Appetite-Regulating Hormones and Eating Behaviors in Children with Autism Spectrum Disorder

by

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Abstract

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that involves deficits in social, behavioral, and communicative domains. As an increasing number of children are diagnosed with ASD, within Canada and globally, there has also been increased findings of higher rates of overweight and obesity among this population. Excessive weight gain is of concern due to the social, physical, and psychological impacts of obesity and its secondary associated disorders. Particularly for individuals with ASD and families, this can lead to an added burden placed onto this already vulnerable population. In order to improve the effectiveness of treatments and curb the development of overweight and obesity in ASD, a more comprehensive understanding of some of the underlying mechanisms such as possible hormonal factors and feeding behaviors is needed. Therefore, the overall objective of this research was to (1) assess the risk factors for unhealthy weight gain and obesity that have been implicated in ASD, (2) examine hormones involved in regulation of appetite and energy balance (leptin, ghrelin, GLP-1, PYY, insulin) and how they may differ based on weight status among children with ASD, and (3) to explore differences in mealtime feeding behaviors among groups of varying weight status with ASD.

In chapter 2, risk factors for unhealthy weight gain and obesity were explored among children with ASD. We discussed the role of selective feeding behaviors, which are often related to sensory challenges and specific behavioral phenotypes, such as restricted and repetitive behaviors. We also discussed the research on physical activity opportunities and sedentary behaviors among this population. Parents also often report more barriers to physical exercise due to the social nature of many activities. Furthermore, we discussed the role of genetics and specific genes that have been implicated in both ASD and obesity development. In addition, many children with ASD often present with secondary comorbidities (e.g., depression), and medications to manage these symptoms can further impact weight status. We

also discussed emerging factors, which we defined as factors independently associated with increased risk for both obesity and ASD, that have not yet been studied as risk factors for unhealthy weight gain and obesity among children with ASD. The latter included the gut microbiota, endocrine influences, and maternal metabolic disorders.

Chapter 3 summarizes the findings of a cross-sectional study comprised of 21 children with ASD between the ages of 5 to 12 years old. Of the recruited children, 15 were of normal weight (NW) status and 6 children were of overweight or obese (OWOB) weight status. Information through anthropometric measurements, blood samples, and questionnaires was collected. The major findings of this study included that under fasting conditions, the group with OWOB weight status was found to have higher leptin concentrations (p=0.018). We also found there were higher reported feeding challenges among the OWOB group (p=0.045).

The major findings of this thesis are that a combination of behavioral, lifestyle, and physiological components contribute to overweight and obesity among children with ASD. This research highlights that behavioral and hormonal factors may also contribute to accelerated weight gain among children with ASD, and there is a need for further research to clarify the interplay among these factors in order to better define potential targets for prevention and intervention strategies.

Preface

This preface is an overview of the work completed in partial fulfillment of the requirements of a MSc., it is followed by more detailed prefaces at the beginning of each chapter.

Chapter 2 of this thesis has been published as Dhaliwal KK, Orsso CE, Richard C, Haqq AM, Zwaigenbaum L. Risk Factors for Unhealthy Weight Gain and Obesity among Children with Autism Spectrum Disorder. *Int J Mol Sci*. 2019 Jul 4;20(13). pii: E3285. doi: 10.3390/ijms20133285.

Dr. A.M. Haqq, Dr. L. Zwaigenbaum and I devised the main conceptual ideas and outline of the review. I wrote the review and conducted the literature search. C.E. Orsso contributed additional support in writing to gut microbiome section of the review. C.E. Orsso, Dr. A.M. Haqq., and Dr L. Zwaigenbaum provided their expertise and contributed to revising the article critically for important intellectual content and editing. Dr. C. Richard provided her expertise in nutrition and contributions to revisions. All authors read and approved the final manuscript.

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All work presented in this thesis was critically assessed for intellectual content by my supervisors, Drs. Andrea Haqq and Lonnie Zwaigenbaum, supervisory committee member, Dr. Caroline Richard, and external committee member, Dr. Jacqueline Pei. Versions of some chapters have led to submitted or published journal articles.

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List of Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder

AMDR: Acceptable Macronutrient Distribution Range

ASA-24: Automated Self-Administered 24-hour Tool

ASD: Autism Spectrum Disorder

BAMBI: Brief Autism Mealtime Behavior Inventory

BMI: Body Mass Index

BPFA: Behavior Pediatrics Feeding Assessment Scale

C-PAQ: Children's Physical Activity Questionnaire

CPS: Canadian Pediatric Society

FFQ: Food Frequency Questionnaire

GFCF: Gluten-Free Casein-Free

GI: Gastrointestinal

GLP-1: Glucagon-Like Peptide- 1

HNRU: Human Nutrition Research Unit

IQR: Interquartile range

Kg: Kilograms

MVPA: Moderate- to Vigorous-intensity Physical Activity

NW Normal Weight

OSA: Obstructive Sleep Apnea

OWOB: Overweight Obese

PA: Physical Activity

PBS: Phosphate-buffered Saline

PYY: Peptide YY

PWS: Prader-Willi Syndrome

RCT: Randomized Controlled Trial

SB: Sedentary Behavior

SCFA: Short-Chain Fatty Acid

SD: Standard Deviation

SGA: Second Generation Antipsychotic

SLP: Speech Language Pathologist

SRS-2 Social Responsiveness Scale-2

SSRI: Selective Serotonin Reuptake Inhibitors

TD: Typically Developing

TNF-α: Tumor Necrosis Factor- α

Chapter 1 Introduction

1.1 Thesis Organization

For my graduate research, I conducted a literature review and study exploring the role of various factors on unhealthy weight gain and obesity in children with Autism Spectrum Disorder (ASD). This thesis comprises of two articles, which have been, or will be, submitted to peer-reviewed journals for publication. The first is a literature review reporting on: (1) risk factors for obesity and unhealthy weight gain in children with ASD and (2) a look at emerging risk factors in novels area of research. This review serves as the background and rationale for the work of chapter 3. The second article is the cross-sectional study designed to consider the differences in appetite-regulating hormones and feeding behaviors in children with ASD of differing weight status.

1.2 Introduction

In Study 1, we conducted a literature review considering factors that may be contributing to overweight and obesity in children with ASD, and the possible role of emerging factors with a plausible relationship to regulation of energy balance and thus weight status in ASD. Findings from Study 1 were intended to inform the design and interpretation of Study 2, a pilot study to examine whether hormonal levels – specifically, ghrelin, leptin, and insulin levels– and mealtime behaviors differ in children with ASD that are overweight and obese (ASD+OWOB) compared to normal weight children with ASD (ASD+NW). In this thesis, the literature review is a published manuscript (Chapter 2). Study 2, including design and methodology, has been reported in a separate manuscript and will be submitted for publication (Chapter 3). This chapter is an introduction to my thesis. It includes the background literature, research objectives, and an outline of each chapter's contribution to my thesis.

1.3 Background

1.3.1 Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, with a prevalence of 1 in 66 in Canadian children and youth (Ofner et al., 2018). The diagnostic criteria for ASD includes persistent deficits in domains of social-emotional reciprocity, nonverbal communication behaviors, and developing, maintaining, and understanding relationships

(American Psychiatric Association, 2013). A diagnosis of ASD also includes the presence of restricted, repetitive patterns of behavior, interests, or activities such as stereotyped and repetitive movement, restricted interests, hyper- or hypo reactivity to sensory inputs, and inflexible and highly rigid routines (American Psychiatric Association, 2013). The clinical phenotype, severity, and frequency of symptoms varies in ASD (Ofner et al. 2018). Its etiology is heterogeneous and not fully determined although there is a growing evidence for contributions of genetic, environmental, and biological factors (Fett-Conte et al., 2015).

The DSM-5 criteria suggest that these symptoms present early in development and cause clinically significant impairment in social, occupational, or other areas (American Psychiatric Association, 2013). In addition, these challenges cannot be better explained by another intellectual disability or developmental delay (American Psychiatric Association, 2013). Along with the social impairments, children with ASD may have co-occurring diagnoses such as anxiety, obsessive compulsive disorders, other developmental disorders (including Attention Deficit Hyperactivity Disorder), and sleep disorders (Romero et al., 2016).

The Canadian Pediatric Society (CPS) recommends a multidisciplinary approach to the diagnostic evaluation of Autism Spectrum Disorder (ASD) (Ip et al., 2019). Specifically, physicians, clinical psychologists, and clinical nurse practitioners with specialized training can diagnose ASD (Zwaigenbaum et al., 2019). A diagnosis can be made by a sole pediatric care provider or could involve a team-based approach involving multiple health care professionals (Zwaigenbaum et al., 2019). ASD is diagnosed in all racial, ethnic, socioeconomic, and social groups (Becerra et al., 2014; Thomas et al., 2012). It is four to five times more likely to affect boys than girls (Christensen et al., 2016). Early detection and intervention are emphasized to improve long term outcomes (Zwaigenbaum et al., 2019). The CPS practice guidelines recommend monitoring and assessments for early behavioral signs in children (e.g., parental concerns of language delays); and those that may have an elevated risk (e.g., family history of ASD, older parental age, and extreme prematurity) (Zwaigenbaum et al., 2019). Evaluations can include the collection of data around developmental history, structured interactive assessments (aimed at informing review of DSM-5 symptoms), and additional assessments of a child's overall development (Zwaigenbaum et al., 2019). The criterion for an ASD diagnosis is based on The Diagnostic and Statistical Manual 5 (DSM-5) for mental health disorders (2013).

Post-diagnosis evaluations are multi-faceted, ranging from etiological testing (e.g., genetic tests), further assessment of ASD-associated challenges (e.g., speech-language therapy and occupational therapy), and family and support interventions (e.g., connecting families with

local community supports and respite care) (Ip et al., 2019). There is also an emphasis on the importance of monitoring for common comorbidities such as gastrointestinal symptoms, nutritional challenges, sleep disorders, and ADHD, among others (Ip et al., 2019). In line with this, weight changes should be monitored closely due to the adverse effects this can have on physical and psychological wellbeing.

1.3.2 Childhood Obesity

Children with ASD are at higher risk of becoming overweight or obese than their typically developing (TD) peers (Kahathuduwa et al., 2019). Obesity is defined as a body mass index (BMI) -for-age $\geq 95^{th}$ percentile and overweight are BMI-for-age $\geq 85^{th}$ percentile (Centers for Disease Control and Prevention, 2018). Childhood obesity is the "most blatantly visible- yet most neglected" health concern worldwide (World Health Organization, 2003). Children with a higher BMI are usually at a higher risk of obesity-associated health problems, including insulin resistance, diabetes, heart disease, and certain cancers (Garg et al. 2014; Gallagher et al., 2015). Obesity can be attributed to genetic, biological, societal, and environmental factors (Faith & Kral, 2006). Obesity in childhood can also adversely affect quality of life, with respect to physical, social, and school functioning (Khodaverdi et al., 2011). For example, obesity can interfere with the ability of children to participate in recreational activities leading to an imbalance between intake and energy expenditures, as well as contributing to social isolation (Puglisi et al., 2010).

Weight stigmatization among youth is also heavily reported; for example, Puhl et al. (2011) found that adolescents perceived that being overweight was the primary reason for being bullied at school (Puhl et al., 2011). Weight-based stigma can lead to social isolation and marginalization, with greater reported rates of children of higher weight status' feeling excluded from social activities and ignored (Puhl et al., 2011; Haye et al. 2017). Weight stigma has many social, psychological, and biological consequences. For example, weight stigma can actually further perpetuate unhealthy weight gain and obesity (Tomiyama et al., 2018) and in their meta-analysis, Emmer et al. (2020), found that weight stigma led to a wide range of negative mental health outcomes (e.g., depression, anxiety, and psychological distress) (Emmer et al., 2020).

Furthermore, overweight and obesity also contribute heavily to health care costs with both direct (e.g., rehabilitation and medical expenses) and indirect (e.g., lost productivity in schools) spending (Dee et al., 2014). The term 'obesogenic' is often used to refer to societal

and environmental factors (e.g., sedentary lifestyles) that have a collective effect in perpetuating weight gain (Henauw et al., 2015; Lake & Townshend, 2006; Lipek et al., 2015).

1.3.3 Obesity in ASD

Kahathuduwa et al. (2019), found that children with ASD had a 41.1% greater risk of developing obesity than TD children (Kahathuduwa et al., 2019). Several factors might contribute to accelerated unhealthy weight gain in children with ASD; these include factors that may be more specific to the ASD phenotype as well as those more common among children generally. It is often difficult to identify the causes of obesity in individual children with ASD because we do not know why potential risk factors affect some susceptible children more than others. Research suggests that diet and physical activity behaviors may be harder to regulate among children with ASD; thus, there may be increased intake of food and reduced energy expenditure, leading to a higher risk for development of obesity in children with ASD (Curtin et al., 2014; Zheng et al., 2017). However, we also do not know the rate to which these behaviors have been targeted in intervention studies and are likely understudied; therefore, we do not know how resistant to change these behaviors may genuinely be. Furthermore, there may also be biological factors such as the possible influences of endocrine factors and the gut microbiome (Davis, 2016; Raghavan et al., 2018). Therefore, this combination of unique factors may put this group at a higher risk of developing obesity and possibly other related diseases.

Multiple studies have also reported obesity and overweight to arise earlier in children with ASD, compared to when obesity and overweight typically appears among TD children (Hill et al., 2015). Specifically, Hill et al. (2015) found that in the general population, the overweight prevalence was 10.9% higher among children between the ages of 6 to 11 years compared to the 2 to 5-year-old group. However, among the group with ASD it was only 1.9% higher in the 6 to 11 years old age group (Hill et al., 2015). Furthermore, Raghavan et al. (2018) followed a birth cohort considering various clinical (such as weight at birth, maternal BMI, etc.) and metabolic parameters (such as cord and early childhood leptin levels). They found that extremely rapid weight gain during infancy was associated with a greater ASD risk (Raghavan et al., 2018). These findings suggest that growth trajectories may differ between TD children and children with ASD, highlighting the need for longitudinal studies that can track growth and development over time.

Some current factors which have been identified as possible contributors to unhealthy weight gain among children with ASD include decreased opportunities for physical activity, which may be due to social and behavioral challenges in children with ASD (McCoy et al., 2016; Stanish et al., 2017). There is also ample evidence of food selectivity in ASD, which could go on to impact direct energy consumption (Broder-Fingert et al., 2014). For example, Esteban- Figuerola et al. (2018) found adequate consumptions of protein, fruits, and vegetables, but lower than recommended consumption of dairy products among children with ASD, when compared to dietary reference intakes (Esteban-Figuerola et al., 2018). There have also been findings of micronutrient deficiencies such as vitamin D and calcium in children with ASD (Esteban-Figuerola et al., 2018). Furthermore, as mentioned earlier, there are secondary comorbidities such as sleep disorders (e.g., insomnia) and GI disorders (e.g., irritable bowel syndrome), which are often reported in children with ASD, which can also impact weight status (Elrod et al., 2016; McElhanon et al., 2014). In line with this, many secondary comorbidities often also may require symptom management and/or treatment, and thus, medications can also impact weight status (Bak et al., 2014). These are some of the risk factors that have been studied; however, there is also a need to further explore possible physiological drivers of weight gain in ASD due to evidence of altered weight trajectories (Hill et al., 2015) and hormonal level differences, specifically of certain appetite hormones such as leptin (Raghavan et al., 2018).

Except in the context of medication effects (e.g., atypical antipsychotics), few studies have looked at hormonal pathways that might contribute to unhealthy weight gain in this population. The majority of studies have tended to focus on behavioral and lifestyle factors contributing to the overweight and obesity reported in ASD. There are a few studies that have started to look at hormones (including appetite influencing hormones), in ASD, to better understand possible early phenotypes and aetiologies for ASD. Ghrelin is an appetite stimulating hormone (Nakazato et al., 2001). The exact role of ghrelin in childhood obesity (without ASD) is not entirely understood as there may be suppression of ghrelin in obesity; however, fasting ghrelin levels have also been found to be lower in children with ASD when compared to NW controls (Cummings et al., 2002; Al-Zaid et al., 2014). Leptin is produced by adipose tissue, proportionate to fat mass (Hallioglu et al., 2003). It is an adipocyte hormone, which acts as a satiety signal (Morton et al., 2005). It is believed that leptin resistance, in obesity, may play a role in in changes to leptin signalling which may then be resulting in changes to energy homeostasis and consequent weight gain (Plum et al., 2006). There have been recent reports of hormone level differences in persons with ASD compared to those

without ASD. Specifically: decreased ghrelin (Al-Zaid et al., 2014) and increased leptin concentrations (Ashwood et al., 2008; Hasan et al., 2019) have been reported in ASD. However, current literature has focused on understanding the possible role of these hormones differences in explaining ASD pathogenesis. Although research in this area is limited, the presence of hormone level differences could also suggest the possibility that neuroendocrine factors may also be a possible factor contributing to higher reported rates of overweight and obesity in this population. And because ASD is a highly heterogeneous condition, for which group differences may obscure individual variation, it is essential to explore hormone levels in relation to weight status.

Research into feeding behaviors and hormonal differences in children with syndromic forms of obesity such as Prader-Willi syndrome (PWS), has informed the pathophysiological mechanisms of obesity in childhood more generally and has led to changes in clinical practice (Butler, 2006). Research into hormonal differences (e.g., hyperghrelinemia) in special populations, such as PWS, has led to the development of targeted and effective treatments (e.g., ghrelin antagonists) for obesity (Haqq et al., 2008; Rodriguez et al., 2018). Similarly, findings on specific biomarkers and their influence on overweight and obesity may have the potential to influence clinical practice and management and treatment of these conditions in ASD.

There is scarce information on how obesity is managed in a primary care setting, among children with ASD. Walls et al., (2018) found that while many primary care pediatricians agreed that they should be the main care providers for managing obesity in children with ASD, they were more likely to refer this group to a developmental pediatrician and/or dietitian, compared to a child that did not have ASD (Walls et al., 2018). These study's findings highlighted that primary care providers found weight management to be more challenging in children with ASD. Findings also suggested that there were certain modifiable factors, such as building on a physician's self-efficacy in counselling around screen time among children with ASD, which could serve to improve the care around weight management for this group (Walls et al., 2018). This study emphasizes the importance of integrating knowledge around risk factors for obesity and overweight among this group, so that health care providers may feel more empowered with knowledge when engaging in informed discussions around weight management with children and parents.

1.4 Study Rationale and Objectives

Although reviews exploring various risk factors for obesity have been previously published, a recent surge of research investigating correlates of obesity in ASD justified an

updated literature review. We considered risk factors that have been considered in previous literature as well as considered emerging risk factors that have not previously been associated with weight status in children with ASD. This is followed by an original, cross-sectional study aimed to better understand relevant knowledge gaps identified in the literature review, specifically a focus on comparing hormonal levels and feeding behaviors among different weight status' among children with ASD. The study objectives include discussing risk factors for unhealthy weight gain and obesity in children with ASD and considering differences in hormonal levels and specific feeding behaviors (such as Food Refusal and Limited Variety of foods) that may contribute to higher rates of obesity in children with ASD.

The matters addressed by this thesis are timely and relevant due to the heightened awareness around public health concerns related to obesity in children, including those with ASD. This research may inform future interventions and provide a better understanding on whether there are hormonal differences, that may serve as biomarkers, that could help in understanding differences among groups of varying weight status'. Early intervention of unhealthy weight gain is essential as children with obesity have an increased risk for adulthood obesity with serious complications including morbidity and mortality (Llewellyn et al., 2016). More targeted research in this area is needed in order to decrease the burden of challenges that this, already vulnerable, population faces.

1.5 Research Questions

This thesis sought to understand the risk factors for obesity and unhealthy weight gain in children with ASD, by answering the following specific research questions:

1. What are the risk factors for unhealthy weight gain and obesity that have been implicated in children with ASD?
2. Do physiological factors, specifically hormones and feeding behaviors (e.g., refusing foods and eating limited varieties of foods), differ among children with ASD with obesity and overweight status and normal weight status?

Chapter 2 Risk Factors for Unhealthy Weight Gain and Obesity among Children with Autism Spectrum Disorder

2.1 Preface

This chapter describes risk factor for obesity and overweight among children with ASD and is adapted from a published article in the International Journal for Molecular Sciences. Dhaliwal KK, Orsso CE, Richard C, Haqq AM, Zwaigenbaum L. Risk Factors for Unhealthy Weight Gain and Obesity among Children with Autism Spectrum Disorder. *Int J Mol Sci*. 2019 Jul 4;20(13). pii: E3285. doi: 10.3390/ijms20133285.

2.2 Abstract

Autism Spectrum Disorder (ASD) is a developmental disorder characterized by social and communication deficits and repetitive behaviors. Children with ASD are also at a higher risk for developing overweight or obesity than children with typical development (TD). Childhood obesity has been associated with adverse health outcomes, including insulin resistance, diabetes, heart disease, and certain cancers. Importantly some key factors that play a mediating role in these higher rates of obesity include lifestyle factors and biological influences, as well as secondary comorbidities and medications. This review summarizes current knowledge about behavioral and lifestyle factors that could contribute to unhealthy weight gain in children with ASD, as well as the current state of knowledge of emerging risk factors such as the possible influence of sleep problems, the gut microbiome, endocrine influences and maternal metabolic disorders. We also discuss some of the clinical implications of these risk factors and areas for future research.

