my findings to other studies\textsuperscript{184}. I observed a gene effect for protein with the MC4R rs17782313 variant, independent of SGA treatment. Qi et al determined dietary intake by a semi-quantitative FFQ in adult females (n=5724) and found greater energy, protein, and fat intakes for those with the CC genotype compared to individuals with the TT genotype for MC4R rs17782313\textsuperscript{148}. They also obtained anthropometric data and stated that these increased energy intakes did not account for the observed findings of adiposity\textsuperscript{148}.

Finally, it would also be very interesting to determine if there was a combined effect of FTO rs9939609 and MC4R rs17782313 variants with regard to energy and macronutrient intake; however, due to low numbers I did not evaluate this.
5.4 Strengths and Limitations

This study has various strengths and limitations. The strengths include multiple days of estimated food records, which decrease the error of variability in diet and better estimate a usual dietary intake for an individual, as well as limit the issue of memory recall\textsuperscript{185,186}. I also observed significant associations of dietary intakes with biomarkers, such as saturated fat intake with LDL-c, which suggests the dietary data collection and information was robust. Furthermore, anthropometric data was measured by trained individuals based on standardized protocols, thereby limiting any error in self-reporting bias or measurement error. Data on fasting blood parameters obtained in a subset of my population also strengthens the study by adding further measures to evaluate. To my knowledge, this is the first study collecting multi-day food records in both male and female children with MHCs, both inpatients and outpatients, across a wide range of MHC diagnoses.

Along with the strengths, the study also had several limitations. Firstly, this study was cross-sectional in nature and therefore causation cannot be inferred. There is convincing evidence from longitudinal studies that SGAs induce weight gain. Due to no baseline food records prior to SGA treatment it is impossible to understand whether the obesity I observed was caused by an increase in energy intake. This study indicated no statistical differences in dietary intakes between SGA-treated and SGA-naïve groups, even though the SGA-treated group had greater adiposity. Another limitation is sample size; due to inadequate power, the difference in energy intake between the SGA-treated and SGA-naïve group could not be detected with only 45 participants. In Table 4-4 (model 1), the estimated marginal means, after adjustments for covariates, suggested a difference of energy intake between groups to be 188 kcal. If this were rounded to a 200 kcal difference between groups, with a standard deviation of 400 kcal, the
sample size required to detect a significant difference at 80% power would be 63 participants in each group.

5.5 Suggestions for Future Research

I would suggest future work to focus on longitudinal studies evaluating various outcomes. Baseline data and follow up assessments at various time intervals are imperative to determine progression of outcomes. Various outcomes and measures that I would suggest are: socioeconomic status, diet, physical activity, resting energy expenditure, body composition, metabolic profile, cardiovascular outcomes, genetic variants, as well as neurohormonal and neurotransmitter evaluations. I would also suggest evaluating how these measures may vary across individual SGAs as well as across various MHC diagnoses. It would be interesting to follow children into adulthood to evaluate how these variables and outcomes may change as they gain more autonomy and independence, as well as to determine the long-term effects of SGAs and MHC diagnoses.

5.6 Conclusions

This study in children with MHCs observed no differences in dietary energy and macronutrient intakes between SGA-treated and SGA-naïve participants. The SGA-treated group had greater measures of adiposity, as well as greater fasting glucose, insulin, and HOMA-IR. These findings suggest that dietary energy intake may not be responsible for increased measures of adiposity in SGA-treated individuals. However, dietary sodium intake was positively associated with HOMA-IR and dietary saturated fat was positively associated with LDL-c, in the SGA-treated group. Further, dietary energy intake was positively association with HOMA-IR in
the SGA-naïve group and trending toward significance in the SGA-treated group. These associations suggest that dietary intakes in SGA-treated children may contribute to cardiometabolic dysfunction. Longitudinal studies as well as baseline dietary records are needed to further evaluate the effect of SGAs on dietary intakes and eating behaviours in children with MHCs.
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181. Austin GL, Krueger PM. Increasing the percentage of energy from dietary sugar, fats, and alcohol in adults is associated with increased energy intake but has minimal association with biomarkers of cardiovascular risk. *J Nutr* 2013;143(10):1651-8.