2.3 Introduction

Autism Spectrum Disorder (ASD) is a developmental disorder characterized by social and communication impairments and repetitive behaviors (Zwaigenbaum et al., 2019); the global prevalence is estimated at 1 in 160 children (World Health Organization., 2018), although current North American estimates are around 1 in 60 children (Christensen et al., 2016; Ofner et al., 2018). Children with ASD are also often at an increased risk for becoming obese (e.g., body mass index [BMI]-for-age ≥95th percentile) or overweight (e.g., BMI-for-age ≥85th percentile) than children with typical development (TD) (Hill et al., 2015; Hyman et al., 2012; Zheng et al., 2017). These BMI levels are associated with adverse health outcomes, including insulin resistance, diabetes, heart disease, and certain cancers (Steinberger Julia & Daniels Stephen R., 2003; Weihrauch-Blüher et al., 2019). Obesity in childhood can also adversely affect physical, emotional, and social functioning, as well as academic performance (Khodaverdi et al., 2011), which might compound disability and reduced quality of life associated with ASD.

Some known key factors that may play a mediating role in the higher rates of obesity observed in children with ASD include eating behaviors (L. Bandini et al., 2017), lifestyle (Askari et al., 2015), secondary comorbidities (Ferguson et al., 2017), and medications usage (Maneeton et al., 2018). There is also evidence showing that reduced gut microbiota diversity, hormonal imbalances (Ashwood et al., 2008; Blardi et al., 2010; Tareen & Kamboj, 2012),

and maternal metabolic disorders (Reynolds et al., 2014; Y. Wang et al., 2017) may influence the development of either ASD or childhood obesity alone. However, it is yet not clear whether and to what extent these emerging factors are contributors for unhealthy weight gain and obesity among children with ASD. We define emerging risk factors as factors independently associated with increased risk for both obesity and ASD that have not yet been studied as risk factors for unhealthy weight gain and obesity among children with ASD.

Preventing unhealthy weight gain and obesity among children with ASD is crucial, as obesity affects overall children's health and well-being and often persists into adulthood (Han et al., 2010). To develop appropriate strategies with increased efficacy, a comprehensive understanding of the risk factors for obesity development in ASD is required. Therefore, the purpose of this narrative review is to critically summarize current knowledge of behavioral, lifestyle, and biological factors potentially contributing to unhealthy weight gain in children with ASD. We also discuss the current state of knowledge of novel emerging risk factors for pediatric obesity in ASD.

Briefly, studies discussed in this manuscript were obtained after conducting a literature search in the main databases MEDLINE, CINAHL, and Google Scholar from inception to May 2019. We searched for multiple variations of the disorder (e.g., autism, autism spectrum disorder, Asperger syndrome) and keywords related to each section of this manuscript (e.g., obesity, overweight, weight gain, oral sensitivities, food selectivity, physical activity, recreational activities). Search was limited to articles in English and reference lists of selected articles, systematic reviews, and meta-analyses were manually reviewed to identify additional relevant articles. A critical synthesis of the literature is presented throughout the main text, describing the limitations of included articles.

2.4 Feeding Behavior

The dietary intake and feeding practices in children with ASD may be different from TD children. The overall objective of this section was to summarize the current understanding around both feeding and mealtime behaviors and also consider the macronutrient and micronutrient intake of children with ASD compared to TD children.

Reported rates of atypical behavior related to sensory experiences are high among children with ASD (Leekam et al., 2007). Compared to sex- and age-matched controls, individuals with autism aged 3 to 56 years old exhibited an abnormal oral sensory processing,

characterized by either greater oral seeking (e.g., child putting everything into their mouth) or oral defensiveness (e.g., avoidance of certain textures and tastes and/or only eating a Limited Variety of foods) (Cermak et al., 2010; Kern et al., 2006). Interestingly, age-group analyses revealed reductions in the differences of sensory processing difficulties between ASD and TD children over time, suggesting that children are the most affected ones (Kern et al., 2006). These sensory difficulties can lead to atypical eating behaviors and feeding practices in ASD, as children may avoid certain foods due to texture and/or taste and only eat a Limited Variety of foods (e.g., food selectivity). In fact, a recent meta-analysis identified that children with ASD experienced about five times more feeding problems and exhibited lower intake of calcium than TD children (Sharp et al., 2013). Thus, children with ASD may be at risk for inadequate micronutrient intake (Shmaya et al., 2015).

Although several studies characterizing feeding behaviors in children with ASD have evaluated the prevalence of overweight and obesity, few have attempted to investigate whether differences in feeding behavior are related to body weight categories. To our knowledge, only one study found that male children with ASD, who were overweight or obese, had more problematic mealtime and feeding behaviors than overweight or obese TD children, as indicated by the higher scores on a Behavior Pediatrics Feeding Assessment Scale (BPFA) in the ASD group (Castro et al., 2016). There were no differences in BPFA scores between children with ASD and TD children, of either thin or adequate weight status (Castro et al., 2016). However, another study of younger male and female children described no differences in feeding behaviors (assessed by questionnaire depicting oral function, eating problems, and others) across weight categories (X. Liu et al., 2016). It is important to note that the sample populations in these two studies differed by age, sex, and cultural origins (Brazilian vs. Chinese), limiting comparison. Moreover, the second study found that children with ASD actually had lower mean BMI z-scores than TD children. Another approach to assessing whether feeding behaviors play a role in obesity is to examine within sample correlations. For example, one study found no significant association between dietary patterns and BMI z-score in children with ASD aged 3 to 11 years (Evans et al., 2012). Therefore, it is not clear from the current literature whether feeding behavior is, and to what degree, a contributor to excess weight gain in children and adolescents with ASD. We speculate that abnormal feeding behaviors and/or dietary intake could influence weight status. For example, a study found children with ASD tended to consume more sweetened beverages and snacks foods (chips, candy, etc.) (Evans et al., 2012). Thus, although children may be eating a limited variety of

foods, these may be unhealthier overall (driving weight gain). However, picky eating could also result in weight loss (Chao, 2018).

Overall total energy intake and macronutrient distribution could also contribute to weight gain among children with ASD. With regard to total energy intake, two recent meta-analyses included three-day food record and food frequency questionnaires (FFQs) data from six prospective studies (Sharp et al., 2013) and 14 observational studies (Esteban-Figuerola et al., 2018b). No significant overall differences in total energy intake were detected between children with ASD and TD children (Esteban-Figuerola et al., 2018b). It is also important to consider macronutrient distribution, which can lead to variations in body weight and cardiometabolic risk profiles (Hjorth et al., 2017; Y. Wan et al., 2017). However, the optimal macronutrient distribution for improving the weight status of children and adolescents is not yet understood (Gow et al., 2014). Data from the same two meta-analyses that examined energy intake also assessed macronutrient intake, finding no significant difference in the intake of carbohydrates and fats between children with ASD and TD children (Esteban-Figuerola et al., 2018b; Sharp et al., 2013). Intake also tended to be within the acceptable macronutrient distribution range (AMDR) (Esteban-Figuerola et al., 2018b; Hyman et al., 2012). Children with ASD consumed less protein than TD children, but both groups were consuming more protein than currently recommended for a healthy diet (Esteban-Figuerola et al., 2018b; Sharp et al., 2013).

Micronutrients are also integral to maintaining healthy body weight and have important functions in various metabolic pathways (Via, 2012). Children with ASD are often placed on restrictive diets, such as the gluten-free, casein-free (GFCF) diet (Hyman et al., 2016), which may reduce intake of certain micronutrients. GFCF diets have been considered as a possible therapeutic intervention for some of the behavioral symptoms of ASD; however, evidence is lacking (Sathe et al., 2017). A recent systematic review identified three studies showing that nutrient inadequacies tended to remain among children with ASD even after controlling for common elimination diets, such as GFCF regimens (Bandini et al., 2010; Herndon et al., 2009; Sharp et al., 2013; Zimmer et al., 2012). Evidence suggests that deficiencies of vitamin A, vitamin D, B-complex vitamins, calcium, and zinc may be associated with increased fat deposition (García et al., 2009). Findings from a meta-analysis confirm intake deficiencies in calcium and vitamin D in children with ASD relative to TD children and dietary intake recommendations (Esteban-Figuerola et al., 2018). However, the causality in the relationship between micronutrient intake and fat deposition remains unestablished (García et al., 2009).

Future studies should also take into account the use of dietary supplements, which are commonly offered to children with ASD (Sathe et al., 2017).

In addition to these feeding behaviors and patterns, anecdotal reports indicate that children with ASD may limit their intake of fruits and vegetables due to factors such as taste and texture (Bandini et al., 2010). The consumption of fruits and vegetables has shown to be inversely associated with weight change and body adiposity (Bertoia et al., 2015; Yu et al., 2018). However, studies based on prospective three-day food records generally demonstrate no difference in the intake of vegetables or fruits between children with ASD and TD children (Graf-Myles et al., 2013; Herndon et al., 2009), with both groups consuming below the recommendations for vegetable intake (Graf-Myles et al., 2013). In contrast, a systematic review of studies using FFQs (which assess subjective, longer-term eating patterns) indicated that children with ASD consume fewer daily servings of fruits and vegetables (Evans et al., 2012). Likewise, Bandini et al. found that FFQ data revealed children with ASD refuse more vegetables than TD children (L. G. Bandini et al., 2010). In agreement with this, a study found that Food Refusal in children with ASD may in some cases be due to a bitter taste sensitivity associated with the TAS2R38 genotype (Riccio et al., 2018). Although little research has investigated the implications of polymorphisms in taste receptors and feeding behaviors in ASD, previous research has demonstrated that TD children exhibit two sensitive alleles for bitter taste had a lower threshold concentration to detected sucrose and a greater sugar consumption compared to children with less sensitive alleles (Joseph et al., 2016). Thus, future research into the prevalence of genetic variants of taste receptors in ASD may help to provide further insight into particular eating behavior differences, such as vegetable intake, among groups (Mennella & Bobowski, 2015).

Overall, much of the recent literature seems to suggest that among those with ASD, overall intake of energy and macronutrients is fairly comparable to the TD population. These findings, however, must be interpreted with caution, because methods for collecting dietary information are often limited by variances in day-to-day food intake (Y. J. Yang et al., 2010), under-reporting of energy intake (Macdiarmid & Blundell, 1998), and behavioral reactions to measurement (e.g., changes in food intake, especially in individuals with obesity) (Subar et al., 2015). Furthermore, although FFQs are designed to capture long-term eating habits, they include a limited number of foods and both FFQs and three-day food recalls are prone to recall bias (Naska et al., 2017). Thus, the relationship between dietary intake and obesity rates may be clouded by limitations in these commonly used measures. In addition, parents of children

with ASD may be more attuned to their children's food selectivity behaviors, than parents of TD children, influencing diet data collection. Future studies using direct methods, such as doubly labeled water, to measure energy expenditure and energy intake, may be more informative (Subar et al., 2015; Westerterp, 2017). Additionally, researchers should further elucidate differences in dietary intake within the ASD group based on oral sensitivities, dietary restrictions, and secondary comorbidities (e.g., GI disorders), and take into account age- and possibly sex-related differences. Eating disorders, such as anorexia nervosa, can also impact feeding behaviors and studies have found comorbidities between eating disorders and ASD, specifically among females (Baron-Cohen et al., 2013; Dudova et al., 2015). Studies suggest that specific behavioral phenotypes, such as rigid and repetitive behaviors and social anhedonia, overlap among both conditions (Baron-Cohen et al., 2013; Kirkovski et al., 2013). This further highlights the importance of stratifying feeding behaviors based on sex differences.

2.5 Physical Activity and Sedentary Behavior

In addition to nutrition and feeding behaviors, physical activity is a another factor that can influence an individual's weight; as levels of physical activity decrease, the risk of obesity increases (Pietiläinen et al., 2008). Research indicates that children with low motor skills, which is common in ASD, also seem to have higher rates of childhood obesity (Lloyd et al., 2013). The goal of this section was to compare the physical activity levels and sedentary behaviors of children with ASD to TD children, in order to further inform their role in understanding why children with ASD may be at greater risk for obesity. Physical activity is defined in terms of sedentary, light, moderate, and vigorous (Thivel et al., 2018). Physical activity has many benefits to children from reducing stress, maintaining a healthy lifestyle, and reducing disease risks (Kohl et al., 2013). Physical activity may also help in managing stereotyped behaviors in ASD (e.g., sudden runs and arm shaking) (Ferreira et al., 2019).

School-based or extracurricular programs provide opportunities for children to be physically active and engage with peers. Physical activity (PA) is considered a protective factor in maintaining a healthy body weight and preventing obesity (Goran et al., 1999). However, opportunities for PA may be limited in children with ASD due to social and behavioral challenges (Andari et al., 2010; Bishop et al., 2016), as well as motor deficits (McPhillips et al., 2014; National Institute of Mental Health., 2019; Serdarevic et al., 2017).

For optimal health benefits, the U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion suggests that children between the ages of 6 and

17 years should engage in moderate- to vigorous-intensity physical activity (MVPA) for at least 60 min, 3 days per week (U.S. Department of Health and Human Services., 2019; WHO, 2019). Studies that have assessed intensity and frequency of PA in children and adolescents with ASD are summarized in (**Table 2.1**). Studies comparing the daily time spent in MVPA, as measured by accelerometers, between children with and without ASD have yielded mixed findings. For example, while Bandini et al. reported similar daily MVPA in children with ASD and TD children (Bandini et al., 2013), Stanish et al. (2017) found that children with ASD who are younger than 16 years old spent less time engaged in MVPA; but for those adolescents over 16 years, the difference in MVPA was not significant (Stanish et al., 2017). In contrast, a systematic review found a consistently negative association between PA and age (Jones et al., 2017). The discrepancies in these findings suggest that longitudinal studies would enhance the understanding on whether age influences PA patterns. Notably, both children with ASD (Stanish et al., 2017) and TD children (Griffiths et al., 2013) were unlikely to meet the recommendations for MVPA.

Studies utilizing parent report questionnaires generally show that children with ASD spend less time engaged in PA than TD children (Healy et al., 2017; McCoy et al., 2016; Must et al., 2015). Although questionnaires are more feasible than objective measures given the associated time demands and costs, parent-reports often underestimate PA (Sarker et al., 2015). In the Bandini et al. study, parents reported that their children with ASD spent significantly less time in PA annually (158 vs. 225 h per year) and participated in fewer types of PA, but no differences in PA between children with ASD and TD children were observed based on accelerometry data (Bandini et al., 2013). Parents of children with ASD also report more barriers to PA (e.g., increased needs for supervision), which could influence their estimates of overall PA (Must et al., 2015). Moreover, a weak to moderate correlation has been found between parent reports of children's PA and accelerometer-measured activity, depending on type of activity and age group (Sarker et al., 2015). It is possible that children react to being monitored by increasing their PA (Dössegger et al., 2014); on the other hand, social desirability bias could cause parents to under- or over-report their children's PA based on weight status (Koning et al., 2018).

Another important variable to consider is sedentary behavior (SB), which is defined as resting behavior with very little expenditure of energy (Owen et al., 2010). Factors contributing to prolonged SB in children may include increased access to television, computers, and phones (Dunton et al., 2011; Matthews et al., 2008) . Prolonged SB has long-term health consequences,

such as increased body weight, cardiovascular diseases, and type 2 diabetes (Biswas et al., 2015; Ekelund et al., 2008). In a recent systematic review, only two of six studies comparing the prevalence rates of SB reported greater participation in SB by children with ASD than TD children (Jones et al., 2017). However, children with ASD (aged 8–18 years old) spent 62% more time on screen activities compared to their TD siblings, as reported by parents (Mazurek & Wenstrup, 2013). Furthermore, children with ASD spent more hours per day playing video games (both boys and girls), but spent less time using social media or playing interactive video games (Mazurek et al., 2012; Mazurek & Wenstrup, 2013). The social and behavioural challenges associated with the ASD place children at risk for inactivity due to decreased opportunities for PA and higher opportunities for SB (Pan & Frey, 2006).

Overall, the relationships between time spent in MVPA or SB and the propensity for children with ASD to be overweight or obese were not directly investigated in the reviewed studies. It is important to note that ASD severity may influence these relationships by affecting behavior as well as social and motor functioning (MacDonald et al., 2014). Indeed, McCoy et al. (2016) found an association between higher parent-reported levels of autism severity, increased odds of being obese, and decreased odds of PA (McCoy et al., 2016). In the future, research based on objective measures of MVPA and SB (e.g., accelerometer data) could yield insights into differences in these variables between children with ASD and TD children. Further sample stratification based on ASD severity could further clarify how symptoms moderate the relationship between PA and SB among children with ASD.

2.6 Genetics

Genetic vulnerabilities and syndromic causes of ASD and obesity have been explored extensively, albeit independently. Both conditions are heritable; thus, understanding possible shared genetic links may yield insights into their interplay. Specifically, sibling and twin studies have shown that ASD tends to run in families (Constantino et al., 2010; Sandin et al., 2017). However, although having a high heritability, ASD has a lot of genetic heterogeneity. Likewise, genetics also play a role in childhood obesity (Chesi & Grant, 2015). When compared to adopted siblings, the risk of being obese is higher among individuals with affected siblings and parents who are already obese (Sørensen & Stunkard, 1993). Because both ASD and obesity have heritable components, investigation of any genetic overlap in their pathways may help explain the higher rates of obesity among individuals with ASD.

Sharma et al. (2012) hypothesized that a common molecular pathway may contribute to the pathogenesis of ASD and obesity, as a pathway-based analysis revealed 36 common genes between these two conditions (Sharma et al., 2012). Specifically, one study has shown that ASD, Attention Deficit Hyperactivity Disorder (ADHD), developmental delays and obesity are highly associated with a microdeletion involving 11p14.1 (Shinawi et al., 2011). Furthermore, deletions in 16p11.2 were associated with genetic vulnerabilities related to both obesity and ASD (Bachmann-Gagescu et al., 2010; Walters et al., 2010). More recently, in a genetic analysis of very obese children with ASD, Cortes and Wevrick (2018) focused on de novo mutations and found that very obese ASD probands had loss of function mutations in DNMT3A and POGZ (Cortes & Wevrick, 2018).

In addition, Prader-Willi Syndrome (PWS) is a genetic disorder caused by paternal 15q11–13 deletions (Dykens et al., 2011). PWS is characterized by hyperphagia, elevated ghrelin concentrations, and increased risk for obesity (Dykens et al., 2011; Haqq et al., 2008). PWS is also associated with higher rates of social-communication impairments and repetitive behaviors (Bennett et al., 2017), although the degree to which symptoms meet diagnostic criteria for ASD varies across studies, emphasizing that ASD symptom measures require careful consideration of developmental profile and overall clinical context (Bennett et al., 2017; Dykens et al., 2017). That said, genetic mechanisms underlying the association between Prader Willi and ASD may underlie obesity risk related to hyperphagia in a subset of individuals with ASD (Ramos-Molina et al., 2018).

In summary, although evidence indicates that certain genetic vulnerabilities are associated with both ASD and obesity, there is a need to further investigation, such as pathway-based analyses to reveal how genetics influence the complex etiologies of both conditions. In addition, it is not currently clear what proportion of children with ASD and obesity would be accounted for by these rare genetic variants; future efforts to parse the relative contribution of genetic versus non-genetic associations would provide important insights into this topic. Genetic testing, in the form of clinical microarrays, are increasingly becoming standard of practice for ASD diagnosis (Anagnostou et al., 2014) and determining whether there are deletions in areas such as 16p11.2 may allow for early interventions and targeted molecular therapy, with potential to prevent obesity in children with ASD.

2.7 Medications

Medications may be another contributing factor to unhealthy weight gain due to interventions to manage symptoms of ASD as well as comorbid conditions, such as ADHD and depression, which may often manifest in ASD (Linke et al., 2017). To manage these and other behavioral symptoms, psychotropics including stimulants, selective serotonin reuptake inhibitors (SSRIs), and antipsychotics are often prescribed (Nihalani et al., 2011). The prescription rate of these drugs in children with ASD has been reported at 27–64% (median 41.9%) (Coury et al., 2012; T. W. Frazier et al., 2011; Jobski et al., 2017; Spencer et al., 2013).

A 2016 meta-analysis by Park (2016) found that 1 in 6 children with ASD were prescribed anti-psychotic medication (Park et al., 2016). Second-generation anti-psychotics (SGA) such as risperidone and aripiprazole, are often prescribed to alleviate behavioral symptoms comorbid with ASD such as hyperactivity, irritability and aggression (Fallah et al., 2019; Fung et al., 2016), but are associated with substantial weight gain (Fallah et al., 2019; Maneeton et al., 2018). A systematic review of seven randomized controlled trials (RCTs) of risperidone use among children and adolescents with ASD, revealed weight gain as an adverse event (Maneeton et al., 2018). Furthermore, dose-related increases in blood glucose, insulin, and leptin have been reported (Srisawasdi et al., 2017) and metabolic changes (e.g., leptin) track closely with changes in fat mass (Shimizu et al., 1997). In addition, a systematic review looking at two RCTs of apriprazole use in children with ASD reported a mean difference of 1.13 kg of weight gain in children using apriprazole compared to a placebo after 8 weeks of treatment (Hirsch & Pringsheim, 2016). Other commonly prescribed antipsychotics in ASD are olanzapine and clozapine (Hsia et al., 2014; Murray et al., 2014). A 2014 meta-analysis found that olanzapine and clozapine were also both associated with severe weight gain (Bak et al., 2014). The mechanism of action behind weight gain associated with atypical antipsychotics relates in part to serotonin receptor blockade and reduction in dopamine (D2) receptor-mediated neurotransmission (Meltzer & Massey, 2011), implicated in weight regulation (Roerig et al., 2011). Thus, monitoring adverse effects of antipsychotics are important to alleviate behavioral symptoms without detrimental effects on metabolic health (Pringsheim et al., 2011).

Selective serotonin reuptake inhibitors (SSRIs) are another class of medications commonly prescribed to children with ASD for comorbid anxiety, depression and obsessive-compulsive behaviors (Reekie et al., 2015; K. Williams et al., 2010). Previous research on the efficacy of citalopram (King et al., 2009) and fluoxetine (Hollander et al., 2012) in children

with ASD have not examined changes in weight gain. However, other research has suggested SSRIs such as citalopram may cause weight gain (Blumenthal et al., 2014). The degree and persistence of weight gain with these medications, particularly from long term use, are not known in children with ASD, and thus would benefit from further study.

2.8 Emerging Factors

2.8.1. Breastfeeding

Breastfeeding is a maternal-mediated pathway which is implicated as a predictive factor in long term maternal-and child body weight outcomes (Amir & Donath, 2007). Breast milk provides energy, nutrients and antibodies, and reduces risks for various infections during infancy (Stolzer, 2011). Researchers have also studied how breastfeeding affects children's cognitive development. Mothers who breastfeed experience greater weight loss and gains in long-term cardiovascular health (Stuebe, Michels, et.al, 2009) and their babies, compared to formula-fed babies, are shown to be less susceptible to childhood and adult obesity overall (Grummer Strawn & Mei et al., 2004).

The rate and duration of exclusive breastfeeding also appears to be a potential risk factor for ASD (Tseng et al., 2019). For example, Boucher et al. (2017) found associations between longer durations of breastfeeding and better cognitive development and fewer autistic traits in children, after controlling for relevant demographic and social confounding variables (Boucher et al., 2017). Tseng et al. (2019) also reported that children with ASD were significantly less likely to have been breastfed than children without ASD (Tseng et al., 2019). Tseng et al. (2019) highlighted some proposed explanations for the role of breastfeeding in ASD pathophysiology, such as the nutrition theory (Al-Farsi et al., 2012), oxytocin stimulation (Shafai et al., 2014), and the secretion of neurotrophic factors (Steinman, 2006; Tseng et al., 2019).

Researchers have also found that breastfeeding may lower the risk of childhood obesity (Ortega-García et al., 2018; Umer et al., 2015). In their meta-analysis, Yan et al. (2014) showed a dose-response effect between breastfeeding duration and reduced risk of childhood obesity (Yan et al., 2014). These studies highlight that reduced breastfeeding may be a contributing factor to obesity, although they did not specifically examine these relationships in ASD. Thus, future studies could examine how breastfeeding affects the growth patterns and long-term weight status of children with ASD.

2.8.2 Sleep

The mechanisms of the sleep-wake cycle play an important role in controlling our bodies homeostasis such as our blood pressure and hormone levels. Thus, inadequate sleep can impair the circadian rhythm of our body and consequences of this can include impaired motor, emotional, immune, and endocrine functioning (National Sleep Foundation, 2011). It is recommended that preschoolers (children between 3 and 5 years old) sleep between 10 to 13 hours per 24-hour period, school age children sleep 9 to 12 hours per 24 hours, and teens sleep 8 to 10 hours per 24 hours.

Evidence suggests that sleep duration and quality of sleep are risk factors for becoming overweight or obese (Beccuti & Pannain, 2011). Numerous studies have confirmed an inverse correlation between sleep quantity, BMI, and the risk for overweight and obesity (Xiaoli Chen et al., 2008; Patel & Hu, 2008). A 2016 meta-analysis found an association between poor sleep quality (independent of sleep duration) and overweight and obesity in children (Fatima et al., 2016). Decreased quality of sleep can lead to endocrine changes affecting appetite regulation and glucose metabolism, with implications on body weight gain (Knutson, 2012). As such, an inverse relationship between total sleep and ghrelin levels has been reported, as well as a positive relationship between total sleep and leptin levels (Chaput et al., 2011). Ghrelin and leptin are appetite regulating hormones that influence food intake. Childhood obesity can present with sleeping problems such as obstructive sleep apnea (OSA) (Narang & Mathew, 2012). OSA is associated with inadequate duration and poorer quality of sleep and may be associated with specific metabolic markers such as insulin resistance and hypertension (Narang & Mathew, 2012).

Studies have found that children with ASD have higher rates of sleep problems when compared to TD controls (Maxwell-Horn & Malow, 2017). One study found associations between poor sleep quality and weight status among children with ASD, with 86% of the obese group presenting with clinically significant sleep problems compared to 76% of those with healthy weight (Zuckerman et al., 2014). Children with ASD are more likely to be diagnosed with insomnia, circadian rhythm disorder, or sleep-disordered breathing such as OSA (Elrod et al., 2016). Metabolic risk factors, as well as day-time sleepiness, may reduce daytime activity levels, contributing to unhealthy weight gain (Zuckerman et al., 2014). Although many findings suggest that children with ASD are at greater risk for sleep problems, associations with BMI remain underexplored within this population. However, sleep duration and quality are

important factors to consider, because increased findings of sleep problems may be compounding the risk for unhealthy weight gain in children with ASD.

2.8.3. Microbiota

Gastrointestinal (GI) disorders, such as diarrhea, chronic constipation (Bresnahan et al., 2015), and abdominal pain are common in ASD (McElhanon et al., 2014). In a study including 163 preschoolers with ASD, 25.8% of the participants reported having at least one severe GI symptom (Prosperi et al., 2017). Studies have also shown that children with ASD and GI problems have higher levels of affective problems, including anxiety, than children with ASD who have normal GI functioning (Ferguson et al., 2017; Mazefsky et al., 2014; Prosperi et al., 2017). This link between GI and behavior disorders suggests that gut microbiota may influence developmental course in ASD (Mayer et al., 2014).

Data from several pediatric studies reveals a unique gut microbiota profile in children with ASD compared to those with TD, but inconsistent findings on the characterization of the bacterial communities (Strati et al., 2017). While one study reported decreased bacteria of the genera *Prevotella*, *Coprococcus* and *Veillonellaceae*, other studies found increased *Lactobacillus*, *Clostridium*, *Candida* spp., and the Firmicutes/Bacteroidetes ratio (D.W. Kang et al., 2013; Strati et al., 2017; B. L. Williams et al., 2011; M. Zhang et al., 2018). Similar to what has been seen in ASD, studies exploring the gut microbiome in obesity have reported an increased Firmicutes/Bacteroidetes ratio, and this ratio could be positively associated with BMI in children and adults with obesity (Chakraborti, 2015; Indiani et al., 2018; Koliada et al., 2017). To further understand the implications of obesity on gut composition, animal studies comparing lean, wild-type, and obese mice (leptin-deficient) have demonstrated an increase in the Firmicutes/Bacteroidetes ratio in obese mice, independent of diet (Ley et al., 2005). Indeed, a high-fat diet was shown to promote more profound increases in Firmicutes (Murphy et al., 2010). Certain features of the gut microbiota, such as individual variability, may explain the lack of a consistent microbiota signature in ASD and obesity. As the gut microbiota is assembled mainly during infancy, before the age of 2 years, diverse factors including birth mode, antibiotics, feeding practices, and environmental exposure to bacteria shape the gut community and contribute to this individual variability (Bäckhed et al., 2015). Thus, characterizing the microbiome from an ecological perspective (bacterial diversity, abundance, community interactions, metabolic profiles), may be more informative in understanding the interplay between gut microbiota, ASD prognosis, and weight gain.

Growing evidence suggests that decreased gut microbiota diversity in ASD (D.W. Kang et al., 2013; F. Liu et al., 2019) may be associated with behavioral and GI symptoms. Sharon et al. took this hypothesis a step forward, reporting that offspring of germ-free mice receiving gut microbiota from individuals with ASD indeed exhibited behaviors related to those observed in ASD (Sharon et al., 2019). This finding, however, must be interpreted with caution given the small sample size used in the experiments and relevance to behavioral expression in the human condition.

Gut microbiome dysbiosis, which refers to changes in the composition and function of gut microbiome especially early in life, are associated with increased production of pro-inflammatory cytokines and alterations in the dynamics of the communication between the gut and brain, known as the gut-brain axis (Jazani et al., 2019; Siniscalco, Brigida, et al., 2018; Siniscalco, Schultz, et al., 2018). These cytokines affect the inflammation pathways, which have been implicated in ASD development (Fiorentino et al., 2016; Siniscalco et al., 2018; Siniscalco et al., 2018). Inflammatory cytokines and an increased gut permeability also promote metabolic endotoxemia (Cani et al., 2007), which plays a role in the development of obesity and metabolic diseases (Boulangé et al., 2016). Indeed, gut microbiome dysbiosis has also been reported in obesity (Y. Kang & Cai, 2017).

A much-debated topic is whether gut permeability contributes to ASD development (Siniscalco, Schultz, et al., 2018), with evidence remaining limited and controversial. To our knowledge, only three studies have investigated gut permeability in children with ASD using varied biomarkers (de Magistris et al., 2010; Esnafoglu et al., 2017; Kushak et al., 2016). Specifically, children with ASD exhibited greater gut permeability than TD children, as assessed by zonulin concentrations (Esnafoglu et al., 2017) or sugar probes (lactulose and mannitol) (de Magistris et al., 2010). In contrast, no difference in gut permeability using the lactulose and rhamnose probe was observed in children with ASD compared to TD children (Kushak et al., 2016). There were marked differences in the design of these studies; in particular, with respect to the selection of comparison groups. One study included children with and without GI complaints in both study (e.g., children with ASD) and control (e.g., children with TD) groups; another study excluded children with GI symptoms from the control group only; and in the third study, all children (study and control groups) had mild GI disorders. Thus, it is not clear whether gut permeability is increased due to the presence of ASD or GI-associated disorders per se. Furthermore, studies have shown significantly lower short-chain fatty acids (SCFAs) in ASD (Adams et al., 2011). As SCFAs are produced by gut microbiota (from dietary fiber fermentation), and their production promotes gut barrier and mucosal integrity (Morrison

& Preston, 2016), it could be speculated that individuals with ASD may have decreased ability to repair the intestinal barrier.

Dietary intake has a direct impact not only on obesity development, but also on the microbiome composition (Valdes et al., 2018); the role of diets in ASD could thereby be explored as a possible way to alleviate both irritable bowel syndrome symptoms and some ASD problem behaviors. An interesting avenue to explore would be fiber interventions in ASD, especially in those children with concomitant obesity. Many studies have found that fiber intake in children with ASD, as well as TD, does not meet recommended levels (L. G. Bandini et al., 2010; Hyman et al., 2012). Fiber-rich foods can alleviate GI symptoms, such as chronic constipation and increase feelings of fullness, as these foods take longer to digest (J. Yang et al., 2012). Fiber intake could also promote a healthier metabolic profile by mediating the gut microbiota (Deehan & Walter, 2016; Zou et al., 2018). Our bodies produce SCFAs by degrading fiber in the gut, which results in the release of anorexigenic gut hormones (Larraufie et al., 2018), improvements of the gut barrier (Willemsen et al., 2003), and triggering of anti-inflammatory cytokines (Macia et al., 2015; Mirmonsef et al., 2012). More specifically, the SCFA propionate was shown to promote increases in peptide YY (PYY) and glucagon like peptide-1 (GLP-1) levels in an in vitro study using human colonic cells (Chambers et al., 2015). Subsequent in vivo studies were conducted in human adults; while acute intake of inulin-propionate ester reduced energy intake by ≈14% with increases in plasma PYY and GLP-1, supplementation over 24 weeks reduced rate of weight gain and intra-abdominal adiposity (Chambers et al., 2015). In addition to alleviating GI symptoms associated with ASD, SCFAs thus also prevented obesity and its comorbidities (De Vadder et al., 2014). However, sensory aversions (e.g., to food texture) associated with ASD may create challenges with increasing intake of fiber rich foods.

Further delineating the microbial signature of individuals with comorbid ASD and obesity may provide further insight into the complex etiologies of both conditions. Although more studies are needed, there is emerging evidence of a dysbiotic gut microbiome influencing children with ASD. If supported by more definitive studies (e.g., metagenomics), evaluation of novel therapeutic strategies would be warranted, such as dietary interventions and fecal transplantations. Some challenges in this area include the need for approaches to directly sample the gut mucosa in order to reliably characterize the microbiome in various group and regions (Zmora et al., 2019). Furthermore, animal studies remain difficult to translate because of the precise control over genetics, the environment, and diet; which is not possible in human studies, making the human microbiome a lot more heterogeneous (Zmora et al., 2019).

2.8.4. Endocrine Influences

Researchers have also begun to explore the role of endocrine factors in the pathogenesis of ASD. It has been hypothesized that specific chemical messengers, such as endocrine hormones, and neuropeptides work together with neurotransmitters (e.g., dopamine and serotonin) to influence the developing fetal brain (Tareen & Kamboj, 2012). Thus, imbalances in the chemical transmissions could lead to defective encoding, which could in turn lead to some of the social behaviors exhibited by those with ASD (Tareen and Kamboj, 2012). Research in this area has been focused on understanding how hormonal imbalances and differences may contribute to the pathogenesis of ASD. In this section, we review evidence related to specific appetite hormones, leptin, adiponectin and ghrelin.

2.8.5. Leptin

Leptin is an anorexigenic (satiety) hormone that regulates how much one consumes and inhibits appetite (Ahima, 2008). Produced by adipose tissue in amounts proportionate to fat mass (Klein et al., 1996), leptin is an important hormone involved in energy homeostasis and growth (H.-K. Park & Ahima, 2015). Evidence suggests that obese individuals exhibit leptin resistance, whereby the brain no longer responds to leptin by inhibiting energy intake and increasing energy expenditure (Mazor et al., 2018; M. G. Myers et al., 2010).

Several studies have reported higher circulating concentrations of leptin in individuals with ASD compared to control groups (Al-Zaid et al., 2014; Ashwood et al., 2008; Blardi et al., 2010; Hasan et al., 2019; Raghavan et al., 2019; Rodrigues et al., 2014), summarized in (**Table 2.2**). Ashwood et al. (2008) found higher concentrations of peripheral blood leptin in individuals with ASD compared to age-matched controls, despite no group differences in BMI (Ashwood et al., 2008). Leptin plays an important role in growth (H.-K. Park & Ahima, 2015) and rapid growth has also been independently implicated as a risk factor for ASD (Chawarska et al., 2011). One study found that children born small-for-gestational age (SGA) had lower leptin cord levels; among those born SGA, children with the most rapid weight gain had the highest childhood leptin levels and were more likely to be diagnosed with ASD (Raghavan et al., 2018), suggesting differences in early weight trajectories between children with ASD and TD children (Hill et al., 2015). Hasan et al. (2019) measured fasting serum concentrations for 20 children with ASD and 20 TD children; the BMI of the group with ASD was significantly lower compared to the control group; however, no children in either group were found to be of obese status (Hasan et al., 2019). The study found that the children with ASD had higher leptin concentrations and lower BMI (Hasan et al., 2019), suggesting that

leptin concentrations could be higher among individuals with ASD, regardless of weight status. The studies summarized in (**Table 2.2)** have consistently found higher concentrations of leptin in children with ASD when compared to TD children. In the future, leptin concentrations could be analyzed based on BMI percentile stratifications to explore relationship to obesity among children with ASD.

2.8.6. Adiponectin

Adiponectin is a protein hormone secreted by the adipocytes (Lihn et al., 2005). Plasma adiponectin levels and BMI are strongly negatively correlated in both men and women (Arita et al., 1999). Adiponectin is an anti-inflammatory protein (Ouchi & Walsh, 2007); decreased levels may lead to increased expression of adhesion molecules and inflammatory molecules, resulting in higher risk for cardiovascular diseases associated with obesity (Kawano & Arora, 2009). Therefore, adiponectin and its receptors may be therapeutic targets for individuals who are obese or overweight (Achari & Jain, 2017; Kawano & Arora, 2009). Adiponectin plays a pivotal role in energy metabolism and concentration of both total adiponectin decreases in obesity and increases after weight loss (Nigro 2014).

Disturbances in immunoinflammatory factors and adipocytokines have been reported among individuals with ASD relative to age- and weight-matched TD controls (Ghaffari et al., 2016). Table 2.3 summarizes published data on adiponectin concentrations in children with ASD compared to controls (Blardi et al., 2010; Fujita-Shimizu et al., 2010; Raghavan et al., 2019; Rodrigues et al., 2014). One study reported lower serum adiponectin levels among individuals with ASD relative to age- and sex-matched healthy controls (Fujita-Shimizu et al., 2010), but two other studies showed no significant differences (Blardi et al., 2010; Rodrigues et al., 2014). Differences in findings among the three studies may be explained by differences in exclusion and inclusion criteria and sample composition, particularly by sex and age. For example, Rodrigues et al. (2014) and Blardi et al. (2010) included both males and females, whereas Fujita-Shimizu et al. only included males (Blardi et al., 2010; Fujita-Shimizu et al., 2010; Rodrigues et al., 2014). Past studies have found sex differences in adiponectin levels and body composition (Ohman-Hanson et al., 2016; Song et al., 2014), whereby adiponectin concentrations decrease into late puberty and become significantly lower in males by adulthood (Ohman-Hanson et al., 2016). Furthermore, recent findings also suggest a link between a high leptin/adiponectin ratio (e.g., higher concentrations of leptin and lower concentrations of adiponectin) and abdominal obesity (Rueda-Clausen et al., 2010). Although higher concentrations of leptin among individuals with ASD is a relatively consistent finding, the role

of adiponectin is less clear. Exploring the relationship between these two hormones and its potential role in the propensity for individuals with ASD to become overweight or obese warrants further examination.

2.8.7. Ghrelin

Ghrelin is an appetite-stimulating hormone (Cummings & Shannon, 2003), but its exact role in obesity is poorly understood, as, counterintuitively, ghrelin is often suppressed in obese individuals, and concentrations increase with weight loss (Makris et al., 2017). Evidence about the role of this hunger hormone in children with ASD is also unclear. Researchers have explored serum ghrelin concentrations in two case control studies of children with ASD (**Table 2.4)**. One study found that male children with ASD had significantly lower concentrations of acylated, des-acylated, and total ghrelin (Al-Zaid et al., 2014). However, findings from a more recent study, that included both boys and girls, showed a trend towards lower concentrations of ghrelin, although not significant, in children with ASD when compared to age-matched TD children (Hasan et al., 2019). Previous studies have found that ghrelin levels can be modified by an increase in sex hormone (Lebenthal et al., 2006), whereby testosterone can lead to marked decreases in ghrelin (Lebenthal et al., 2006), which may contribute to differences in findings between these two studies. Future studies should examine ghrelin levels relative to weight status as well as ASD diagnosis and consider sex differences.

Although researchers have begun to explore the role of hormones in contributing to higher rates of obesity among children with ASD, they have focused primarily on hormonal differences in relation to ASD pathogenesis. Furthermore, some of the studies discussed above did not report a difference in BMI or weight status among children with ASD, when compared to TD children. However, the relatively smaller sample sizes, compared to larger scale studies (which have reported greater rates of obesity in children with ASD), may have contributed to these differences in findings (Hill et al., 2015; Zheng et al., 2017). Future studies, which stratify study groups based on weight status (overweight, obese, etc.), sex, and age would help to understand whether there are potential biological differences associated with specific weight status. Therefore, further research into possible differences in these hormones' concentrations, in children with ASD, may yield insights into hormonal impacts on unhealthy weight gain and obesity.

2.8.8. Maternal Metabolic Disorders

Although maternal metabolic disorders such as diabetes, hypertension and obesity could place children with ASD at higher risk for becoming overweight or obese, this hypothesis has not been explored directly. Instead, researchers have focused on examining maternal metabolic disorders as potential risk factors for ASD in children; separately, others have studied how maternal metabolic disorders may increase risk of obesity in children.

Maternal obesity prior to pregnancy is a risk factor for ASD (Li et al., 2016; Reynolds et al., 2014; Sanchez et al., 2018). Evidence has also shown significant associations between maternal diabetes and hypertension and ASD risk (Krakowiak et al., 2012; H. Wan et al., 2018; Xu et al., 2014). Several mechanisms may contribute to these in-utero effects. In a systematic review, Xu et al. suggested several potential pathways through which maternal diabetes may increase the risk for ASD in offspring: (a) maternal hyperglycemia can result in hypoxia and impair neural development in the fetus (Burstyn et al., 2011; Eidelman & Samueloff, 2002; Kolevzon et al., 2007) (b) maternal hyperglycemia can cause oxidative stress associated with ASD risk (Xinhua Chen & Scholl, 2005; Ming et al., 2005), and (c) increased maternal adiposity can cause chronic inflammation that can affect neuronal development (Onore et al., 2012; Xu et al., 2014).