Appendices

Appendix A: Nutrition study informed consent and assent

Appendix B: Data collection form

Appendix C: Physical activity questionnaire

Appendix D: Assessment of adolescents puberty development form

Appendix E: Dietary intake form

Appendix F: DNA study informed consent and assent
Subject Information and Consent Form

Assessment of dietary intake and physical activity habits in second-generation antipsychotic-treated youth compared to antidepressant-treated youth

Principal Investigator: Dina Panagiotopoulos, MD, FRCPC
Assistant Professor of Pediatrics
Endocrinologist, BC Children's Hospital
Telephone: 604 875 2624

Co-Investigators: Debbie Reid, MSc, RD, University of British Columbia
Jana Davidson, MD, FRCPC, University of British Columbia

Who do I contact if I have questions about the study during my participation?
If you have any questions or desire further information about this study before or during participation you can contact Dr. Dina Panagiotopoulos at 604-875-2624.

Who do I contact if I have any questions or concerns about my rights as a subject during the study?
If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University Of British Columbia Office Of Research Services at 604-822-8598 or, if long distance, toll free at 1-877-822-8598, or email RSIL@ors.ubc.ca.

1. Introduction
You (“You” refers to you, your child or your ward) are being invited to take part in this research study because you are being assessed and followed at BC Children’s Hospital Mental Health.

2. Your Participation is Voluntary
Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

If you do not wish to participate, you do not have to provide any reason for your decision not to participate nor will you lose the benefit of any medical care to which you are entitled or are presently receiving. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. Who is Conducting the Study? The study is being conducted by Dr. Dina Panagiotopoulos.

4. Background: In children, adolescents and adults, there is evidence that certain medications called second generation antipsychotics (SGAs; Risperidone, Quetiapine, Olanzapine, Clozapine, Ziprasidone, Aripiprazole) used to treat mental health conditions may lead to an increased risk of weight gain, diabetes, high blood pressure, high cholesterol levels and abnormal
liver tests. While less is known about these types of side-effects with antidepressant-treatment, there is research in adults showing an increased risk for weight gain and diabetes however, the risk of these side-effects are not well documented or understood in children. The most common side effect found in our research of SGAs is weight gain, although there is little research available looking at whether dietary habits contribute to SGA and antidepressant-related weight gain. Therefore, we are conducting a study to assess dietary and physical activity habits of youth treated with SGAs and antidepressants.

5. WHAT IS THE PURPOSE OF THE STUDY? The purpose of this study is to describe dietary and physical activity habits of youth treated with SGAs compared to youth treated with antidepressants.

6. WHO CAN PARTICIPATE IN THE STUDY? Youth aged 6-19 years who are being treated with either an SGA or an antidepressant.

7. WHAT DOES THE STUDY INVOLVE? This study involves giving your permission to participate in 3 interviews asking about what kinds of foods you ate, how much you ate, when you ate during the last 24 hours, what you drank in the last 24 hours, and what kinds of physical activities you participated in over the last week. Each interview will last approximately 30 minutes. The total time required for this study will be approximately 1.5 hours over 1 week.

Researchers will also review your electronic and paper chart to collect information routinely obtained by the medical staff as part of the initial assessment and ongoing follow up of children treated with either an SGA or an antidepressant. The routine information that will be collected will include, but may not be limited to: age, date of birth, sex, ethnic background, diagnosis, complete medical and family history, medications, height, weight, waist circumference, blood pressure, physical examination and routine laboratory test results. Your name will be replaced by a study ID when your information is entered into the study database. Only Dr. Panagiotopoulos and the research personnel involved in this study will have access to your information.

8. RISKS AND BENEFITS? Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. However, your identification will be protected by assigning a numerical code without any other identifying factors. These codes will not contain your name or any other personally identifying information. Only these codes (study IDs) will be used in the study database. Access to your personal data is granted only under the strictest supervised research protocols and would involve research personnel only. Your personal information may be disclosed if required by law. There may not be a direct benefit to you from taking part in this study. However, we hope that the information learned from this study can be used in the future to benefit other children treated with these types of medicines.

9. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE? Your participation in this research is entirely voluntary. You may withdraw from this study at any time. If you decide to enter the study and to withdraw at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled, and your future medical care will not be affected. The study doctor(s)/investigators may decide to discontinue the study at any time, or withdraw you from the study at any time, if they feel that it is in your best interests. If you choose to enter the study and withdraw or are withdrawn at a later time, all data collected about you during your enrolment in the study will be retained for analysis.
10. WHAT HAPPENS IF SOMETHING GOES WRONG? Signing this consent form in no way limits your legal rights or your child’s, or your ward’s against the investigators or anyone else involved in this study.

11. WHAT WILL THE STUDY COST ME? This study will not cost you anything. You will not be paid to participate in this study.

12. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL? Your confidentiality will be respected. No information that discloses your identity will be released or published without your, or your child’s or your ward’s specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada, and the UBC Research Ethics Boards for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigator’s office.
**SUBJECT CONSENT TO PARTICIPATE**

I have read and understood the subject information and consent form.
I have had sufficient time to consider the information provided and to ask for advice if necessary.
I have had the opportunity to ask questions and have had satisfactory responses to my questions.
I understand that all of the information collected will be kept confidential and that the result will only be used for scientific objectives.
I understand that my participation in this study is voluntary and that I am completely free to decline to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
I understand that I am not waiving any of my legal rights as a result of signing this consent form.
I understand that there is no guarantee that this study will provide any benefits to me.
I have read this form and I freely consent to participate in this study.
I have been told that I will receive a dated and signed copy of this form.

**Optional:**

I give permission for the investigator/research assistant to contact me about future studies.

The parent/guardian and the investigator are satisfied that the information contained in this consent form was explained to the child to the extent that he/she is able to understand it, that all questions have been answered, and that the child assents to participating in the research.

<table>
<thead>
<tr>
<th>Printed name of subject</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Printed name of subject’s parent or legally acceptable representative</td>
<td>Signature</td>
<td>Date</td>
</tr>
<tr>
<td>Printed name of principal investigator/Signature designated representative</td>
<td>Signature</td>
<td>Date</td>
</tr>
</tbody>
</table>
SUBJECT’S ASSENT TO PARTICIPATE IN RESEARCH (Youth aged 14 – 18 years)

I have had the opportunity to read the consent form, to ask questions about my participation in this research, to discuss my participation with my parents/guardians. All my questions have been answered. I may quit this research at any time, and this will not interfere with the availability to me of other health care. I have received a signed and dated copy of this consent form. I assent to participate in this study.

<table>
<thead>
<tr>
<th>Name (printed)</th>
<th>Signature of subject</th>
<th>Date</th>
</tr>
</thead>
</table>

Version 5  
June 01, 2012
SUBJECT ASSENT FORM
Youth aged 7-13 years

Assessment of dietary intake and physical activity habits in second-generation antipsychotic-treated youth compared to antidepressant-treated youth

Invitation
I am being invited to be part of a research study. This research study tries to find better ways to treat and help children like me. It is up to me if I want to be in this study. No one will make me be part of the study. Even if I agree now to be part of the study, I can change my mind later. No one will be mad at me if I choose not to be part of this study.

Why Are We Doing This Study?
I am a youth, age 7-13 years being treated with either a second-generation antipsychotic medication (SGA) or antidepressant. This study is trying to understand which things I eat and drink every day and what kinds of exercise I do.

What Will Happen in This Study?
If I agree to be in this study, a dietitian will ask me questions about what kinds of foods I eat, what I drink, when I eat/drink, and what kinds of activities I like to do. The dietitian will interview me three times. Each interview will take about 30 minutes. The total time required for this study is 1.5 hours over about a week. The researchers will also look at my chart to get information like my height, weight, date of birth, and medications that I am taking. This information will help the doctors to understand why some kids treated with a certain type of medication (called SGAs and antidepressants) might gain weight during their treatment.

If my parents/legal guardians and I choose not to take part in the study, I will still have my height, weight, and blood pressure measured, my family history taken and the usual blood tests performed if the doctors think it will help me. I will also be asked about what I usually eat and drink and what kinds of exercise I do and how often I do exercise.

Who Is Doing This Study?
Dr. Dina Panagiotopoulos from BC Children’s Hospital, along with staff from the Child and Youth Mental Health Services will be doing this study. They will answer any questions that I have about the study. I can also call them at 604 875 2624, if I am having any problems or if there is an emergency and I cannot talk to my parents/legal guardians.

Can Anything Bad Happen to Me?
There is nothing bad that can happen to me in this study.
Who Will Know I Am in the Study?
Only my doctors and people who are involved in the study will know I am in it. When the study is finished, the doctors will write a report about what was learned. This report will not say my name or that I was in the study. My parents/legal guardians and I do not have to tell anyone I am in the study if we don’t want to.

When Do I Have To Decide?
I have as much time as I want to decide to be part of the study. I have also been asked to discuss my decision with my parents/legal guardians.

If I put my name at the end of this form, it means that I agree to be in the study. It doesn’t mean I have to stay until the end of the study. I can still withdraw at anytime during the course of the study. If I want, I can have a signed copy of this form.