Concurrently, there has been considerable research on how maternal metabolic disorders may increase children's obesity risk. In their systematic review, Wang et al. (2017) found a strong positive association between parental and child obesity and overweight status across various countries, indicating a genetic predisposition toward obesity, with other factors playing a mediating role, such as obesogenic lifestyles and behaviors (Wang et al., 2017). In another recent systematic review and meta-analysis, Kawasaki et al. reported an association between gestational diabetes mellitus and higher BMI z-scores among offspring (Kawasaki et al., 2018). Deierlein et al. (2011) found an association between fetal exposure to maternal glucose concentration in the high–normal range and children being overweight or obese at 3 years of age, independent of maternal pre-pregnancy BMI (Deierlein et al., 2011). Furthermore, Lawlor et al. conducted a sibling analysis to control for shared genetics and environment and reported that children exposed to diabetes in utero had higher BMI than their unexposed siblings (Lawlor et al., 2011).

These findings may help explain how certain maternal metabolic disorders increase risk for obesity. Factors such as lifestyle behaviors and genetic predisposition may have compounded effects on weight gain for children with ASD. Additional research on in-utero

effects of maternal metabolic disorders may help explain why many children with ASD tend to become overweight or obese. Longitudinal studies to assess parental weight status and track neurodevelopmental outcomes and weight in offspring would provide important insights into the extent to which parental obesity status influences the development of obesity in children with ASD. A better conceptualization of the role of maternal metabolic disorders and any shared pathophysiology between ASD and obesity would help mothers understand how to best reduce their children's risk for both health conditions.

2.9 Future Directions and Perspectives

The current treatments for childhood obesity generally involve a combination of (1) non-pharmacological interventions (e.g., behavioral treatments, weight-reducing diets), (2) pharmacological interventions, (3) and surgical treatments (Han et al., 2010). Typically, behavioral treatments and weight-reducing diets, such as family-based interventions, are the first therapeutic steps (Ash et al., 2017). However, these may be problematic for children with ASD, who struggle with social and behavioral communication, changes in routine, and sensory processing difficulties (Jones et al., 2017; Leekam et al., 2007). Furthermore, challenges with self-management and, in many cases, impairments in decision-making skills play an important role in the challenges associated with this first line of treatment in children with ASD (E. A. Bennett et al., 2017). The second line of intervention is through common pharmacological treatments for childhood obesity, such as orlistat, sibutramine, and metformin. These, however, may cause abdominal pain, fecal incontinence, nausea, and vomiting (Freemark, 2007; Heck et al., 2000). Administering medications that can cause GI problems to children with ASD, who typically already have co-morbid GI disorders, may cause additional difficulties (L. W. Wang et al., 2011). Moreover, because many children already take medication to manage symptoms of ASD and other comorbid medical conditions, additional medications may increase the risk of side effects, as well as pharmacological interactions and medication burden (Mohammed et al., 2016; Taylor, 2008). Finally, severe and morbid forms of pediatric obesity may warrant surgical interventions such as bariatric surgery (Canoy & Yang, 2015). Although the prevalence of severe morbid obesity (that would warrant consideration of bariatric surgery) among children with ASD is unclear, a study reported that children with the de novo 16p11.2 deletion, which is associated with autism, were also severely obese (BMI ≥ 120% of 95th percentile) (Bochukova et al., 2010). Bariatric surgery, however, also comes with its risks and complications associated with Roux-en-Y gastric bypass, such as pulmonary embolism, shock, intestinal obstruction, postoperative bleeding, staple line leaks and severe malnutrition (Han et

al., 2010). Furthermore, adolescents are more likely to have remission of type 2 diabetes and hypertension after bariatric surgery, when compared to adults (Inge et al., 2019), emphasizing that optimal timing for surgery in order to reverse metabolic complications of obesity is still unclear. Furthermore, little research has been done in this area to address treatment needs that may be specific to this population (Bennett et al., 2017). A systematic review looking more broadly at children with intellectual disabilities suggested the need for further research into how obesity treatment can be more specifically tailored for children with intellectual disabilities (Bennett et al., 2017). Finding more intensive treatments and combination of techniques are warranted for children with intellectual disabilities, such as more training for parents to support children with defiant behaviors (Bennett et al., 2017; Maïano et al., 2014).

Furthermore, although much is known about behavioral and lifestyle factors, little is known about possible biological drivers of obesity among children with ASD. There is also a need to identify whether specific biological drivers can be monitored and assessed at an earlier age, such as at the time of ASD diagnosis. Research in this area is particularly important, because evidence suggests that weight trajectories, at an earlier age, may be different among children with ASD. Therefore, clinical health surveillance of these weight trajectories in ASD and monitoring of growth patterns may serve as a useful method in preventing unhealthy weight gain and obesity. Based on this review, biological factors (gut microbiota, endocrine hormones, maternal metabolic disorders) may be driving increased propensity to become overweight, but further research is needed. Finally, given some of the unique challenges faced by children with ASD, results from pediatric obesity trials in the general population may not generalize to patients with ASD. Thus, as a field, we may require more targeted treatment options and ASD-specific randomized, controlled trials. In an era of precision medicine, there is a need to take into account the interplay between behavioral and biological characteristics influencing unhealthy weight gain in ASD.

2.10 Conclusion and Recommendations

Body weight is determined by energy balance, which is influenced by environmental (e.g., nutrition), behavioral (e.g., food selectivity, PA, SB), and biological (e.g., genetics, metabolic dysfunction) factors. Because the aetiologies of ASD and obesity are so complex, risk factors specifically associated with one condition or the other are difficult to disentangle. Nevertheless, it is important to understand that many risk factors for becoming obese or overweight are heightened in individuals with ASD, as suggested by growing evidence. Figure 2.1 summarizes the risk factors discussed within this review. A limitation of this narrative

review is that we compared various risk factors for unhealthy weight gain and obesity in children with ASD to TD children. Although similarities were found with regard to specific risk factors between children with ASD and TD children (e.g., physical activity, etc.), this does not necessarily mean these are not clinically relevant to children with ASD and should still be taken into account in future studies, including clinical trials.

Overall, evidence suggests that oral sensitivities may mediate food selectivity and food and nutrient intake and other factor such as PA, SB, sleep, genetics, and medication usage may all contribute to some degree, and ultimately have a compounded effect on weight gain in ASD. Additionally, researchers have begun to investigate the roles of sleep problems, the gut microbiome, the endocrine system, and developmental risk factors. Going forward, studies of obesity in ASD should incorporate assessment of both biological and lifestyle-related factors, as well as test for mediating and moderating relationships such as ASD severity, oral sensitivities, and sex and age differences. It is important to consider these multiple factors in conjunction with individual factors to clarify whether unhealthy weight gain affects children across the entire ASD spectrum, or whether certain children are more vulnerable than others. Understanding each of these individual risk factors and components is important to effectively prevent and treat unhealthy weight gain among children with ASD and to facilitate the development of potential early intervention strategies. An understanding of individual risk factors would enable the development of personalized approaches to help children with ASD manage their weight, including dietary recommendations, medical therapies, and nutrition and exercise regimens. Overall in conjunction with the clinical guidelines for pediatric obesity (Styne et al., 2017) and ASD care (Anagnostou et al., 2014), clinicians should consider more tailored medical surveillance in children with ASD that considers the above factors in a care and management plan.

2.11 Tables

Table 2.1 Physical activity in ASD

Study	Design	Study Group	Control Group	Measure	Result	BMI
Bandini et al. (2013)	Cross-sectional	53 male and female children with ASD (age: 3–11 years)	58 male and female TD children (age: 3–11 years)	Accelerometer data Questionnaire (parent report on type and frequency)	Similar daily MVPA for both groups (ASD: 50.0 min/day; TD: 57.1 min/day). Children with ASD participate in significantly fewer types of physical activities (6.9 vs. 9.6, $p < 0.0001$) and spend less time annually participating in these activities than TD children (158 vs. 225 h per year, $p < 0.0001$).	No significant difference between the two groups BMI-z score not significantly associated with percent time spent in MVPA
Stanish et al. (2017)	Cross-sectional	35 male and female children with ASD (age: 13–21 years)	60 male and female TD children (age: 13–18 years)	Accelerometer data (total average daily PA) Questionnaire (type and frequency of PA)	Children with ASD who are younger than 16 spend less time in MVPA (ASD: 26 min/day vs. 51 min/day) and participate in fewer activities. No significant difference in MVPA among individuals older than 16 years.	N/A
Must et al. (2015)	Cross-sectional	53 children with ASD (age: 3–11 years)	58 TD children (age: 3–11 years)	Parent report questionnaire (type and frequency)	An inverse correlation between the total number of barriers reported and the number of PA hours per year (ASD: 119 h; TD 169 h; $p < 0.05$).	No significant difference in BMI percentiles
McCoy et al. (2016)	Cross-sectional	915 male and female children with ASD	41,879 male and female TD children from the	Parent report questionnaire (type and frequency)	Adolescents with ASD are less likely to engage in PA ($p< 0.05$) Higher autism severity is associated with increased odds of being obese (OR: 2.8;	Adolescents with ASD are more likely to be overweight and obese (ASD: 22%; TD 14.1%; $p< 0.05$).

		(age: 10–17 years)	2011–2012 National Survey of Children's Health (age: 10–17 years)		95% CI: 1.39, 3.74), and decreased odds of PA (OR: 0.30; 95% CI: 0.20, 0.46).	
Healy et al. (2017)	Cross-sectional	67 male and female children with ASD (age: 13 years)	74 randomly selected male and female TD children (age: 13 years)	Parent report questionnaire (type and frequency)	Significantly lower participation in MVPA ($p < 0.001$) and sports reported for children with ASD ($p < 0.001$).	No statistically significant difference between the two groups in mean BMI and overweight/obese status.

Abbreviations: ASD, Autism Spectrum Disorder; TD, Typically Developing; MVPA, Medium–Vigorous Physical Activity; BMI, Body Mass Index.

Table 2.2 Leptin in ASD.

Study	Design	Study Group	Control Group	Measure	Result	BMI
Ashwood et al. (2008)	Case control	70 male and female children with ASD (age: 2–15 years)	50 age matched TD children	Peripheral plasma concentrations of leptin	Leptin levels were higher in children with autism compared with typically developing non-ASD controls ($p < 0.006$)	No statistical differences in BMI or z-scores between ASD or controls
Blardi et al. (2010)	Case control	35 male and female children with ASD (mean age 14.1 years)	35 TD sex and age matched children	Baseline: 6 mL blood sample after an overnight fast 1 year after: 6 mL blood sample after an overnight fast	Leptin concentrations of children with ASD were significantly higher than TD children at baseline ($p < 0.001$) and after a year ($p < 0.001$)	No significant difference between children with ASD and TD children on weight or height at baseline or after 1 year BMI z-score not provided
Al-Zaid et al. (2014)	Case control	31 male children with ASD (age: 3–8 years)	28 age- and sex-matched TD children (age: 3–8 years)	7 mL of venous blood samples were collected after an overnight fast	Leptin concentrations were higher in the group with ASD when compared to the TD group ($p \leq 0.01$)	Weight was higher in the children with ASD (19.3 kg in TD children and to 22.7 kg in children with ASD) ($p = 0.05$) No significant difference in BMI between groups ($p = 0.28$)
Rodrigues et al. (2014)	Case control	30 male and female children with ASD (ages not provided)	19 TD children matched for age, gender, maternal age at child birth	10 mL plasma blood samples	Plasma levels of leptin were higher ($p < 0.01$) in children with ASD, compared to TD children	Article suggests differences in BMI (unclear of significance and values)
Raghavan et al. (2018)	Prospective cohort	39 male and female children with ASD	616 male and female TD children	Plasma umbilical cord blood sample and non-fasting childhood (median age= 18.4 months) venous blood sample	Mean cord leptin was lower in children later diagnosed with ASD ($p = 0.05$) Children with the highest leptin levels had an increased ASD risk (OR: 5.41; 95% CI: 1.53, 19.05)	Birthweight was greater in TD children and compared to children with ASD ($p = 0.03$) Extremely rapid weight gain was associated with greater ASD risk

Hasan et al. (2019)	Case control	20 children with ASD (16 males and 4 females) (mean age: 5.9 years)	20 age matched TD children (13 males and 7 females) (mean age: 6.0 years)	5 mL blood samples from participants (serum)	Serum levels of leptin were higher in children with ASD compared to TD children ($p = 0.038$)	TD children had greater mean weight ($p < 0.001$), height ($p < 0.001$), and BMI ($p < 0.05$), compared to children with ASD

Abbreviations: ASD, Autism Spectrum Disorder; TD, Typically Developing; BMI, Body Mass Index

Table 2.3 Adiponectin in ASD.

Study	Design	Study Group	Control Group	Measure	Result	BMI
Blardi et al. (2010)	Case control	35 male and female children with ASD (mean age 14.1 years)	35 TD sex and age matched children	Baseline: 6 mL blood sample after an overnight fast 1 year after: 6 mL blood sample after an overnight	Adiponectin levels in autistic patients were not significantly different from those found in controls at each time.	No significant difference between children with ASD and TD children on weight or height at baseline or after 1 year BMI z-score not provided
Fujita-Shimizu et al. (2010)	Case-control	31 male children with ASD (age: 6–19 years)	31 age-matched male TD children (age: 6–19 years)	Fasting blood samples	Serum levels of adiponectin in the group with ASD were significantly lower (p = 0.005) than the TD group	No significant difference in weight, height, waist circumference, and BMI between the two groups BMI z-score or BMI weight categories not provided
Rodrigues et al. (2014)	Case control	30 male and female children with ASD (ages not provided)	19 TD children matched for age, gender, maternal age at child birth	10 mL of blood (plasma)	No difference in the plasma concentration of adiponectin in children with ASD compared to TD children	Articles suggests differences in BMI (unclear of significance) BMI z-score or BMI weight categories not provided
Raghavan et al. (2018)	Prospect ive cohort	55 male and female children with ASD	792 male and female TD children	Plasma umbilical cord blood sample and non-fasting childhood (median age = 19.03 months) venous blood sample	Mean cord blood adiponectin was higher in TD children compared to the group with ASD (p = 0.01) No significant difference in early childhood adiponectin	Birthweight was greater in TD children and compared to children with ASD (p = 0.03) Extremely rapid weight gain was associated with greater ASD risk

Abbreviations: ASD, Autism Spectrum Disorder; TD, Typically Developing; BMI, Body Mass Index.

Table 2.4 Ghrelin in ASD.

Study	Design	Study Group	Control Group	Measure	Result	BMI
Al-Zaid et al. (2014)	Case control	31 male children with ASD (age: 3–8 years)	28 age- and sex-matched TD children (age: 3–8 years)	7 mL of venous blood samples were collected after an overnight fast	Acylated ghrelin concentrations were lower in the group with ASD than TD children ($p \leq 0.001$) Deacylated ghrelin concentrations were lower in group with ASD compared to TD children ($p \leq 0.005$)	Weight was higher in the children with ASD (19.3 kg in TD children and to 22.7 kg in children with ASD) ($p = 0.05$) No significant difference in BMI or height BMI z-score or BMI weight categories not provided
Hasan et al. (2019)	Case control	20 male and female children with ASD (16 males and 4 females) (mean age: 5.9 years)	20 age-matched healthy control children (13 males and 7 females) (mean age: 6.0 years)	5 mL blood samples from participants (serum)	Serum levels of ghrelin were lower in children with ASD compared to TD children, but not statistically significant (p =0.32)	TD children had a greater mean weight (31.17 kg), height (1.32 m^2), and BMI (17.6 kg/m^2) compared to children with ASD with a mean weight of 21.26 kg, height of 1.17 m^2, and BMI of 15.5 kg/m^2 BMI z-score or BMI weight categories not provided

Abbreviations: ASD, Autism Spectrum Disorder; TD, Typically Developing; BMI, Body Mass Index.

2.12 Figures

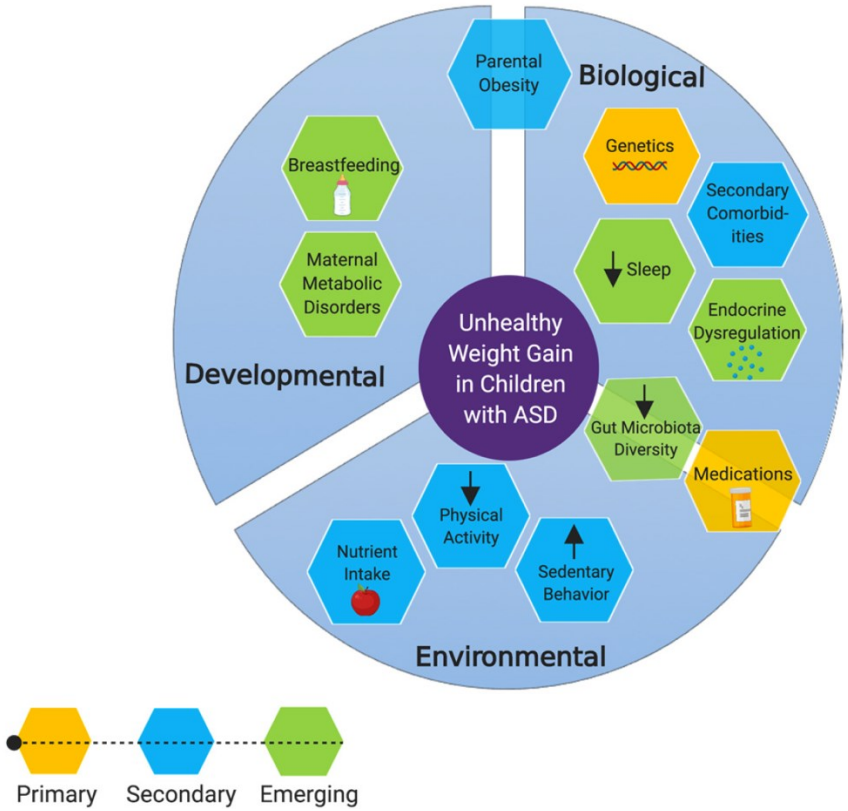

Figure 2.1. Risk factors for becoming obese or overweight among individuals with ASD. Primary factors include risk factors which have been directly implicated in obesity and unhealthy weight gain, in children with ASD. Secondary factors are those which are not specific to children with ASD but could result in unhealthy weight gain. Emerging factors are those on which we have postulated hypotheses based on indirect evidence. *Created with BioRender.

Chapter 3 Assessing the Difference in Energy Balance Hormones and Mealtime Behaviors Among Children with Autism Spectrum Disorder (ASD).

3.1 Preface

The following chapter is based on data collected from 21 youth with Autism Spectrum Disorder, 15 of normal weight status and 6 of overweight or obese status, at the University of Alberta. The study aimed to examine any differences in concentration of hormones (ghrelin, leptin, GLP-1, and PYY) according to weight status among children with ASD. We also explore the role of mealtime behaviors on weight status among children with ASD.

3.2 Introduction

This research study was carried out to examine differences in hormonal levels and mealtime behaviors, between children with ASD of differing weight statuses. As there are increasing reports of higher rates of obesity and overweight among children with ASD (Kahathuduwa et al., 2019), there is a need to explore metabolic and clinical parameters within this group which may then provide further insight into whether these factors may be possible contributors to some children gaining unhealthy amounts of weight, while others do not. Findings may allow for the development of clinical health surveillance strategies at an earlier stage (such as at the time of ASD diagnosis), and thus allow for possible prevention of unhealthy weight gain and obesity.

We explored various hormonal regulators of appetite due to the role they play in energy intake and weight status (Austin & Marks, 2009). Literature suggests there may be increased leptin concentrations and decreased ghrelin levels among children with ASD, relative to TD children (Al-Zaid et al., 2014; Ashwood et al., 2008). Leptin is an orexigenic hormone, and levels are positively correlated with fat mass (Hallioglu et al., 2003; Sahu, 2003) and ghrelin is an appetite-stimulating hormone (Nakazato et al., 2001). Because these hormones have various roles in regulating appetite, we wanted to explore whether they may also have a role in the higher rates of overweight and obesity we see in this population. We also measured GLP-1 and PYY levels, as exploratory measures, because they also have functions on satiety and appetite regulation (Bloemendaal et al., 2014; Guo et al., 2006).

We also considered specific mealtime behaviors due to the role that these behaviors can have on the type and amount of energy consumption. Problematic eating behaviors are consistently reported among children with ASD (Mayes & Zickgraf, 2019; Stough et al., 2015). These disruptive mealtime behaviors (e.g., refusing to eat certain types of food) are another factor that has been associated with weight status among children (Dubois et al., 2007). Therefore, we wanted to examine if mealtime behaviors might be related to weight status among children with ASD. We measured mealtime behaviors through the Brief Autism Mealtime Behavior Inventory (BAMBI), a questionnaire designed to gather information on specific feeding challenges in children with ASD (Lukens & Linscheid, 2008). The BAMBI collects information around three factors: Food Refusal, Limited Varieties of food, and Features of ASD (Lukens & Linscheid, 2008).