Subject’s printed name _______________________ Subject’s signature _______________________ Date _______________________
## Appendix B

### Assessment of dietary intake and physical activity habits in second-generation antipsychotic-treated youth compared to antidepressant-treated youth

#### Data Collection Sheet

**Demographics**

<table>
<thead>
<tr>
<th>DOB</th>
<th>Ethnicity (check one)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1: Asian (Chinese, Japanese, Korean)</td>
</tr>
<tr>
<td></td>
<td>2: South Asian (Indian/Pakistani)</td>
</tr>
<tr>
<td></td>
<td>3: First Nations</td>
</tr>
<tr>
<td></td>
<td>4: Hispanic/Mexican</td>
</tr>
<tr>
<td></td>
<td>5: Black/African/Caribbean</td>
</tr>
<tr>
<td></td>
<td>6: Caucasian</td>
</tr>
<tr>
<td></td>
<td>7: Other __________________________ (specify)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of Admission/Visit</th>
<th>Gender: 1: M □ 2: F □</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Puberty status</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanner Stage:</td>
<td>1: Primary Relative (mother, father, sibling)</td>
</tr>
<tr>
<td>(Females only):</td>
<td>2: Secondary Relative (GM, GF, cousin, aunt, uncle)</td>
</tr>
<tr>
<td></td>
<td>1: Type 1</td>
</tr>
<tr>
<td></td>
<td>2: Type 2</td>
</tr>
<tr>
<td></td>
<td>3: Gestational</td>
</tr>
<tr>
<td></td>
<td>4: No</td>
</tr>
<tr>
<td></td>
<td>5: Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1: Type 1</td>
</tr>
<tr>
<td></td>
<td>2: Type 2</td>
</tr>
<tr>
<td></td>
<td>3: Gestational</td>
</tr>
<tr>
<td></td>
<td>4: No</td>
</tr>
<tr>
<td></td>
<td>5: Unknown</td>
</tr>
</tbody>
</table>

| Hyperlipidemia | 1: yes |
|               | 2: no |
|               | 3: unknown |

| Cardiovascular Disease | 1: yes |
|                       | 2: no |
|                       | 3: unknown |

| Schizophrenia, Schizoaffective Disorder, Psychosis, and/or Bipolar Disorder | 1: yes |
|                                                                             | 2: no |
|                                                                             | 3: unknown |

**Risk Factors**

<table>
<thead>
<tr>
<th>Smoking?</th>
<th>1: Yes ____/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>2: No</td>
<td></td>
</tr>
</tbody>
</table>

| Screen time per day? | _________ hours daily |

Study ID ___________________________
Diagnosis
Axis 1 (primary)

Additional Axis 1

Axis 2
☐ Specify
☐ No D’x (V71.09)
☐ D’x Deferred (799.9)

Axis 3

Axis 5 (CGAF)

Vitals
HEIGHT (cm):
WEIGHT (kg):
BP:
Pulse:
ECG:
0: Not taken 1: normal 2: atypical
WAIST CIRCUM (cm):
HIP CIRCUM (cm):

SGA Medications

Daily Dose (mg)
Duration (months)

1

2

3

Other Medications

Daily Dose (mg)

1

2

3

4

5

6

7

Labs
Fasting Glucose (mmol/L) TSH (mU/L)
Fasting Insulin (pmol/L) AST (U/L)
ALT (U/L) Prolactin µg/L
Total Cholesterol (mmol/L) GGT (U/L)
Triglycerides (mmol/L) Amylase (U/L) Hgb g/L
HDL (mmol/L) WBC x10^9
LDL (mmol/L) Plts x10^9

Study ID ________________________
**Physical Activity Questionnaire**

We would like to know about the physical activity you have done in the last 7 days. This includes sports or dance that make you sweat or make your legs feel tired, or games that make you huff and puff, like tag, skipping, running, and climbing.

**REMEMBER**
- There are no right or wrong answers – THIS IS NOT A TEST
- Please answer all questions as honestly and accurately as you can – this is very important

1. This question is about the PHYSICAL ACTIVITY you do **for more than 5 minutes** at a time in one day in the last 7 days.

**INSTRUCTIONS:**
- Tick (✓) YES for each activity you did in the last 7 days.
- Write down how many minutes you did the activity for each day of the week.
- The activities you do as part of PE (physical education) should ONLY be listed under PE and not listed under other activities. All other questions are about activities IN YOUR SPARE TIME (recess, lunch, after school or on weekends).

For example, if you did the following activities the last 7 days:
- On Monday and Thursday you had 45 minutes of physical education at school;
- On Monday you bicycled for 20 minutes;
- On Saturday you played soccer for 30 minutes.

**You would fill out the chart as follows.**

<table>
<thead>
<tr>
<th>Have you done the following activity?</th>
<th>Yes (✓)</th>
<th>If Yes, how many minutes did you do this activity on the following days?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Monday</td>
</tr>
<tr>
<td>PE (Physical Education at school)</td>
<td>✓</td>
<td>45 min</td>
</tr>
<tr>
<td>Bicycling</td>
<td>✓</td>
<td>20 min</td>
</tr>
<tr>
<td>Soccer</td>
<td>✓</td>
<td>min</td>
</tr>
</tbody>
</table>

**PROCEED WITH THE QUESTION**

<table>
<thead>
<tr>
<th>Have you done the following activity?</th>
<th>Yes (✓)</th>
<th>If Yes, how many minutes did you do this activity on the following days?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Monday</td>
</tr>
<tr>
<td>PE (Physical Education at school)</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Walking for pleasure</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Walking for exercise</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Walking for transportation</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Bicycling for exercise</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Bicycling for pleasure</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Bicycling for Transportation</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Jogging/Running</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Swimming</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Gymnastics: bars, beam, tumbling trampoline</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Exercise: push-ups, sit-ups, weight lifting</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Martial arts</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Dance</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Basketball</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Baseball/Softball</td>
<td></td>
<td>min</td>
</tr>
<tr>
<td>Football</td>
<td></td>
<td>min</td>
</tr>
</tbody>
</table>

PAQ - Version: June 5, 2012
### Have you done the following activity? Yes (✓)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soccer</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Volleyball</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Skating: ice, roller, roller blade</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Racket Sports: badminton, tennis, racketball, ping-pong</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Ball Playing: four square, dodge ball, kickball</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Active Games: chase, tag, hopscotch, hide and seek</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Skipping</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Skateboarding/scooter (non-motorized)</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Hockey: ice, floor, field / Ringette</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Skiiing/Snowboarding</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Cross-country skiing</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Golf</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Chores: vacuuming, mowing, raking, …</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Active video games (dance-dance revolution, Wii)</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Other (specify):</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Other (specify):</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
</tbody>
</table>

2. This question is about other EDUCATION, ENTERTAINMENT, or SOCIAL activities you do in your spare time. Have you done the following activities in the last week?

### Have you done the following activity? Yes (✓)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computer/Internet</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Video Games (inactive/sitting only)</td>
<td>min</td>
<td>min</td>
<td>min</td>
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<tr>
<td>Watching TV or movies</td>
<td>min</td>
<td>min</td>
<td>min</td>
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</tr>
<tr>
<td>Homework/ Studying</td>
<td>min</td>
<td>min</td>
<td>min</td>
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<tr>
<td>Reading (not for school)</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Sitting and talking with friends (not on the phone)</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
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</tr>
<tr>
<td>Talking on the phone</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
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</tr>
<tr>
<td>Sitting and listening to music</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
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<td>min</td>
</tr>
<tr>
<td>Arts &amp; Crafts: drawing, painting</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
<tr>
<td>Other (specify):</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
<td>min</td>
</tr>
</tbody>
</table>

3. Were you sick last week, or did anything prevent you from doing your normal physical activities?

☐ Yes  ☐ No

THANK YOU
The drawings on this page show different stages of development of the breasts. A female passes through each of the five stages shown by these sets of drawings. Please look at each set of drawings and read the sentences under the drawing. Then choose the set of drawings closest to your stage of breast development and mark it 1. Then choose the drawing that is the next closest and mark it 2.

1. Drawing A
2. Drawing B
3. Drawing C
4. Drawing D
5. Drawing E

The nipple is raised a little in this stage. The rest of the breast is still flat.

This is the breast bud stage. In this stage, the nipple is raised more than in stage 1. The breast is a small mound. The areola is larger than in stage 1.

The areola and the breast are both larger than in stage 2. The areola does not stick out away from the breast.

The areola and the nipple make up a mound that sticks up above the shape of the breast. (Note: This stage may not happen at all for some girls. Some girls develop from stage 3 to stage 5, with no stage 4.)

This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back to the general shape of the breast.