The main objectives of this study were to explore: (1) how hormones involved in the regulation of appetite and energy balance (leptin, ghrelin, GLP-1, PYY, insulin) may vary

based on weight status and (2) to examine whether mealtime feeding behaviours (measured by the BAMBI) may differ based on weight status among children with ASD. For objective one, we hypothesized that there would be a significant difference between both groups, with the group with ASD of overweight and obese (ASD+OWOB) status having lower ghrelin and higher leptin concentrations and increased insulin resistance relative to the group with ASD of normal weight (ASD+NW) status. For objective two, we hypothesized that we would find significant differences in BAMBI scores with the ASD+OWOB group scoring significantly higher (i.e., more problematic eating behaviours) than the ASD+NW group. As a secondary exploratory aim, we also examined any potential moderating effect of ghrelin and leptin levels on the relationship between BAMBI scores and BMI Z-score.

3.3 Materials and Methods

3.3.1 Population

This cross-sectional study was completed in one visit to the Human Nutrition Research Unit (HNRU) at the University of Alberta. Participants included 21 children with a confirmed diagnosis of ASD between the ages of 5-12 years (4 females and 17 males). Two groups of children with confirmed diagnoses of ASD were recruited: (1) children of obese/overweight status, (2) children of normal weight status. We collected anthropometric measurements, blood samples, and information about mealtime/feeding behaviors (among other questionnaires). This age group was selected to understand weight status before possible influences of pubertal status on weight gain and development. Recruitment of participants was done primarily through registrants of an ongoing research program (the 'Autism Treatment Network' or ATN, in the local Edmonton area), through local clinics, and snowballing sampling techniques. The study was approved by the University of Alberta's Health Research Ethics Board (ID: Pro00082489). Inclusion Criteria included (1) a diagnosis of ASD confirmed by a medical professional using DSM-5 or DSM-IV-TR criteria, and in most cases, using standardized symptom measures such as the Autism Diagnostic Observation Schedule, (2) children between the age 5 to 12 years old, and (3) written informed consent obtained from parents/legal guardians (as well as written assent, as applicable, from participants) and their willingness to complete study procedures. Assent was assessed through the willingness to have blood drawn while considering both verbal and non-verbal cues, such as opening up the arm at the time of blood collection. Respect for specific requests was also regarded through the availability of social stories, distraction tools (e.g., an iPad), and lidocaine 2.5% and prilocaine 2.5% (EMLA)

numbing cream. Exclusion criteria included: (1) chronic diseases impacting body composition such as diabetes mellitus, inflammatory bowel disease, liver or kidney disease, and (2) recent (within 3 months) hospitalizations due to severe infections or surgery. Eligibility and exclusion criteria were assessed through a Medical History Questionnaire, which provided information around relevant medical diagnoses.

3.3.2 Experimental Design

Participants, along with a parent/guardian, arrived at the HNRU at the University of Alberta between 0730 and 0900 after an overnight fast. After signing consent and assent forms, anthropometric measurements of height, weight, and waist circumference were collected. Blood samples (11ml per sample) were drawn through a butterfly clip before snack consumption (after 8 hours of fasting). Parents were also asked to complete the following questionnaires: Children's Physical Activity Questionnaire (C-PAQ), Tanner Scale, Brief Autism Mealtime Behavior Inventory (BAMBI), Medical History Questionnaire, and the Social Responsiveness Scale 2 (SRS-2). The Automated Self-Administered 24- Hour (ASA-24) Dietary Assessment Tool was completed at home.

3.3.3 Anthropometric Measurements

Anthropometric assessments included measurements of the participants' height, weight and, waist circumference. Height was measured in triplicate using a Heightronic Digital Stadiometer (235 Heightronic TM, Concepts, Quick Medical, Snoqualmie, WA) to the nearest 0.1 cm. Participants were asked to stand straight with their back, shoulders, and heels against the wall and ensuring their head was in the Frankfurt plane. The mean of these three measurements was used. Bodyweight was measured in triplicate using a calibrated digital scale (Health o meter® Professional Remote Display, Sunbeam Products Inc., FL, USA, capacity of 500 lb x 0.2 lb / 227 kg x 0.1 kg) to the nearest 0.1 kg. Waist circumference was measured in triplicate using a Lufkin W606PM anthropometric measuring tape (centimeters) at the top of the iliac crest and after a normal expiration. The mean of the three measurements was calculated.

3.3.4 Puberty Assessments

Puberty was assessed using the Tanner staging scale for children at or above the age of 9. Pubertal stages were collected to understand the degree of sexual maturation of children, as this can often impact body weight and hormonal status (Appendix A).

3.3.5 Brief Autism Mealtime Behavior Inventory (BAMBI)

Participants and primary caregivers/parents were asked to complete the BAMBI. The BAMBI is a questionnaire that assesses the mealtime behaviors of children within the last six months (Lukens & Linscheid, 2008). It is a validated questionnaire designed to capture mealtime behaviors, specifically in children with ASD. The BAMBI assesses mealtime behaviors in 3 categories: 1) Limited Variety, 2) Food Refusal, and 3) Features of Autism. Feeding problems were defined as eating a limited number of food, inadequate variety of foods, and displaying food rejection, which can thus impact nutritional intake, weight gain, and linear growth (Field et al., 2003; Lukens & Linscheid, 2008; Munk & Repp, 1994). The test sample included the primary caregivers of children (between the ages of 3 and 11 years old) with a caregiver-reported diagnosis of ASD and TD children. The three subscales produce an overall score which allows for an identification of 81% of problematic feeders (DeMand et al., 2015). Information from this questionnaire will be supplemented by diet information collected through the Automated Self-Administered 24-Hour Assessment (ASA-24). Psychometric properties of the BAMBI include internal consistency Cronbach's alpha= 0.88; an alpha coefficient of 0.87 for the Limited Variety factor; 0.76 for the Food Refusal factor; and 0.63 for the Features of Autism factor. The overall test-retest reliability is r (33) = 0.87, $p < 0.01$; and inter-rater reliability (r (16)) = 0.78, $p< 0.01$), for total scores. Food refusal is defined as the rejection of food, which may also have an impact on the number of calories necessary for development (Field et al., 2003; Lukens & Linscheid, 2008). The 'Limited Variety' factor is used to capture data on specific food preferences and likes and dislikes. And finally, the 'Features of Autism' factor is used to collect information on the child's characteristic symptoms of ASD at the time of meals (e.g., flexibility with routines, aggressive behaviors, etc.). The BAMBI has been evaluated for criterion-related validity by assessing correlations between the BAMBI total frequency score and Behavioral Pediatric Feeding Assessment Scale. Significant positive correlations between the total BAMBI score and child behavior frequency score and parental feelings/strategies scores were found. Construct validity for each factor of the BAMBI has been evaluated through correlations between individual factor scores

and external criterion measures (such as servings of meat, vegetables, and fruits which were negatively correlated with BAMBI scores). Finally, construct validity has been evaluated through examining the ability of the BAMBI to discriminate between the group of children with ASD and TD children (F (1,106) = 72.91, $p < .01$) (Lukens & Linscheid, 2008) (Appendix D).

3.3.6 Automated Self-Administered 24-Hour Dietary Assessment (ASA 24)

Parents were asked to fill out a food diary through the ASA 24 system. A 24-hr recall collects information on total calories consumed, as well as information on specific breakdowns of macronutrients (e.g., carbohydrates, proteins, etc.) and micronutrients within a 24-hour period- this dietary information provided further insight into interpreting findings from the BAMBI. The ASA 24 asks respondents to report eating occasions and time of consumption. It was collected in order to compare total intake of calories (KCal) and macronutrient breakdowns between groups.

3.3.7 Medical History Questionnaire

Data was collected on information related to birth history, relevant medical diagnoses such as diabetes mellitus, medications, digestive/GI disorder, etc., and relevant family history such as overweight/obesity, type 2 diabetes (Appendix C).

3.3.8 Social Responsiveness Scale, Second Edition (SRS-2)

The Social Responsiveness Scale, 2nd Edition (SRS-2) is a 65-item questionnaire completed by the primary caregiver/parent or teacher (Constantino, 2013). The SRS-2 was completed by the primary caregiver/parent who attended the study visit with the child. It provides an overall rating of social impairment as well as scores on five ASD-specific subdomains: (1) Social Awareness, (2) Social Cognition, (3) Social Communication, (4) Social Motivation, and (5) Restricted Interests and Repetitive Behaviors. It is designed to assess individuals from age 2.5 years to adulthood. Total scores are standardized as T-scores (e.g., mean =50, SD = 10). This scale is used for children clinically affected by ASD as well as among children in the general population (T. W. Frazier et al., 2014). Psychometric properties of the SRS-2 include internal consistency alpha= 0.95-0.97; test-retest reliability= 0.72-0.95; and inter-rater reliability= 0.61-0.91.

3.3.9 Children's Physical Activity Questionnaire (C-PAQ)

Information around physical activity was also collected as this was hypothesized to be a potential covariate in the study between hormonal concentrations and weight status. The C-PAQ asks parents to report on their child's physical activity and sedentary activities across school time and leisure time over the past seven days (Corder et al., 2009). It collects information across four areas of activity: sports, leisure time, activities at school (e.g., physical education classes), and other activities (e.g., sedentary activities such as TV viewing, computer use, homework, play). A total is calculated using the time spent within each category (Appendix B).

3.3.10 Preparation of Samples

Blood plasma samples were collected into polypropylene tubes containing AEBSF (4mM final) and serum separator tubes supplemented with aprotinin (10 uL per 1mL plasma or serum) and centrifuged. The plasma was treated with 1N HCl (200uL 1N HCl per 1mL plasma) and stored at -80°C until the date of analysis. Following centrifugation, both plasma and serum were stored at -80°C. Plasma samples were assayed using MesoScale Discovery (MSD). All analyses were measured in triplicate. We were unable to analyse glucose concentrations at this time, due to delays in non-essential lab services (COVID-19 circumstances).

3.4 Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) software (version 24; IBM Corp., Armonk, NY, USA) was used to analyze the data. Baseline demographic and biological data was described as Median (Interquartile Range). These values were reported due to the non-normal distribution of many variables (**Table 3.1**).

For objective one, ASD+NW and ASD+OWOB groups were compared, with respect to hormonal concentrations, using the Mann- Whitney *U* test, presented in (**Table 3.2**). Values were reported as Mean (Median) ± Standard Deviation (Interquartile Range). These values were reported due to the non-normal distribution of many variables and small sample size in order to assess any standardized mean differences which may be important group differences but not detected statistically. This was followed by testing for correlations between age, BMI z-score, SRS-2 scores, pubertal status, insulin, leptin, ghrelin, GLP-1, and PYY through a Spearman's Rank-Order correlation (due to non-normality of data). Spearman's Partial correlation analyses were further performed to evaluate the relationships between leptin

concentrations and ghrelin concentrations and insulin, leptin, ghrelin, GLP-1, and PYY adjusted for potential confounders (age, sex, and pubertal status).

For the second objective, ASD+NW and ASD+OWOB groups were compared, with respect to mealtime behaviors, using the Mann- Whitney *U* test, presented in (**Table 3.3**). Correlation analyses, through a Spearman's rank order correlation, were performed to assess the relationship between BAMBI scores and clinical and biochemical parameters. Furthermore, as a secondary exploratory aim, given that leptin and ghrelin influence appetite, we proposed that these hormones would moderate the relationship between BAMBI scores and BMI Z-score. This was assessed through a moderator analysis, while controlling for age and pubertal status and bootstrapping of standard error estimates. We used the PROCESS macro for SPSS, written by Hayes (2017). BAMBI scores were selected as the dependent variable, and BMI Z-scores were the independent variable. Moderators can impact the direction and strength of the relationship between the independent and dependent variables (Baron & Kenny, 1986). They are a third variable that can enhance, buffer, or be antagonistic to the predictor and outcome variable relationship (P. A. Frazier et al., 2004). To test our proposed moderation relationship, we used Model 1 in PROCESS to analyze the interaction model (Hayes & Matthes, 2009). PROCESS uses bootstrapping, a nonparametric approach of standard error estimates that uses resampling (Hayes, 2018).

The original target sample size was set at 20 participants per group. This would have allowed for an 80% power to detect a moderate effect size (ES) of approximately 0.6 standardized deviations in ghrelin concentrations, with a significance level of 0.05 using a two-sided two-sample t-test. However, given some challenges in recruitment due to factors such as parental concerns about blood draws and timeline, we were unable to reach these targets; thus, our current study is likely underpowered for some design and test combinations. However, as described above, adaptations were made to the original statistical plan to ensure adequate power for some primary analyses. Effect sizes for the available sample sizes are also presented in the data tables. The magnitude of the group differences were examined using Cohen's (1992) operationally defined values for effect sizes (r = 0.10– 0.29 suggests a small; 0.30– 0.49, a moderate; and > 0.50, a large effect size) (Cohen, 1992). Our original analytic plan involved all null hypotheses for between group comparisons at baseline to be examined using an independent sample *t*-test. To test Hypothesis 1, we planned to complete a MANOVA with group (ASD vs TD) and weight status (obese or overweight vs. non-overweight) as the two predictor variables, and hormone levels as the dependent variables, with posthoc group comparisons including age, sex, and pubertal status as covariates. To test Hypothesis 2, we

planned to conduct a similar comparison of atypical eating behaviours, indexed by BAMBI scores. We also planned to test the relationship between hormonal factors and BMI Z-score within and between groups using multiple linear regression techniques with adjustment for covariates as above. However, due to recruitment challenges (including parental concerns with blood draws and a lack of recruitment of a control TD group) and consequently a small sample size, these statistical plans were modified as described above.

3.5 Results

3.5.1 Clinical characteristics of participants

The final sample included 21 participants with baseline characteristics presented in (**Table 3.1)**. There were no statistically significant differences in age, female/male ratio, physical activity hours within a one-week period, total calories consumed per day, and SRS-2 total scores between NW and OWOB groups. However, when comparing standardized mean differences, the mean age of the OWOB group (9.47 ± 2.07 years in the NW group and 10.67 ± 1.97 years in the OWOB group) differed by > 1 year. Although this difference was not significant (p=0.15), it may still have contributed to group differences in pubertal status. More male participants took part in the study with a ratio of about 1 female to 4-5 males, in line with current literature on the sex ratio in ASD (Ofner et al., 2018). The median BMI Z-score in the group with NW was -0.14 (IQR: -0.43-0.33) and 1.45 (IQR: 1.02-2.22) in the group with OWOB (p<0.005). Five participants in the group with NW reported taking either an SSRI or antidepressant, and one participant in the group with OWOB reported taking a stimulant medication. We were unable to collect blood samples from two participants, due to the unavailability of a nurse/phlebotomist at that time of the blood draw, and one participant was unwilling to have their blood drawn (three in total). We also had three participants from whom we were not able to collect the SRS-2 data, due to this questionnaire being added to the protocol at a later time; thus, we were unable to get a hold of some families to complete this questionnaire retroactively. For these missing data points, group mean imputations were inserted (Khan et al., 2018).

3.5.2 Hormonal levels between groups

Under fasting conditions, the NW group had lower plasma leptin compared to the OWOB group (p=0.018). The groups did not differ in fasting concentrations of ghrelin, GLP-1, PYY, and insulin (**Table 3.2**).

3.5.3 BAMBI scores between groups

The ASD+NW group had lower median scores on the BAMBI of 39.00 (IQR 30.00-48.00) compared to the ASD+OWOB group, which reported median scores of 49.50 (IQR 41.75-56.75) (p=0.045). When comparing each factor within the BAMBI, it was found that the ASD+OWOB scored higher in eating more Limited Variety of foods and displaying more Features of ASD (p=0.014 and p=0.006, respectively) (**Table 3.3**).

3.5.4 Correlations Between Leptin and Metabolic Parameters

Correlation analyses was further performed to assess the relationship between specific clinical and biochemical parameters and leptin concentrations. The analyses showed a positive correlation of leptin concentration with age, pubertal status, insulin concentrations (r = 0.62, p = 0.003; r = 0.48, p = 0.028; and r = 0.45, p = 0.041) and a negative correlation with ghrelin concentrations (r= -0.52, p=0.016) (**Table 3.4**). No significant correlations were found between leptin and SRS-2 scores, PYY levels, GLP-1 levels in children with ASD. After adjusting for age, sex, and pubertal status, leptin concentrations showed a positive correlation with BMI Z-scores (r = 0.73, p = 0.001) (**Table 3.4**).

3.5.5 Correlation Between Ghrelin and Metabolic Parameters

Correlation analyses were performed to assess the relationship between specific clinical and biochemical parameters and ghrelin levels. The analyses showed a negative correlation of ghrelin concentration with age, pubertal status, insulin and leptin concentrations *(r = -0.78, p < 0.0005; r = -0.54, p = 0.011; r = -0.65, p = 0.010; and r= -0.52, p= 0.020)* (**Table 3.5**). After adjusting for age, sex and pubertal status, ghrelin concentrations showed no significant correlations (**Table 3.5).**

3.5.6 Correlations Between BAMBI Scores and Metabolic Parameters

Correlation analyses between levels of these hormones (leptin and ghrelin), and clinical parameters and BAMBI scores were tested through a Spearman's rank-order correlation. Results presented in (**Table 3.6)** highlight that BAMBI scores were significantly correlated with BMI Z-scores (r=0.44, p=0.044*)*. We did not find any correlation between leptin and ghrelin concentrations and BAMBI scores.

3.5.7 Moderator Analysis of Ghrelin and Leptin Levels on BAMBI scores and BMI Z-scores

Our exploratory aim was to examine whether the relationship between mealtime feeding behaviors (measured by the BAMBI) and weight status of children with ASD, may be moderated by levels of leptin and ghrelin. This aim was assessed through a moderator analysis while controlling for age, sex, and pubertal status.

For the moderator analysis of leptin and ghrelin levels on BAMBI scores and BMI Z-score, linearity was observed, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.16. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus standardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1. There were no outliers as assessed through casewise diagnostics, not revealing greater than ±3 standard deviations and values for Cook's distance above 1. For the moderator analysis of ghrelin concentrations on BAMBI scores and BMI Z-scores, linearity assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.59. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus standardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1. There were no outliers as assessed through casewise diagnostics, not revealing greater than ±3 standard deviations and values for Cook's distance above 1.

Moderation analyses indicated that leptin and ghrelin levels did not influence the relationship between BAMBI scores and BMI Z-scores. The results of this analysis with BAMBI scores as a moderator can be seen in (**Tables 3.7** and **3.8)**.

3.6 Discussion

The main findings of our study included increased leptin concentrations in the ASD+OWOB group compared to the ASD+NW group. Furthermore, leptin was positively correlated with BMI Z-score, after controlling for age, sex, and pubertal status. We also found total BAMBI scores to be higher in the ASD+OWOB group, and comparisons of individual factors also revealed higher scores in the 'Limited Variety' and 'Features of Autism' subdomains in the ASD+OWOB group.

3.6.1 Leptin Findings

Leptin is an adipokine produced primarily by the white and brown adipose tissue (Cancello et al., 1998; F. Zhang et al., 1997). Plasma leptin levels are positively correlated with body fat mass, which was also found in our study (Al Maskari & Alnaqdy, 2006). Leptin has action in the hypothalamus in regulating food intake and body weight through anorexigenic signals (Sahu, 2003). Obesity is often associated with increased leptin concentrations, known as leptin resistance (Enriori et al., 2006; Lin et al., 2000). Therefore it is theorized that it's expected anorexigenic effects may be diminished in obesity, due to factors such as a disrupted negative feedback loop which blocks leptin signaling (Knight et al., 2010; Perry & Wang, 2012).

In our study, we found leptin concentrations to be significantly higher in the ASD+OWOB group compared to the ASD+NW group. Secondary analyses found positive correlations between leptin and both age and pubertal status. We were expecting to see these correlations, with previous studies finding a positive correlation between leptin and age and pubertal status in children (Antunes et al., 2009). We also found a positive correlation between leptin and BMI Z-scores, after controlling for age, sex, and pubertal status, in line with previous studies (Antunes et al., 2009; Bahrami et al., 2014; Fleisch et al., 2007). For example, Antunes et al. (2009) found a positive correlation between serum leptin concentrations and BMI Z-score in children between the ages of 2-19 years old (r= 0.136; p= 0.010). Similarly, Fleisch et al. (2007) found baseline leptin concentrations to be a positive predictor of increased BMI (p = 0.0147). Bahrami et al. (2014) also found leptin levels correlated with BMI in children between the ages of 10-18 (r=0.272, p<0.001). Thus, consistent with findings in non-autistic children research, the anorexigenic effect of leptin may be diminished in the presence of obesity, leading to disrupted leptin signaling and thus higher concentrations in the ASD+OWOB group.

We also found a significant difference between the NW and OWOB group on parent-reported sexual development (as assessed through the Tanner staging scale). However, this finding may be due, in part, to mean standardized differences in age between the two groups, with the OWOB group being older. Clinically it is also often reported that children with obesity go into puberty, generally, at an earlier age (Chen et al., 2017). Previous studies have also found a possible role of leptin in sexual maturation and puberty development in children (Farooqi, 2002; Lebenthal et al., 2006; Sanchez-Garrido & Tena-Sempere, 2013).

When analyzing leptin levels, in relation to other hormones, we found a positive correlation between leptin and insulin, before adjusting for age, sex, pubertal status. Previous studies have also reported this positive correlation among children (Bahrami et al., 2014; Zuo et al., 2013). Because obesity and overweight often involve leptin resistance and insulin resistance (Soliman et al., 2012; Zimmet et al., 1999), these findings in children with ASD are in line with what has been reported in the TD population. We also found a negative correlation between leptin and ghrelin, before adjusting for age, sex, and pubertal status. This negative correlation has been previously reported among children and adolescents (H. S. Park et al., 2005; Stylianou et al., 2007; Wilasco et al., 2012). For example, Wilasco et al. (2012) found an inverse relationship between leptin and total ghrelin, in their study of children aged 4 months to 11 years ($r = -0.237$, $p = 0.012$). This is likely due to their antagonistic roles in appetite modulation. Ashwood et al. (2008) compared mean plasma leptin concentrations between children with ASD and TD children. Leptin concentrations ranged from 0.87–3.4 ng/ml in the group with ASD and 0.49–1.66 ng/ml in the TD group (Ashwood et al., 2008). Our present study found a mean of 9.355 ng/mL in our group with ASD+ NW group and 16.144 ng/mL in the ASD+OWOB group. One possible factor which may account for differences in concentration levels between both studies may be due to differences in age groups recruited. For example in the Ashwood et al. (2008) research, children were 4.25 years old (2.4–15.5), however in our current study the median age was 10.00 years (IQR: 8.5-11.5), and previous findings have suggested a positive correlation between leptin and age (Bahrami et al., 2014).

Previous research findings of elevated leptin concentrations in children with ASD, compared to TD groups, coupled with current findings of it being positively correlated with BMI Z-scores, could allow for future studies to examine whether leptin concentrations are markedly higher in ASD+OWOB groups compared to TD+OWOB groups. This research direction may help to inform further understanding of the potential implications of hormonal differences both between children with ASD and TD children and children with ASD of different weight statuses.

Previous research has also suggested that leptin may be a possible early-onset phenotype of ASD, with elevated leptin levels earlier on in children with ASD (Ashwood et al., 2008; Hasan et al., 2019). Specifically, Raghavan et al. (2018) followed a Boston Birth Cohort and found that of the children that were born small for gestational age and had lower cord levels of leptin, those with the most rapid weight gain went on to have the highest childhood (median age of 7.5 years) leptin levels and were also more likely to be diagnosed with ASD (Raghavan et al., 2018). This finding suggests that leptin should be monitored more closely in children with ASD to assess the possible relationship it has on both the development of ASD and possible downstream metabolic effect on weight status.

3.6.2 Ghrelin Findings

Ghrelin, the hunger hormone, is an orexigenic gastric peptide hormone (Inui, 2001). It is produced by stomach cells, the hypothalamus, and the pituitary (among other tissues) (Delporte, 2013). Both central and peripheral administration of ghrelin regulates appetite and energy balance (Nakazato et al., 2001; Tschöp et al., 2000). In obesity, fasting ghrelin levels have been found to be lower than NW controls (Cummings et al., 2002). Ghrelin rises right before a meal, but the expected post-prandial fall has been found to be attenuated in obesity (English et al., 2002). In our study, univariate analyses found that ghrelin concentrations were not significantly different between groups (p= 0.30, d=0.24), when stratified based on weight status (**Table 3.2**); however we also considered the standardized mean differences (NW= 1487.98 pg/mL ± 443.83, OWOB= 1223.81 pg/mL ± 655.11) due to previous studies finding decreased ghrelin concentrations in children with ASD (Al-Zaid et al., 2014; Hasan et al., 2019). Further correlation analyses of ghrelin concentrations were compared to clinical parameters and found to be negatively correlated with age and pubertal status. Ghrelin concentrations were also negatively correlated with both insulin and leptin, in line with previous studies (Stylianou et al., 2007). However, after adjusting for age, sex, and pubertal status, there were no correlations between ghrelin and the various clinical and biochemical parameters. These findings may suggest that ghrelin is more regulated by age, sex, and pubertal status than insulin, leptin, or weight status, however further studies would need to be completed in order to confirm this.

Previous research has shown that ghrelin concentrations are suppressed in TD groups with OWOB (Shiiya et al., 2002; Tschöp et al., 2001). In addition, studies have shown that ghrelin concentrations may decrease with puberty (Whatmore et al., 2003). Due to the small

sample size and small effect size (d=0.24) we had insufficient power to draw any conclusions on possible differences in ghrelin concentrations between groups. A larger sample size would allow for detection of smaller ghrelin concentration differences between ASD+NW and ASD+OWOB groups than was possible in the current study. Al-Zaid et al. (2014) found significantly lower plasma acylated and desacylated ghrelin concentrations in children with ASD compared to TD children, that did not differ substantially in BMI, although the group with ASD reported significantly higher mean weight (kg) (Al-Zaid et al., 2014). They found 170.5 ± 59.3 pg/mL of acylated ghrelin in the TD group and 116.7 ± 50.3 pg/mL in the group with ASD. They also found 299.3 ± 139.7 pg/mL of desacylated ghrelin in the TD group and 214.4 ± 80.5 pg/mL in the group with ASD. Our study, on the other hand, considered total ghrelin concentrations. Hasan et al. (2019) found lower serum concentrations of ghrelin among children with ASD compared to controls, however the BMI of the group with ASD was significantly lower than the TD group (Hasan et al., 2019). This information, taken together, may suggest that ghrelin may indeed be lower in children with ASD, and BMI status may also contribute to decreased ghrelin levels. Our present findings, coupled with previous research on overall lower concentrations of ghrelin in children with ASD, may provide some insight into hormonal dysregulation and implications for weight status in these patients.

3.6.3 Insulin Findings

Insulin is involved in maintaining glucose homeostasis and also has a role in signalling the brain for energy balance (Miller, 2017; Plum et al., 2006). Its levels are found to be proportional to the degree of adiposity (Cammisotto et al., 2005). Insulin is produced by pancreatic beta cells (Schuit et al., 2001). It is critical for the integration of several peripheral metabolic signals and is also able to stimulate the synthesis and secretion of leptin from white adipose tissue (Perry & Wang, 2012). In obesity, there is a decrease in insulin sensitivity (Kahn & Flier, 2000; Kahn et al., 2006). In our study, we found that although there was no significant difference in the NW and OWOB in levels of insulin, there may have been trends towards significance (p=0.080, d=0.39), with higher mean insulin levels in the ASD+OWOB group. Further analyses also revealed a positive correlation with leptin, which may be further indicative of some of the roles they share in food intake and energy metabolism (Paz-Filho et al., 2012). Previous research has found insulin resistance (characterized by increased concentrations of insulin) among OWOB weight status groups (Bahrami et al., 2014; Hrafnkelsson et al., 2009). For example, Bahrami et al. (2014) found insulin levels to be higher

in their overweight group compared to the NW adolescents (p=0.040, d= 0.19). Furthermore, Hrafnkelsson et al. (2009) found that in a cross-sectional study of 7-year-old children, those of overweight status had higher serum fasting insulin levels (p<0.001, d= 0.66). The role of insulin regulation in children with ASD would be further informed by examining plasma glucose concentrations. This would allow for the calculation of Homeostatic model assessment insulin resistance (HOMA-IR) (Conwell et al., 2004).

3.6.4 PYY Findings

Peptide YY (PYY) is a satiety hormone (Guo et al., 2006). It belongs to the pancreatic polypeptide family and is produced by the L cells of the gut (De Silva & Bloom, 2012). Circulating levels of PYY are influenced by meal composition and are lowest during fasting and increase post-prandially (Guo et al., 2006). Some research has reported that in obesity, there are lower circulating fasting levels of PYY, which may reduce satiety, and that concentrations may have a smaller rise postprandially (Batterham et al., 2003; Miller, 2017). Studies have also shown that in obesity the stimulation of PYY through caloric intake may be blunted (Mittelman et al., 2010). However, other studies have not reported differences in PYY levels between groups of different weight status (Cahill et al., 2014). PYY's levels and actions may also depend on the form of obesity (e.g., diet-induced vs. genetic) (Vrang et al., 2006). For example, $PYY_{3–36}$, the main circulating form of PYY, has been to reduce food intake and adiposity, when injected into mouse models of diet-induced obesity (Adams et al., 2006; Vrang et al., 2006). In our study, we did not find any significant group differences in baseline PYY levels between the OWOB and NW group. In order to understand the role of PYY, and any differences between groups, further research that compares pre- and post-prandial fluctuations and various meal compositions (e.g., high vs. low protein) is warranted (Van der Klaauw et al., 2013). This research would help determine whether there are different fluctuations between groups and how this may go on to impact nutrient breakdown and metabolism. Currently, our findings suggest that fasting levels of PYY do not vary based on weight status in children with ASD.

3.6.5 GLP-1 Findings

GLP-1 is an incretin hormone released from the small intestine and L-cells of the colon in proportion to nutrients ingested (Gutzwiller et al., 1999; P. E. MacDonald et al., 2002; Perry

& Wang, 2012). GLP-1 has been shown to delay gastric emptying and enhance satiety (Nauck et al., 1997; Tang-Christensen et al., 1996; D. L. Williams et al., 2006). It is released into circulation after nutrient ingestion (P. E. MacDonald et al., 2002). Hira et al., (2019) reviewed the role of GLP-1 in obesity and found mixed findings on the secretory response of GLP-1 post-meal ingestion and at basal levels (Hira et al., 2020). In our study, we did not find any significant group differences in baseline fasting GLP-1 levels between the OWOB and NW group. However, similar to PYY, GLP-1 levels also differ based on meal consumption, thus comparing levels pre- and post-prandially would allow us to understand whether its actions vary between groups (Van der Klaauw et al., 2013).

3.6.6. Mealtime and Feeding Behavior Findings

In our study, BAMBI scores were significantly higher in the ASD+OWOB compared to the ASD+NW group. Comparing the groups on each BAMBI factor, we found that the ASD+OWOB group tended to score higher on eating more Limited Varieties of foods and displaying more Features of ASD. One previous study, conducted by Ismail et al. (2019) found that when they stratified children with ASD based on weight status (with underweight and NW children in one group and OWOB in another group), overall BAMBI scores did not differ between groups. However, after comparing each factor 'Food Refusal' was significantly higher in the group of underweight and NW status (Kamal Nor et al., 2019). Our study was not able to detect any difference in 'Food Refusal' scores between both groups, although mean differences suggested 'Food Refusal' may have been detectably higher in the ASD+NW group (9.20 ± 3.23 vs. 7.17 ± 3.54; $p = 0.11$, $d = 0.35$) if we had a larger sample. Kamal Nor et al. (2019) also included children of underweight status, which was a group not present in our current study (Kamal Nor et al., 2019). This study also included a wider age range of children (2-18 years of age), and thus, this may have impacted reported eating behaviors, which tend to evolve from infancy to adolescence (Birch et al., 2007).

Furthermore, our ASA-24 data considered breakdowns of various macronutrient groups; we found a significant difference in the total sugar consumed by the OWOB group compared to the NW group. Previous literature has shown that increased food variety can promote obesity, due to the role it can have on increased food intake (Epstein et al., 2009; McCrory et al., 2012). However, the type of macronutrient content also has an impact on the direction of the weight change (Johnson & Wardle, 2014). For example, a study conducted in adults (18-50 years) found snack food intake was associated with higher BMI, whereas grains

and protein intake was negatively correlated with BMI (Sea et al., 2004). Therefore, our dietary findings of greater total sugar consumption and limited food varieties may have contributed, in part to weight gain in this group. However, due to the relatively small sample size of participants who completed these online food records, more dietary data would need to be collected before drawing conclusions about between-group differences.

Correlation analyses found BAMBI scores to be positively correlated with BMI Z-scores. This finding suggests that higher levels of atypical feeding behaviors are associated with higher BMI Z-scores. Previous research has found that obesity may be correlated to ASD severity (Levy et al., 2019), which is in line with our findings of significantly higher scores of 'Features of Autism' in the OWOB group. The 'Features of Autism' factor describes a child's characteristic symptoms of ASD at the time of meals (such as flexibility with routines, aggressive behaviors, etc.) (Lukens & Linscheid, 2008).

Our second aim involved examining whether ghrelin and leptin levels had a moderator effect between BAMBI scores and BMI Z-score. We proposed that because leptin and ghrelin have roles in feeding circuits affecting body weight homeostasis (Cowley & Grove, 2004) and ghrelin is a regulator of hedonic eating behaviors (Malik et al., 2008), these hormones may be moderating the relationship between mealtime behaviors and BMI Z-score. Ghrelin acts through the growth hormone secretagogue receptor (GHSR), and these receptors interact with ghrelin in several brain areas (e.g. the midbrain, an area important for reward processing (Perelló & Zigman, 2012). Buss et al. (2014) also found a positive correlation between ghrelin levels and hedonic eating behaviours in NW and OW groups (Buss et al., 2014). However, these eating behaviors were weak or tended to be negatively correlated in the groups with obesity (Buss et al., 2014). This was postulated to be due to the impaired ghrelin signaling in obesity (Briggs et al., 2010; Buss et al., 2014). We did not detect any moderating effects after controlling for age, sex, and pubertal status.

3.7 Future Directions

Previous studies comparing ghrelin and leptin concentrations between children with ASD and TD children have focussed on how these altered levels may be an early onset phenotype for ASD (Ashwood et al., 2008; Raghavan et al., 2018). It has been suggested that these endocrine factors, along with neurotransmitters, may be facilitating the encoding of different social behaviors in the developing brain (Tareen & Kamboj, 2012). Therefore, understanding whether these endocrine factors have downstream effects on weight status is a critical avenue to continue exploring. Future studies that can also examine mealtime behaviors

longitudinally could inform the understanding around whether problematic feeding behaviors arise early in life and whether they track closely with weight trajectories. Problematic feeding behaviors may emerge as early as infancy in children with ASD, with Lucas and Cutler (2015) finding some mothers reporting dysregulated breastfeeding (vigorous sucking without stopping) among their infants, who were later diagnosed with ASD (Lucas & Cutler, 2015).

The current approaches for the treatment of childhood obesity generally involves a combination of non-pharmacological interventions (e.g., behavioral therapies, weight-reducing diets), pharmacological interventions, and surgical treatments (Han et al., 2010). Approaches are typically no different among children with intellectual disabilities, such as in some cases of ASD; however, there is a need for further research into how obesity treatment can be more specifically tailored for children with intellectual disabilities (Bennett et al., 2017). Although our hormonal findings are not clinically relevant to practice presently, further studies on any unique hormonal signatures in children with ASD may allow for novel avenues for treating unhealthy weight trajectories among this population. Research into physiological drivers of weight gain is particularly important, because evidence suggests that weight trajectories may be different among children with ASD, with obesity arising at an earlier age in ASD (Hill et al., 2015). This may suggest that obesity arises even before some lifestyle risk factors (e.g. decreased PA and increased SB) are associated with weight status. Therefore, clinical health surveillance of anthropometric parameters and monitoring of growth patterns may also serve as a useful method in preventing unhealthy weight gain and obesity.

3.8 Strengths and Limitations

The major strengths of our study included its collection of relevant clinical parameters such as pubertal status, ASD severity, and mealtime behaviors to assess many possible factors that may be contributing to weight status in children with ASD. In addition to this, the stratification based on weight status allowed for an assessment of hormonal level differences and mealtime behaviors differences between groups with ASD of varying weight status.

Limitations of our study include the limited sample size and the lack of a TD control group. A larger sample size would allow for sufficient power in detecting group differences in both clinical and hormonal parameters. Furthermore, the cross-sectional design only allowed for comparisons at one time point. Therefore, a longitudinal study would allow for an assessment of whether changes in hormone levels are associated with changes in weight gain over time. It could also further the understanding around whether these differences in hormone levels are causative of the weight gain or associative with the different weight status'. The

current design does not allow for causality between hormonal concentrations and other parameters to be established. Another limitation was the lack of a TD control group. Without the TD group, we cannot confirm whether previously reported findings of altered ghrelin and leptin levels in ASD are also true of our study. Furthermore, a TD control group would allow for a better understanding of how the present findings of increased leptin levels in the ASD+OWOB compared to the TD+OWOB group. This would further our understanding of possible leptin dysregulation in ASD. Despite these limitations, the present study's findings suggest that there are differences in leptin concentrations between NW and OWOB groups with ASD. Thus, further research into characterization of hormonal signatures between each weight status, may allow for a better understanding of how endocrine regulation may be impacting weight status among children with ASD. Furthermore, the finding of higher reported problematic feeders in the ASD+OWOB group is another important finding because this could allow for mealtime behaviors to be monitored more closely in this group.

3.9 Conclusion

The major findings of this research were that there are significantly elevated levels of leptin in the ASD+OWOB group compared to the ASD+NW group. We also found that BAMBI scores were significantly higher in the OWOB group and there was a correlation between BMI Z-scores and BAMBI scores. The ASD+OWOB group scored higher in eating more 'Limited Varieties' of foods and displaying 'Features of ASD'. Overall, these findings are informative to our current understanding of leptin in ASD. There is a need to track leptin levels longitudinally in children with ASD in order to examine if it is indeed an early-onset phenotype for ASD development and also for the possible role it may have in weight status among children with ASD. In addition, it is essential to evaluate problematic mealtime behaviors in children with ASD due to its associations with BMI Z-scores. Further research into hormonal level differences and mealtime behaviors may further develop the understanding around what health care providers, parents, and individuals with ASD may be able to do to prevent or treat unhealthy weight gain.

3.10 Tables

Table 3.1. Baseline characteristics of children with Autism Spectrum Disorder (ASD) Stratified into Normal Weight and Overweight and Obese Weight Status

Characteristic	**N**	**ASD Normal Weight**	**ASD Overweight-Obese**	***P* Value**	***d***
Age, y	15, 6	9.47 (10.0) ± 2.07 (8.0-11.0)	10.67 (11.5) ± 1.97 (9.25-12.0)	0.15	0.33
N of Females/males		3/12	1/5	0.87	
BMI z-score	**15, 6**	**-0.14 (-0.43-0.33)**	**1.45 (1.02-2.22)**	**<0.005**	**0.76**
Tanner Stage	**15, 6**	**1.5 (1.00-1.86)**	**3.0 (3.00-4.00)**	**0.036**	**0.47**
C-PAQ	15, 6				
Sports (hrs)		3.50 (1.50-7.00)	2.38 (0.00-3.25)	0.095	0.37
Leisure (hrs)		5.40 (3.75-15.75)	2.38 (1.06-5.93)	0.066	0.41
School (hrs)		1.67 (1.00-2.50)	1.25 (0.75-3.13)	0.79	0.060
Other (hrs)		37.5 (33.77-61.00)	51.1 (27.65-70.13)	0.79	0.068
ASA24 Total Calories/Day	3, 3	1360.36	2259.97	0.28	0.45
Carbohydrates (g)	3,3	175.30	316.96	0.13	0.62

Protein (g)	3,3	83.83	65.13	0.51	0.27
Total fat (g)	3,3	54.47	67.92	0.83	0.09
Total sugar (g)	**3,3**	**80.33**	**127.71**	**0.050**	**0.80**
SRS-2 (T-score)	14, 4	76.67 (78.00) ± 11.81 (76.00-85.00)	82.33 (83.5) ± 6.59 (79.00-86.75)	0.21	0.28

Data reported as Median (IQR) and Mean (Median) ± SD (IQR) for the SRS-2 T-scores; Two-sample Wilcoxon Rank-Sum test Sum (Mann-Whitney) used. p values for statistically significant differences are shown in bold.

Table 3.2. Hormonal Levels of children with Autism Spectrum Disorder (ASD) Stratified into Normal Weight and Overweight and Obese Weight Status

Characteristic	**N**	**ASD Normal Weight Median (IQR)**	**Mean ±SD**	**ASD Overweight-Obese Median (IQR)**	**Mean ±SD**	***p* value**	***d***
Leptin pg/mL	**12, 6**	**9863.42 (6818.30-11604.88)**	**9354.88 ± 3965.75**	**15945.27 (10669.35-22373.33)**	**16143.81 ± 6597.16**	**0.018**	**0.51**
Ghrelin, pg/mL	12, 6	1487.98 (1126.99-1683.84)	1487.98 ± 443.83	1048.13 (627.57-1857.05)	1223.81 ± 655.11	0.30	0.24
GLP-1, pg/mL	12, 6	58.65 (53.80-61.37)	58.65 ± 8.12	57.66 (52.17-77.60)	57.32 ± 6.96	0.42	0.19
PYY, pg/mL	12, 6	233.88 (219.411-265.05)	248.04 ± 48.27	233.86 (192.62-308.84)	247.49 ± 63.79	0.85	0.05
Insulin, μIU/mL (n=12,6)	12, 6	63.08 (50.75-70.74)	63.08 ± 15.41	89.15 (56.90-107.30)	85.79 ± 25.89	0.080	0.39

Data reported as Median (IQR) and Mean ± SD; Two-sample Wilcoxon Rank-Sum test Sum (Mann-Whitney) used. p values for statistically significant differences are shown in bold.