Fig. 1
The drawings of this page show different stages of development of the testes, scrotum, and penis. A boy passes through each of the five stages shown by these drawings. Please look at each of the drawings and read the sentences under the drawing. Then choose the drawing closest to your stage of development. Mark a "1" on the line above that drawing. Then choose the drawing that is next closest to your stage of development and mark it "2." In choosing the right picture, look only at the stage of development, not at pubic hair.

1. Drawing A
2. Drawing B
3. Drawing C
4. Drawing D
5. Drawing E

The testes, scrotum, and penis are about the same size and shape as they were when you were a child.

The testes and scrotum have gotten a little larger. The skin of the scrotum has changed. The scrotum, the sack holding the testes, has lowered a bit. The penis has gotten only a little larger.

The penis has grown mainly in length. The testes and scrotum have grown and dropped lower than in stage 2.

The penis has grown even larger. It is wider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes have gotten bigger.

The penis, scrotum, and testes are the size and shape of that of an adult male.

Fig. 4
Appendix E  

Record of Food and Liquids Taken                     Date__________

Instructions:
1. List all food and liquids taken for the whole day
2. Give amounts eg 1 or ½ serving chicken, rice, broccoli etc. 114ml or 4 ounces milk, 1 portion margarine, 1 portion salad dressing, 1 package sugar etc
3. Include name of foods eaten eg: kind of cereal, kind of milk (skim, 2%, whole), type of sandwich
4. Write one item per line

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount</th>
<th>Type of Food</th>
<th>For Office Use Only</th>
</tr>
</thead>
</table>
SUBJECT INFORMATION AND CONSENT FORM

Role of gene polymorphisms in predicting the development of metabolic complications in youth treated with atypical antipsychotics

(DNA Banking)

Secondary Title: Targeting Genomic & Epigenomic Mechanisms Contributing to Cardiometabolic Complications in Children Treated with Second-Generation Antipsychotics and Antidepressants to Mitigate Risk

Principal Investigator: Dina Panagiotopulos, MD, FRCP
Assistant Professor
Department of Paediatrics, Division of Endocrinology
University of British Columbia
Endocrinologist, BC Children’s Hospital
Telephone: 604 875 2624

Co-Investigators: Angela Devlin, PhD
CFRI Scientist Level 1
Jana-Lea Davidson, MD, FRCP
Psychiatrist, BC Children’s Hospital

1. INTRODUCTION

You ("You" herein refers to you or your child) are being invited to take part in this research study for one of two reasons:

1. you are being treated with either a second-generation antipsychotic medication or an antidepressant medication, OR
2. you have been assessed at a mental health unit for mental health challenges but are not being treated with either of the above medication types and would be an appropriate comparison (called a "control")

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

If you do not wish to participate, you do not have to provide any reason for your decision not to participate nor will you lose the benefit of any medical care to which you are entitled or are presently receiving. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.
3. **WHO IS CONDUCTING THE STUDY?** The study is being conducted by Drs. Panagiotopoulos, Devlin, and Davidson.

4. **BACKGROUND:** In adults, there is evidence that certain medications called second generation antipsychotics (SGAs; Risperidone, Quetiapine, Olanzapine, Clozapine, Ziprasidone, Aripiprazole) as well as antidepressants used to treat mental health conditions may lead to an increased risk of weight gain, diabetes, high blood pressure, abnormal cholesterol, and abnormal liver tests. Our research has shown that youth treated with SGAs are 10 times more likely to develop these side effects. For this reason, we want to look at variations in certain genes (called genetic polymorphisms) that may predict which youth develop these side effects.

5. **WHAT IS THE PURPOSE OF THE STUDY?** The purpose of this study is to learn whether the presence of certain gene variations (genetic polymorphisms) puts youth with mental health conditions at a greater risk of weight gain, diabetes, abnormal cholesterol levels, high blood pressure and abnormal liver tests.

6. **WHO CAN PARTICIPATE IN THE STUDY?** Youth aged 2-18 years who are being assessed and followed at one of the mental health units in British Columbia are eligible to participate.

7. **WHAT DOES THE STUDY INVOLVE?** This study involves giving your permission for researchers to take a mouth swab (rubbing the inside of the cheek with a cotton swab) or blood sample from you to look at your DNA to see if there is a relationship between small changes in certain genes (genetic polymorphisms) and side effects from medications. If routine blood work is being done at this time, 3 mLs of blood will be used to look at your DNA. If blood work is not being done at this time, a buccal sample will be used to look at your DNA. Certain genes in your child’s DNA will be looked at in Dr. Devlin’s lab in the Child and Family Research Institute at BC Children’s Hospital. The genes (DNA) that we will be looking at are ones that are related to weight gain and heart disease. If you give your permission, we will collect and store your child’s DNA sample for up to 10 years. If you do not agree to us storing your child’s DNA, samples will be destroyed using bleach.