Table 3.3. BAMBI scores of children with Autism Spectrum Disorder (ASD) Stratified into Normal Weight and Overweight and Obese Weight Status

Characteristic	**N**	**ASD Normal Weight Median (IQR)**	**Mean ± SD**	**ASD Overweight-Obese**	**Mean ± SD**	***P* Value**	***d***
BAMBI Score	**15, 6**	**39.00 (30.00-48.00)**	**38.53 ± 10.85**	**49.50 (41.75-56.75)**	**48.83 ± 6.27**	**0.045**	**0.44**
Limited Variety		**20.00 (14.00-25.00)**	**20.07 ± 7.35**	**30.00 (26.75-32.25)**	**29.00 ± 4.69**	**0.014**	**0.57**
Food Refusal		9.00 (6.00-11.00)	9.20 ± 3.23	5.50 (5.00-9.50)	7.17 ± 3.54	0.11	0.35
Features of ASD		**9.00 (6.00-11.00)**	**8.33 ± 2.69**	**13.00 (10.75-14.75)**	**12.67 ± 3.27**	**0.006**	**0.57**

Data reported as Median (IQR) and Mean ± SD; Two-sample Wilcoxon Rank-Sum test Sum (Mann-Whitney) used. p values for statistically significant differences are shown in bold.

Table 3.4. Spearman correlations of leptin concentration to other clinical and metabolic parameters in children with ASD and non-parametric partial correlation of leptin concentrations, controlling for age, sex, and pubertal status.

Parameters	***r***	***p***	***Adjusted r***	***Adjusted p***
Age	**0.62**	**0.003**		
Pubertal status	**0.48**	**0.028**		
BMI z-score	0.41	0.063	**0.73**	**0.001**
SRS-2	0.18	0.43	0.093	0.72
Insulin, µIU/mL	**0.45**	**0.041**	-0.083	0.74
Ghrelin, pg/mL	**-0.52**	**0.016**	0.20	0.42
PYY, pg/mL	-0.15	0.51	-0.15	0.54
GLP-1, pg/mL	-0.045	0.85	-0.16	0.53

ASD: Autism Spectrum Disorder; BMI Z-score: body mass index Z-score; SRS-2: Social Responsiveness Scale 2; PYY: Peptide YY; GLP-1: Glucagon-like peptide 1. p values for statistically significant differences are shown in bold.

Table 3.5. Spearman correlations of ghrelin concentrations to other clinical and metabolic parameters and non-parametric partial correlation of ghrelin concentrations, controlling for age, sex, and pubertal status**.**

Parameters	**r**	***p***	***Adjusted r***	***Adjusted p***
Age	**-0.78**	**P<0.0005**		
Pubertal status	**-0.54**	**0.011**		
BMI Z-score	0.058	0.803	0.077	0.76
SRS-2	-0.13	0.58	0.061	0.81
Insulin, µIU/mL	**-0.65**	**0.01**	-0.26	0.30
Leptin, pg/mL	**-0.52**	**0.02**	0.20	0.42
PYY, pg/mL	-0.04	0.85	-0.033	0.90
GLP-1, pg/mL	-0.012	0.96	0.11	0.66

ASD: Autism Spectrum Disorder; BMI Z-score: body mass index Z-score; SRS-2: Social Responsiveness Scale 2; PYY: Peptide YY; GLP-1: Glucagon-like peptide 1. p values for statistically significant differences are shown in bold.

Table 3.6. Spearman's correlations of BAMBI scores to other clinical and metabolic parameters in children with ASD

Parameters	**r**	***p***
Age	-0.033	0.887
BMI z-score	**0.44**	**0.044**
Pubertal status	0.21	0.369
SRS-2	0.318	0.160
Leptin, **pg**/mL	0.177	0.442
Ghrelin, pg/mL	-0.070	0.764

ASD: Autism Spectrum Disorder; BMI Z-score: body mass index Z-score; SRS-2: Social Responsiveness Scale 2; PYY: Peptide YY; GLP-1: Glucagon-like peptide 1. p values for statistically significant differences are shown in bold.

Table 3.7. Leptin levels as a Moderator on the Relationship of BAMBI scores and BMI Z-scores. Controlling for age, sex, and pubertal status.

	BAMBI Scores			
Predictors	β	SE_{BS}	t	p
Leptin	**.0022**	**.00080**	**2.93**	**.011**
BMI Z score	-2.89	2.63	-1.089	.29
Interaction	-.00060	.00040	-1.32	.21
Age	**-6.79**	**1.60**	**-4.23**	**.00080**
Pubertal status	**7.70**	**2.53**	**3.044**	**.0088**
Sex	-15.11	7.65	-1.98	.068

ASD: Autism Spectrum Disorder; BMI Z-score: body mass index Z-score; BAMBI: Brief Autism Mealtime Behavior Inventory. p values for statistically significant differences are shown in bold.

Table 3.8. Ghrelin levels as a Moderator on the Relationship of BAMBI scores and BMI Z-scores. Controlling for age, sex, and pubertal status.

	BAMBI scores			
Predictors	β	SE_{BS}	t	p
Ghrelin	-0.0056	0.0068	-0.82	0.43
BMI Z score	2.83	2.35	1.20	0.25
Interaction	-0.0025	0.0037	-0.68	0.51
Age	**-4.99**	**1.97**	**-2.53**	**0.024**
Pubertal status	6.27	2.99	2.10	0.054
Sex	1.0097	5.94	0.17	0.87

ASD: Autism Spectrum Disorder; BMI Z-score: body mass index Z-score; BAMBI: Brief Autism Mealtime Behavior Inventory. p values for statistically significant differences are shown in bold.

Chapter 4 Discussion and Conclusions

4.1 Introduction

The higher rates of overweight and obesity in children with ASD is due to several factors, and the specific combination of factors also varies from child to child. Some of the reviewed contributors to unhealthy weight gain included selective eating behaviors, lack of opportunity for physical activity, genetics, and secondary comorbidities (such as GI disturbances like chronic constipation and diarrhea), among other factors (Dhaliwal et al., 2019). In study 2, we aimed to further investigate two of these specific factors: hormonal level differences and selective eating behaviors, to understand whether there may be any differences among children of NW and OWOB weight status. Our first objective was to explore how hormones involved in the regulation of appetite and energy balance (leptin, ghrelin, GLP-1, PYY, insulin) may differ based on weight status among children with ASD. Our second objective was to explore whether mealtime behaviors (measured by the BAMBI), would also vary based on weight status. For objective one, we hypothesized that there would be a significant difference between both groups, with the group with ASD+OWOB group having lower ghrelin and higher leptin concentrations and increased insulin resistance relative to the ASD+NW group. For objective two, we hypothesized that we would find significant differences in BAMBI scores, with the OWOB group scoring significantly higher (e.g., more atypical eating behaviours) than the ASD+NW group. We also hypothesized that ghrelin and leptin levels would have a moderating effect on BAMBI scores and BMI Z-score.

4.2 Risk Factors for Obesity and Overweight in ASD

Possible factors driving weight gain in children with ASD were explored in Chapter 2. Generally, body weight is influenced by many factors ranging from environmental (e.g., nutrition), behavioral (e.g., physical activity and sedentary behaviors), and biological (e.g., genetics and hormonal regulation) factors. Studies have shown that many risk factors could be heightening the risk for overweight and obesity among children with ASD. For example, oral sensitivities may mediate food selectivity influencing food and nutrient intake among children with ASD (Beighley et al., 2013; Cermak et al., 2010). There are also factors such as decreased physical activity and increased sedentary behaviors, which could further promote an imbalance in energy intake and expenditure (L. G. Bandini et al., 2013; Healy et al., 2017). Furthermore, genetics, and medication usage (such as antipsychotics) may also influence BMI (Cortes & Wevrick, 2018; S. Y. Park et al., 2016; Shinawi et al., 2011). Ultimately these factors may have a compounded effect on increasing the risk for unhealthy weight gain in ASD.

We also explored more novel avenues that may have some role in the higher rates of overweight and obesity among children with ASD. These 'emerging' factors included: sleep problems (Maxwell-Horn & Malow, 2017), the gut microbiome (Strati et al., 2017), and hormonal dysregulation (Ashwood et al., 2008; Hasan et al., 2019). Overall, understanding all of these possible contributors allows for progress towards identifying and then effectively managing unhealthy weight gain among individual children. Monitoring for risk factors could also facilitate the development of potential intervention strategies.

4.3 Appetite-Regulating Hormones in ASD

Findings from Chapter 3 add to our current knowledge around how fasting levels of leptin and mealtime behaviors vary between children of different weight status' with ASD. Previous research has focused on examining leptin with regards to the role it may play in ASD pathogenesis. For example, increased leptin levels have been considered as a possible early-onset phenotype, due to findings of higher levels among children diagnosed with ASD (Raghavan et al., 2018, Ashwood et al., 2008). Our research study focused on understanding whether there are any differences in hormonal levels between children with ASD of varying weight status. Currently, after comparing hormonal levels based on weight stratification, we found significantly elevated concentrations of leptin and trends towards elevated concentrations of insulin. These findings suggest that leptin levels might be elevated in ASD,

regardless of weight status, although we know that obesity can also contribute to increasing these levels.

Although the exact mechanism through which leptin may be associated with ASD risk is not fully understood, leptin has an important role in immune system regulation, specifically in neurodevelopment (e.g., neurogenesis and synaptogenesis) (Garza et al., 2008). In addition, the alteration of leptin levels (e.g., from ingestion of the mother's milk) in early life can also impact hypothalamic development and feeding circuits (Bouret, 2010). Furthermore, maternal obesity, which was highlighted as a possible risk factor for ASD in chapter 2, may also result in impaired leptin signaling, with findings of elevated leptin levels in offspring (Kirk et al., 2009).

In children with ASD, Ashwood et al., (2008) also found that when they stratified children into regressive (when a child appears to be developing typically but then loses acquired skills in area such as language and motor development) and early onset ASD, those with early onset ASD had significantly higher plasma leptin levels compared to children with regressive ASD ($p < .042$) (Ashwood et al., 2008; Mughal et al., 2020). Ashwood et al. (2008) discussed that these altered leptin levels might be influencing its role in the neuropathology of ASD by crossing the blood-brain barrier and promoting inflammation in certain brain areas (Ashwood et al., 2008; Banks, 2001; Matarese et al., 2005). Therefore, future research that can examine the role of leptin signaling in ASD and whether this early-onset form of ASD is also associated with higher rates/higher severity of OWOB in this group, would contribute to the understanding of the implications of elevated leptin levels in ASD.

Ghrelin has been found to have a neuroprotective role in conditions such as Alzheimer's and Parkinson's disease (Santos et al., 2013). Ghrelin's neuroprotective effect is related to its role as a metabolic signal in targeting AMPK in dopamine neurons (Bayliss et al., 2016). To understand ghrelin's role in ASD, Yamashita et al. (2019) collected lymphoblastoid cell lines from children with ASD and TD children. These were cultured with either Phosphate-buffered Saline (PBS) or human ghrelin. The study found elevated concentrations of specific inflammation-related genes (e.g., Tumor Necrosis Factor, TNF-α) in the group with ASD and also found that ghrelin was able to reduce expression levels of certain inflammatory markers (e.g., TNF-α), suggesting it may serve as a potential therapeutic anti-inflammatory agent (Yamashita et al., 2019). Inflammation and neuroimmune dysregulation has been heavily reported in ASD (Siniscalco, Schultz, et al., 2018; Tonhajzerova et al., 2015; Tsilioni et al., 2019). Studies have also suggested that suppressed ghrelin signalling may be associated with gastrointestinal disorders such as irritable bowel syndrome and chronic gastritis (Cheung &

Wu, 2013; Koutouratsas et al., 2019), which are commonly reported among children with ASD (McElhanon et al., 2014). Therefore, future studies should examine the role of ghrelin in ASD pathogenesis as well as how any dysfunction in signalling may be impacting gastrointestinal symptoms in this group. This may allow for a better understanding of ghrelin's role in influencing appetite, energy intake, and weight status in ASD.

Although previous studies have not compared insulin levels between children with ASD and TD populations, insulin is another hormone that may be implicated in the pathogenesis of ASD diagnosis and excessive weight gain. Maternal obesity and gestational diabetes were discussed in chapter 2 as potential risk factors for ASD. Xiang et al. (2015) found that maternal type 1 diabetes increased the risk for ASD in children (Xiang et al., 2015). They suggested that mechanisms such as hypoxia in the fetus and oxidative stress were some possible pathways that increased risk of ASD in offspring (Xiang et al., 2015). Obesity can also result in impaired insulin signalling, such as through insulin resistance (B. B. Kahn & Flier, 2000; S. E. Kahn et al., 2006). Therefore, future studies that can compare insulin levels between groups with ASD and TD groups would allow for further understanding of whether insulin could be another unique factor increasing the risk for obesity in ASD.

Ultimately, further studies need to be completed to examine whether these hormones discussed above, may be additional possible direct drivers of this obesity and overweight we see in children with ASD or instead if they are consequences of this unhealthy weight status. This research would then allow for further clarification around whether these hormonal levels need to be monitored (including at what stage of development) as possible factors influencing physical growth and development.

4.4 Feeding Behaviors in ASD

Atypical feeding behaviors have been reported in ASD. These behaviors can range from specific food preferences (e.g., inclusion and exclusion of particular textures of foods) to being inflexible with mealtime routines (e.g., seating arrangements) (Lukens & Linscheid, 2008; Martins et al., 2008). Some of the possible factors contributing to these feeding behaviors include sensory sensitivities and processing impairments, which may lead to food selectivity and refusal (Cermak et al., 2010). There is a lot of research around many specific mealtime behaviors in children with ASD (e.g., flexibility with mealtime routines, preferring a specific texture of food, etc.).

In our study, we found that BAMBI scores were significantly higher in the ASD+OWOB group compared to the ASD+NW group. When looking at individual BAMBI

factors, it was found that the OWOB group scored higher on eating more 'Limited Varieties' of foods and showing more 'Features of ASD'. Further analyses also showed that BAMBI scores were positively correlated with BMI Z-scores. In their study, Kamal Nor et al. (2019) reported lower 'Food Refusal' scores in their childhood overweight/obese population, and lower scores were also correlated with higher weight in children with ASD (Kamal Nor et al., 2019). Similar to this study, we found higher median scores of limited food variety and higher median scores of 'Features of ASD', in the OWOB group. These results also further emphasize previous findings of children with more severe symptoms of ASD being 1.7 times more likely to be of overweight or obese weight status (Levy et al., 2019). The researchers suggested that co-occurring behavioral challenges, in the more severe cases of ASD, may be further perpetuating some of the currently known factors influencing weight status among this population (Levy et al., 2019).

Interventions for feeding challenges among children with ASD warrants a multidisciplinary approach; this could involve physicians, dieticians, occupational therapists, behavioral psychologists, speech-language pathologists (SLP), etc. Primary care physicians can determine the role of GI disorders (such as acid reflux and constipation), allergies, and other secondary comorbidities that may be influencing feeding behaviors (Child Mind Institude, 2020). Dieticians can assess food and dietary intake in children (such as monitoring for any nutrient deficiencies) (Autism Ontario, 2012). They are also able to help individuals and families plan meals, find alternative sources of nutrition, and identify problematic (e.g., picky eating) behaviors (Autism Ontario, 2012). Furthermore, occupational therapists can assess sensory integration challenges, evaluate oral processing, and provide interventions such as activities involving deep touch pressure to improve eating (Cermak et al., 2010). Behavioral psychologists can also develop strategies such as systematic desensitization and operant conditioning to increase the acceptance of foods (Chawner et al., 2019). Finally, and also importantly, SLPs may be able to evaluate any feeding and swallowing challenges and develop strategies to combat feeding problems (e.g., helping strengthen oral muscles) (American Speech Language Hearing Association, 2020). These strategies highlight the need for a standardized definition of problematic eating behaviors that can capture the many challenges children with ASD face when it comes to feeding. These roles also offer insight into the importance of multidisciplinary teams when considering prevention and intervention strategies related to feeding behaviors in children with ASD.

4.5 Limitations and Challenges

This research is novel in exploring fasting concentrations of specific appetite-regulating hormones in order to understand any possible differences between OWOB and NW groups. Some of the limitations include firstly that findings presented in Chapter 3 are from a cross-sectional study and thus causation cannot be determined. Therefore, to understand the role of these hormones as either contributing to weight status, or just being associated with weight status, longitudinal studies that collect measures around various biochemical markers in both TD children and children with ASD would need to be completed.

Secondly, present findings only considered baseline fasting hormones levels, therefore, we did not explore possible differences pre- and post-prandially. Examining whether there is a difference in how these specific hormones may be impacted by nutrient intake could develop our understanding around their role in appetite regulation and metabolism.

Another limitation of our current study was the lack of a TD control group. A TD control group would have allowed for a more robust interpretation of hormonal levels differences in findings between the various weight groups. A TD control group would also allow us to confirm previous research findings of differences in leptin levels in children with ASD compared to TD children. This limitation was associated with challenges faced in the recruitment of a TD group. There may have been less motivation to participate in a study as a control group, and our recruitment rate ultimately did not allow us to include such a group at this time.

Our current study used the ASA-24, an online tool for recording food and drinks consumed over a specific period. However, this is another limitation because participants and parents/primary caregivers completed these after the study visits, and thus, fewer records were completed in relation to the questionnaires that were administered at the time of the study visit. Also, the ASA-24 has not been validated among children. Therefore, before further interpretations around these dietary findings can be made and generalized, more data on the relationship between diet (e.g., through collection of a food frequency questionnaire) and BAMBI scores would need to be collected (Olukotun & Seal, 2015). Parents described challenges with logging into the system, not being able to find all the specific foods and drinks in the database, and the burden associated with the amount of time required to complete each record.

A challenge of our current study was the relatively small sample size, thus limiting our statistical power. A larger sample size would allow for a better understanding of group

differences. There were recruitment challenges due to parental concerns about the blood draw, as some children with ASD can have specific sensitivities and anxieties around blood draws. Some approaches taken to overcome this challenge included providing a social story to prepare children before the study visit, numbing cream, and distraction tools such as an iPad.

4.6 Gaps in knowledge and Future Directions

Gaps in current knowledge include understanding whether these hormonal concentrations are causative or associative of weight status in ASD. Furthermore, while there is a comprehensive understanding of behavioral and lifestyle contributors to elevated weight status in children with ASD, the role of physiological drivers (e.g., hormonal levels, gut microbiota, maternal metabolic disorders, etc.) continues to be elusive. Future studies should consider assessing hormonal regulation of satiety both pre and post-prandially, across various weight groups to understand any fluctuations of hormonal control and how these signals modulate appetite in ASD and how this could be impacting weight status. Greater insight into hormonal differences at baseline between children with ASD and TD groups may allow for the development of intervention strategies and identify children on unhealthy weight trajectories.

Another gap in knowledge is that there is no standard definition of problematic eating behaviors in ASD. Bandini et al. (2010) defined it as a combination of food refusal and limited food repertoire (Bandini et al., 2010), however the definition varies across studies. Therefore, a standardized definition, along with specific criteria around what would be considered problematic eating, would be beneficial in capturing these behaviors among children with ASD. Future research should also consider how food selectivity can differ for individual children with ASD, and if this may be influenced by factors such as ASD severity, physiological factors (e.g., appetite-regulating hormones), and gastrointestinal symptoms. Research that can further integrate biochemical data (e.g., hormonal levels) and feeding behaviors could establish whether future research should consider hormonal factors or whether there is no specific difference that would warrant further investigation.

Furthermore, anecdotal reports suggest that there may be food-*seeking* behaviors in ASD (e.g., stealing food, thinking about food), which may result in increased energy intake. However, there is a gap in current knowledge around these specific behaviors in ASD. Past research, specifically assessing food-seeking behaviors in children with PWS has led to the development of a hyperphagia questionnaire for this population (Dykens et al., 2007); however, this has not been validated in children with ASD. Although current research seems to suggest there is no difference in overall energy intake between children with ASD and TD children, the

specific source of the calories and the range and variety within diets need to be investigated further with respect to food-seeking behaviors.

Overall, future studies that consider possible factors contributing to weight status among children with ASD should collect comprehensive data on feeding behaviors, diet, physical activity via questionnaires and direct measurements (e.g., accelerometers), information on secondary comorbidities and medication usage, sleeping behaviors, and maternal history related to maternal metabolic disorders and breastfeeding. This comprehensive collection of data would help understand how these factors together might influence overall weight status in ASD.

4.7 Clinical Relevance of Findings

Findings from this thesis that are the most clinically relevant for the management of obesity and unhealthy weight gain in ASD include: 1) the summary of risk factors presented in chapter 2 and 2) findings of higher reported rates of problematic feeding in the ASD+OWOB group in chapter 3. The review of risk factors can serve as an important tool that individuals with ASD, families, and health care providers can use to understand what factors may be contributing to individual risk. It can promote dialogue between health care providers and families around evaluating possible risk factors for unhealthy weight, which could result in strategies to combat the risk where needed. Furthermore, the findings of higher BAMBI scores in the ASD+OWOB group can also help families identify specific eating behaviors (e.g., eating limited varieties of foods) that need to be monitored more closely, due to the risk they may pose for unhealthy weight status.

By having an understanding of the risk factors, health care providers and families can engage in informed discussions around possible drivers of weight gain, specific to each child. This allows for shared decision making around developing intervention strategies. The literature review findings also serve as a tool through which health care providers may be able to further monitor specific behavioral and lifestyle factors through a screening, brief intervention, and referral to treatment (SBIR) approach (Agerwala & McCance-Katz, 2012). SBIR approaches could involve interactive clinical skills development for physicians and discussion around risk factors with families, even before the presentation of overweight or obesity (Agerwala & McCance-Katz, 2012). Furthermore, SBIR approaches may also allow primary care pediatricians to feel more adequately trained for managing obesity in children with ASD (Walls et al., 2018).