Researchers will also review your child’s electronic and paper chart to collect information routinely obtained by the medical staff as part of the initial assessment and ongoing follow up of mental health services. The routine information that will be collected will include, but may not be limited to: age, date of birth, sex, ethnic background, diagnosis, complete medical and family history, medications, height, weight, waist and hip circumference, blood pressure, physical examination and routine laboratory test results. If your child is already participating in the Why Weight study or the Determinants of Weight Gain and Diabetes Risk with SGA Treatment study then information already collected for those studies will be collected for this study before the end of the previous studies.

Only Drs. Panagiotopoulos, Davidson and Devlin and the research personnel involved in this study will have access to your child’s information.

8. **RISKS AND BENEFITS?** Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. However, your identification will be protected by assigning a numerical code without any other identifying factors. These codes will not contain
your name or any other personally identifying information. Only these codes (study IDs) will be used in the study database and to label your DNA samples. Your name will not appear on the DNA sample. Access to your personal data is granted only under the strictest supervised research protocols and would involve research personnel only. Your personal information may be disclosed if required by law. There may not be a direct benefit to you from taking part in this study. However, we hope that the information learned from this study can be used in the future to benefit other children treated for mental health conditions, specifically in predicting which youth are at risk for developing metabolic side effects from AAP and antidepressant treatment.

9. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE? Your participation in this research is entirely voluntary. You may withdraw from this study at any time. If you decide to enter the study and to withdraw at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled, and your future medical care will not be affected. The study doctor(s)/investigators may decide to discontinue the study at any time, or withdraw you from the study at any time, if they feel that it is in your best interests. If you choose to enter the study and withdraw or are withdrawn at a later time, all data collected about you during your enrolment in the study will be retained for analysis. If you decide to withdraw, your DNA sample will be destroyed in Dr. Devlin’s lab using a 0.5% bleach solution.

10. WHAT HAPPENS IF SOMETHING GOES WRONG? Signing this consent form in no way limits your legal rights or your child’s, or your ward’s against the sponsors, investigators or anyone else involved in this study.

11. WHAT WILL THE STUDY COST ME? This study will not cost you anything. You will not be paid to participate in this study.

12. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL? Your, and your child’s, or your ward’s confidentiality will be respected. No information that discloses your identity will be released or published without your, or your child’s or your ward’s specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada, and the UBC Research Ethics Boards for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators’ office.

13. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION? If you have any questions or desire further information about this study before or during participation you can contact Dr. Dina Panagiotopoulos at 604-875-2624.

14. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT DURING THE STUDY? If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University Of British Columbia Office Of Research Services at 604-822-8598 or, if long distance, email to RSIL@ors.ubc.ca.
Role of gene polymorphisms in predicting the development of metabolic complications in youth treated with atypical antipsychotics (DNA Banking)

Secondary Title: Targeting Genomic & Epigenomic Mechanisms Contributing to Cardiometabolic Complications in Children Treated with Second-Generation Antipsychotics and Antidepressants to Mitigate Risk

<table>
<thead>
<tr>
<th>SUBJECT CONSENT TO PARTICIPATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have read and understood the subject information and consent form.</td>
</tr>
<tr>
<td>I have had sufficient time to consider the information provided and to ask for advice if necessary.</td>
</tr>
<tr>
<td>I have had the opportunity to ask questions and have had satisfactory responses to my questions.</td>
</tr>
<tr>
<td>I understand that all of the information collected will be kept confidential and that the result will only be used for scientific objectives.</td>
</tr>
<tr>
<td>I understand that my participation in this study is voluntary and that I am completely free to decline to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.</td>
</tr>
<tr>
<td>I understand that I am not waiving any of my legal rights as a result of signing this consent form.</td>
</tr>
<tr>
<td>I understand that there is no guarantee that this study will provide any benefits to me</td>
</tr>
<tr>
<td>I have read this form and I freely consent to participate in this study.</td>
</tr>
<tr>
<td>I have been told that I will receive a dated and signed copy of this form.</td>
</tr>
</tbody>
</table>

☐ I give permission to have my DNA specimen (blood or buccal genetic sample) collected

☐ I give permission to have my child’s information collected and stored in a confidentially password protected manner and identified by coded numbers only

☐ I give permission for the investigator/research assistant to contact me about future studies

The parent/guardian and the investigator are satisfied that the information contained in this consent form was explained to the child to the extent that he/she is able to understand it, that all questions have been answered, and that the child assents to participating in the research.

<table>
<thead>
<tr>
<th>Printed name of subject</th>
<th>Signature</th>
<th>Date</th>
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<table>
<thead>
<tr>
<th>Printed name of subject’s parent or legally acceptable representative</th>
<th>Signature</th>
<th>Date</th>
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</table>

<table>
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<tr>
<th>Printed name of principal investigator/Signature designated representative</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
Role of gene polymorphisms in predicting the development of metabolic complications in youth treated with atypical antipsychotics (DNA Banking)

Secondary Title: Targeting Genomic & Epigenomic Mechanisms Contributing to Cardiometabolic Complications in Children Treated with Second-Generation Antipsychotics and Antidepressants to Mitigate Risk

SUBJECT’S ASSENT TO PARTICIPATE IN RESEARCH (Youth aged 14 – 18 years)

I have had the opportunity to read the consent form, to ask questions about my participation in this research, to discuss my participation with my parents/guardians. All my questions have been answered. I may quit this research at any time, and this will not interfere with the availability to me of other health care. I have received a signed and dated copy of this consent form. I assent to participate in this study.

<table>
<thead>
<tr>
<th>Name (printed)</th>
<th>Signature of subject</th>
<th>Date</th>
</tr>
</thead>
</table>
SUBJECT ASSENT FORM
Youth aged 7-13 years

Short Study Title: Gene Polymorphisms and Metabolic Side Effects of Atypical Antipsychotics and Antidepressants

Invitation
I am being invited to be part of a research study. This research study tries to find better ways to treat and help children like me. It is up to me if I want to be in this study. No one will make me be part of the study. Even if I agree now to be part of the study, I can change my mind later. No one will be mad at me if I choose not to be part of this study.

Why Are We Doing This Study?
This study is trying to understand whether changes in my DNA can affect whether I develop side-effects (like weight gain, diabetes) if I am treated with a certain type of medicine called atypical or second generation antipsychotic or antidepressant. This study will involve giving my permission for the researchers to take a mouth swab or blood sample from me to look at my DNA. There may not be an immediate benefit to me from taking part in this study. However, information from this study may eventually help treat children like me.

What Will Happen in This Study?
If I agree to be in this study, the researchers will take a mouth swab (rub a cotton swab on the inside of my mouth) or take a blood sample (if one is already being taken for another reason) from me to look at my DNA. If it is ok with me, the researchers will keep my DNA sample for up to 10 years. The researchers will also look at my chart to get information like my height, weight, date of birth, blood pressure and blood work results. If I am already in the Why Weight study or the Determinants of Weight Gain and Diabetes Risk Study, the information already collected for these studies will be used for this study before the end of the previous studies.

If my parents/legal guardians and I choose not to take part in the study, I will still have my height, weight, and blood pressure measured, my family history taken and the usual blood tests performed if the doctors think it will help me.

Who Is Doing This Study?
Dr. Dina Panagiotopoulou and other doctors from Children’s Hospital, along with the staff from the Child and Youth Mental Health Services, will be doing this study. They will answer any questions that I have about the study. I can also call them at 604 875 2624, if I am having any problems or if there is an emergency and I cannot talk to my parents/legal guardians.

Can Anything Bad Happen to Me?
There is nothing bad that can happen to me in this study.

Who Will Know I Am in the Study?
Only my doctors and people who are involved in the study will know I am in it. When the study is finished, the doctors will write a report about what was learned. This report will not say my name or that I was in the study. My parents/legal guardians and I do not have to tell anyone I am in the study if we don’t want to.

When Do I Have To Decide?
I have as much time as I want to decide to be part of the study. I have also been asked to discuss my decision with my parents/legal guardians.

If I put my name at the end of this form, it means that I agree to be in the study. It doesn’t mean I have to stay until the end of the study. I can still withdraw at anytime during the course of the study. If I want, I can have a signed copy of this form.

☐ I give permission to have my DNA sample stored for 10 years to be used for research purposes related to mental illness

☐ I do not give permission to have my DNA sample stored for 10 years to be used for research purposes related to mental illness

________________________ _______________________ ____________
Subject’s printed name    Subject’s signature    Date