Current Canadian guidelines for growth monitoring among pediatric populations recommend measurements (e.g., height, weight, etc.) at all primary care visits (Canadian Task Force on Preventive Health Care, 2015). In addition to this, the American Academy of Pediatrics (2015) also recommends that pediatricians utilize a life course approach to identify children who may be at risk for obesity development (Daniels et al., 2015). Therefore, these recommendations highlight the need for extra vigilance when assessing growth among children with ASD, due to the elevated risks. Routine checkups in pediatric populations vary with age and are recommended by the child's doctor (My Health Alberta & Healthwise Staff 2018). Specifically, from birth to 3 years old visits are much more frequent (e.g., 3 to 5 days old, 1 month, 2 months, etc.) and then after 3 years old visits are typically scheduled annually (My Health Alberta & Healthwise Staff 2018). More frequent checkups such as twice annually after the age of 3 years, may be warranted in children diagnosed with ASD, however, because the age of ASD diagnosis can vary (with a diagnosis as early as 2 years old although more commonly diagnosed around the age of 4 to 5 years old) checkup schedules may vary and be adjusted accordingly (Zwaigenbaum et al., 2019). Clinical surveillance of weight trajectories in ASD may help prevent unhealthy weight gain and obesity. Furthermore, parents also play an essential role in monitoring for problematic mealtime behaviors and growth in children. Therefore, if parents have particular concerns, they should be followed up by health care providers to examine any specific risks and discuss follow-up strategies.

4.8 Conclusion

The major findings of this research were that multiple risk factors, and likely some combination of each, are resulting in higher reported rates of overweight and obesity in children with ASD. Risk factors, including emerging factors, could broadly be described in three categories: biological (e.g., genetics), developmental (e.g., maternal metabolic disorders), and environmental (e.g., physical activity). From the original study, we found significantly elevated levels of leptin in the group with OWOB compared to the NW group. Leptin levels also correlated with BMI Z-scores, after controlling for age, sex, and pubertal status. We also found some trends towards elevated insulin concentrations in our group with OWOB. From our second objective, we found that BAMBI scores were significantly higher in the OWOB group and were positively correlated with BMI Z-scores. Specifically, the ASD+OWOB weight status scored significantly higher on eating more limited varieties of foods and showing more 'Features of ASD'. Overall, considering this current study, along with previous research, there is a need for future work that can provide further insight into ways we can better assess for,

prevent, and treat overweight and obesity in children with ASD. Some of the unique risk factors and challenges children with ASD may face (e.g. oral sensitivities) highlight the need for more tailored approaches so that we are able to prevent the burden of unhealthy weight status and its secondary impacts in this population.

Bibliography

Achari, A. E., & Jain, S. K. (2017). Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *International Journal of Molecular Sciences*, *18*(6). https://doi.org/10.3390/ijms18061321

Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal flora and gastrointestinal status in children with autism—Comparisons to typical children and correlation with autism severity. *BMC Gastroenterology*, *11*, 22. https://doi.org/10.1186/1471-230X-11-22

Adams, S. H., Lei, C., Jodka, C. M., Nikoulina, S. E., Hoyt, J. A., Gedulin, B., Mack, C. M., & Kendall, E. S. (2006). PYY [3-36] Administration Decreases the Respiratory Quotient and Reduces Adiposity in Diet-Induced Obese Mice. *The Journal of Nutrition*, *136*(1), 195–201. https://doi.org/10.1093/jn/136.1.195

Agerwala, S. M., & McCance-Katz, E. F. (2012). Integrating Screening, Brief Intervention, and Referral to Treatment (SBIRT) into Clinical Practice Settings: A Brief Review. *Journal of Psychoactive Drugs*, *44*(4), 307–317.

Ahima, R. S. (2008). Revisiting leptin's role in obesity and weight loss. *The Journal of Clinical Investigation*, *118*(7), 2380–2383. https://doi.org/10.1172/JCI36284

Al Maskari, M. Y., & Alnaqdy, A. A. (2006). Correlation between Serum Leptin Levels, Body Mass Index and Obesity in Omanis. *Sultan Qaboos University Medical Journal*, *6*(2), 27–31.

Al-Farsi, Y. M., Al-Sharbati, M. M., Waly, M. I., Al-Farsi, O. A., Al-Shafaee, M. A., Al-Khaduri, M. M., Trivedi, M. S., & Deth, R. C. (2012). Effect of suboptimal breast-feeding on occurrence of autism: A case-control study. *Nutrition (Burbank, Los Angeles County, Calif.)*, *28*(7–8), e27-32. https://doi.org/10.1016/j.nut.2012.01.007

Al-Zaid, F. S., Alhader, A. A., & Al-Ayadhi, L. Y. (2014). Altered ghrelin levels in boys with autism: A novel finding associated with hormonal dysregulation. *Scientific Reports*, *4*, 6478. https://doi.org/10.1038/srep06478

American Psychiatric Association (APA). 2013. Diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) Washington, DC: American Psychiatric Association.

Anagnostou, E., Zwaigenbaum, L., Szatmari, P., Fombonne, E., Fernandez, B. A., Woodbury-Smith, M., Brian, J., Bryson, S., Smith, I. M., Drmic, I., Buchanan, J. A., Roberts, W., & Scherer, S. W. (2014). Autism spectrum disorder: Advances in evidence-based practice. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *186*(7), 509–519. https://doi.org/10.1503/cmaj.121756

Andari, E., Duhamel, J.-R., Zalla, T., Herbrecht, E., Leboyer, M., & Sirigu, A. (2010). Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(9), 4389–4394. https://doi.org/10.1073/pnas.0910249107

Antunes, H., Santos, C., & Carvalho, S. (2009). Serum leptin levels in overweight children and adolescents. *The British Journal of Nutrition*, *101*(8), 1262–1266. https://doi.org/10.1017/S0007114508055682

Arita, Y., Kihara, S., Ouchi, N., Takahashi, M., Maeda, K., Miyagawa, J., Hotta, K., Shimomura, I., Nakamura, T., Miyaoka, K., Kuriyama, H., Nishida, M., Yamashita, S.,

Okubo, K., Matsubara, K., Muraguchi, M., Ohmoto, Y., Funahashi, T., & Matsuzawa, Y. (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and Biophysical Research Communications*, *257*(1), 79–83.

Ash, T., Agaronov, A., Young, T., Aftosmes-Tobio, A., & Davison, K. K. (2017). Family-based childhood obesity prevention interventions: A systematic review and quantitative content analysis. *The International Journal of Behavioral Nutrition and Physical Activity*, *14*. https://doi.org/10.1186/s12966-017-0571-2

Ashwood, P., Kwong, C., Hansen, R., Hertz-Picciotto, I., Croen, L., Krakowiak, P., Walker, W., Pessah, I. N., & Van de Water, J. (2008). Brief report: Plasma leptin levels are elevated in autism: association with early onset phenotype? *Journal of Autism and Developmental Disorders*, *38*(1), 169–175. https://doi.org/10.1007/s10803-006-0353-1

Askari, S., Anaby, D., Bergthorson, M., Majnemer, A., Elsabbagh, M., & Zwaigenbaum, L. (2015). Participation of Children and Youth with Autism Spectrum Disorder: A Scoping Review. *Review Journal of Autism and Developmental Disorders*, *2*(1), 103–114. https://doi.org/10.1007/s40489-014-0040-7

Austin, J., & Marks, D. (2009). Hormonal Regulators of Appetite. *International Journal of Pediatric Endocrinology*, *2009*. https://doi.org/10.1155/2009/141753

Autism Ontario. (2012). Dieticians. *Autism Ontario Knowledge Base.* Retrieved May 8, 2020, from https://autismontario.novosolutions.net/default.asp?id=270

Bachmann-Gagescu, R., Mefford, H. C., Cowan, C., Glew, G. M., Hing, A. V., Wallace, S., Bader, P. I., Hamati, A., Reitnauer, P. J., Smith, R., Stockton, D. W., Muhle, H., Helbig, I., Eichler, E. E., Ballif, B. C., Rosenfeld, J., & Tsuchiya, K. D. (2010). Recurrent 200-kb deletions of 16p11.2 that include the SH2B1 gene are associated with developmental delay and obesity. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, *12*(10), 641–647. https://doi.org/10.1097/GIM.0b013e3181ef4286

Bäckhed, F., Roswall, J., Peng, Y., Feng, Q., Jia, H., Kovatcheva-Datchary, P., Li, Y., Xia, Y., Xie, H., Zhong, H., Khan, M. T., Zhang, J., Li, J., Xiao, L., Al-Aama, J., Zhang, D., Lee, Y. S., Kotowska, D., Colding, C., … Jun, W. (2015). Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host & Microbe*, *17*(5), 690–703. https://doi.org/10.1016/j.chom.2015.04.004

Bahrami, E., Mirmoghtadaee, P., Ardalan, G., Zarkesh-Esfahani, H., Tajaddini, M. H., Haghjooy-Javanmard, S., Najafi, H., & Kelishadi, R. (2014). Insulin and leptin levels in overweight and normal-weight Iranian adolescents: The CASPIAN-III study. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*, *19*(5), 387–390.

Bak, M., Fransen, A., Janssen, J., van Os, J., & Drukker, M. (2014). Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. *PLoS ONE*, *9*(4). https://doi.org/10.1371/journal.pone.0094112

Bandini, L., Curtin, C., Phillips, S., Anderson, S. E., Maslin, M., & Must, A. (2017). Changes in food selectivity in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *47*(2), 439–446. https://doi.org/10.1007/s10803-016-2963-6

Bandini, L. G., Anderson, S. E., Curtin, C., Cermak, S., Evans, E. W., Scampini, R., Maslin, M., & Must, A. (2010). Food selectivity in children with autism spectrum disorders and typically developing children. *The Journal of Pediatrics*, *157*(2), 259–264. https://doi.org/10.1016/j.jpeds.2010.02.013

Bandini, L. G., Gleason, J., Curtin, C., Lividini, K., Anderson, S. E., Cermak, S. A., Maslin, M., & Must, A. (2013). Comparison of physical activity between children with autism spectrum disorders and typically developing children. *Autism: The International Journal of Research and Practice*, *17*(1), 44–54. https://doi.org/10.1177/1362361312437416

Banks, W. A. (2001). Leptin transport across the blood-brain barrier: Implications for the cause and treatment of obesity. *Current Pharmaceutical Design*, *7*(2), 125–133. https://doi.org/10.2174/1381612013398310

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, *51*(6), 1173–1182. https://doi.org/10.1037//0022-3514.51.6.1173

Baron-Cohen, S., Jaffa, T., Davies, S., Auyeung, B., Allison, C., & Wheelwright, S. (2013). Do girls with anorexia nervosa have elevated autistic traits? *Molecular Autism*, *4*(1), 24. https://doi.org/10.1186/2040-2392-4-24

Batterham, R. L., Cohen, M. A., Ellis, S. M., Le Roux, C. W., Withers, D. J., Frost, G. S., Ghatei, M. A., & Bloom, S. R. (2003). Inhibition of Food Intake in Obese Subjects by Peptide YY $_{3–36}$. *New England Journal of Medicine*, *349*(10), 941–948. https://doi.org/10.1056/NEJMoa030204

Bayliss, J. A., Lemus, M. B., Stark, R., Santos, V. V., Thompson, A., Rees, D. J., Galic, S., Elsworth, J. D., Kemp, B. E., Davies, J. S., & Andrews, Z. B. (2016). Ghrelin-AMPK Signaling Mediates the Neuroprotective Effects of Calorie Restriction in Parkinson's Disease. *Journal of Neuroscience*, *36*(10), 3049–3063. https://doi.org/10.1523/JNEUROSCI.4373-15.2016

Beccuti, G., & Pannain, S. (2011). Sleep and obesity. *Current Opinion in Clinical Nutrition and Metabolic Care*, *14*(4), 402–412. https://doi.org/10.1097/MCO.0b013e3283479109

Becerra, T. A., von Ehrenstein, O. S., Heck, J. E., Olsen, J., Arah, O. A., Jeste, S. S., Rodriguez, M., & Ritz, B. (2014). Autism Spectrum Disorders and Race, Ethnicity, and Nativity: A Population-Based Study. *Pediatrics*, *134*(1), e63–e71. https://doi.org/10.1542/peds.2013-3928

Beighley, J. S., Matson, J. L., Rieske, R. D., & Adams, H. L. (2013). Food selectivity in children with and without an autism spectrum disorder: Investigation of diagnosis and age. *Research in Developmental Disabilities*, *34*(10), 3497–3503. https://doi.org/10.1016/j.ridd.2013.07.026

Bennett, E. A., Kolko, R., Chia, L., Elliott, J. P., & Kalarchian, M. A. (2017). Treatment of Obesity among Youth with Intellectual and Developmental Disabilities: An Emerging Role for Telenursing. *Western Journal of Nursing Research*, *39*(8), 1008–1027. https://doi.org/10.1177/0193945917697664

Bennett, J. A., Germani, T., Haqq, A. M., & Zwaigenbaum, L. (2015). Autism spectrum disorder in Prader-Willi syndrome: A systematic review. *American Journal of Medical Genetics. Part A*, *167A*(12), 2936–2944. https://doi.org/10.1002/ajmg.a.37286

Bennett, J. A., Hodgetts, S., Mackenzie, M. L., Haqq, A. M., & Zwaigenbaum, L. (2017). Investigating Autism-Related Symptoms in Children with Prader-Willi Syndrome: A Case Study. *International Journal of Molecular Sciences*, *18*(3). https://doi.org/10.3390/ijms18030517

Bertoia, M. L., Mukamal, K. J., Cahill, L. E., Hou, T., Ludwig, D. S., Mozaffarian, D., Willett, W. C., Hu, F. B., & Rimm, E. B. (2015). Changes in Intake of Fruits and Vegetables and Weight Change in United States Men and Women Followed for Up to 24 Years: Analysis from Three Prospective Cohort Studies. *PLOS Medicine*, *12*(9), e1001878. https://doi.org/10.1371/journal.pmed.1001878

Birch, L., Savage, J. S., & Ventura, A. (2007). Influences on the Development of Children's Eating Behaviours: From Infancy to Adolescence. *Canadian Journal of Dietetic Practice and Research : A Publication of Dietitians of Canada = Revue Canadienne de La Pratique et de La Recherche En Dietetique : Une Publication Des Dietetistes Du Canada*, *68*(1), s1–s56.

Bishop, S. L., Havdahl, K. A., Huerta, M., & Lord, C. (2016). Sub-dimensions of social-communication impairment in autism spectrum disorder. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *57*(8), 909–916. https://doi.org/10.1111/jcpp.12510

Biswas, A., Oh, P. I., Faulkner, G. E., Bajaj, R. R., Silver, M. A., Mitchell, M. S., & Alter, D. A. (2015). Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis. *Annals of Internal Medicine*, *162*(2), 123. https://doi.org/10.7326/M14-1651

Blardi, P., de Lalla, A., Ceccatelli, L., Vanessa, G., Auteri, A., & Hayek, J. (2010). Variations of plasma leptin and adiponectin levels in autistic patients. *Neuroscience Letters*, *479*(1), 54–57. https://doi.org/10.1016/j.neulet.2010.05.027

Bloemendaal, L. van, IJzerman, R. G., Kulve, J. S. ten, Barkhof, F., Konrad, R. J., Drent, M. L., Veltman, D. J., & Diamant, M. (2014). GLP-1 Receptor Activation Modulates Appetite- and Reward-Related Brain Areas in Humans. *Diabetes*, *63*(12), 4186–4196. https://doi.org/10.2337/db14-0849

Blumenthal, S. R., Castro, V. M., Clements, C. C., Rosenfield, H. R., Murphy, S. N., Fava, M., Weilburg, J. B., Erb, J. L., Churchill, S. E., Kohane, I. S., Smoller, J. W., & Perlis, R. H. (2014). An Electronic Health Records Study of Long-Term Weight Gain Following Antidepressant Use. *JAMA Psychiatry*, *71*(8), 889–896. https://doi.org/10.1001/jamapsychiatry.2014.414

Bochukova, E. G., Huang, N., Keogh, J., Henning, E., Purmann, C., Blaszczyk, K., Saeed, S., Hamilton-Shield, J., Clayton-Smith, J., O'Rahilly, S., Hurles, M. E., & Farooqi, I. S. (2010). Large, rare chromosomal deletions associated with severe early-onset obesity. *Nature*, *463*(7281), 666–670. https://doi.org/10.1038/nature08689

Boucher, O., Julvez, J., Guxens, M., Arranz, E., Ibarluzea, J., Sánchez de Miguel, M., Fernández-Somoano, A., Tardon, A., Rebagliato, M., Garcia-Esteban, R., O'Connor, G., Ballester, F., & Sunyer, J. (2017). Association between breastfeeding duration and

cognitive development, autistic traits and ADHD symptoms: A multicenter study in Spain. *Pediatric Research*, *81*(3), 434–442. https://doi.org/10.1038/pr.2016.238

Boulangé, C. L., Neves, A. L., Chilloux, J., Nicholson, J. K., & Dumas, M.-E. (2016). Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Medicine*, *8*(1), 42. https://doi.org/10.1186/s13073-016-0303-2

Bouret, S. G. (2010). Neurodevelopmental Actions of Leptin. *Brain Research*, *1350*, 2–9. https://doi.org/10.1016/j.brainres.2010.04.011

Bresnahan, M., Hornig, M., Schultz, A. F., Gunnes, N., Hirtz, D., Lie, K. K., Magnus, P., Reichborn-Kjennerud, T., Roth, C., Schjølberg, S., Stoltenberg, C., Surén, P., Susser, E., & Lipkin, W. I. (2015). Association of maternal report of infant and toddler gastrointestinal symptoms with autism: Evidence from a prospective birth cohort. *JAMA Psychiatry*, *72*(5), 466–474. https://doi.org/10.1001/jamapsychiatry.2014.3034

Briggs, D. I., Enriori, P. J., Lemus, M. B., Cowley, M. A., & Andrews, Z. B. (2010). Diet-induced obesity causes ghrelin resistance in arcuate NPY/AgRP neurons. *Endocrinology*, *151*(10), 4745–4755. https://doi.org/10.1210/en.2010-0556

Broder-Fingert, S., Brazauskas, K., Lindgren, K., Iannuzzi, D., & Van Cleave, J. (2014). Prevalence of overweight and obesity in a large clinical sample of children with autism. *Academic Pediatrics*, *14*(4), 408–414. https://doi.org/10.1016/j.acap.2014.04.004

Burstyn, I., Wang, X., Yasui, Y., Sithole, F., & Zwaigenbaum, L. (2011). Autism spectrum disorders and fetal hypoxia in a population-based cohort: Accounting for missing exposures via Estimation-Maximization algorithm. *BMC Medical Research Methodology*, *11*(1), 2. https://doi.org/10.1186/1471-2288-11-2

Buss, J., Havel, P. J., Epel, E., Lin, J., Blackburn, E., & Daubenmier, J. (2014). Associations of ghrelin with eating behaviors, stress, metabolic factors, and telomere length among overweight and obese women: Preliminary evidence of attenuated ghrelin effects in obesity? *Appetite*, *76*, 84–94. https://doi.org/10.1016/j.appet.2014.01.011

Butler, M. G. (2006). Management of obesity in Prader–Willi syndrome. *Nature Clinical Practice. Endocrinology & Metabolism*, *2*(11), 592–593. https://doi.org/10.1038/ncpendmet0320

Cahill, F., Ji, Y., Wadden, D., Amini, P., Randell, E., Vasdev, S., Gulliver, W., & Sun, G. (2014). The Association of Serum Total Peptide YY (PYY) with Obesity and Body Fat Measures in the CODING Study. *PLOS ONE*, *9*(4), e95235. https://doi.org/10.1371/journal.pone.0095235

Cammisotto, P. G., Gélinas, Y., Deshaies, Y., & Bukowiecki, L. J. (2005). Regulation of leptin secretion from white adipocytes by insulin, glycolytic substrates, and amino acids. *American Journal of Physiology-Endocrinology and Metabolism*, *289*(1), E166–E171. https://doi.org/10.1152/ajpendo.00602.2004

Canadian Task Force on Preventive Health Care | Obesity in Children. (2015). Retrieved May 9, 2020, from https://canadiantaskforce.ca/guidelines/published-guidelines/obesity-in-children/

Cancello, R., Zingaretti, M. C., Sarzani, R., Ricquier, D., & Cinti, S. (1998). Leptin and UCP1 genes are reciprocally regulated in brown adipose tissue. *Endocrinology*, *139*(11), 4747–4750. https://doi.org/10.1210/endo.139.11.6434

Cani, P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J.-F., Gibson, G. R., Casteilla, L., … Burcelin, R. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, *56*(7), 1761–1772. https://doi.org/10.2337/db06-1491

Canoy, D., & Yang, T. O. (2015). Obesity in children: Bariatric surgery. *BMJ Clinical Evidence*, *2015*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4606917/

Castro, K., Faccioli, L. S., Baronio, D., Gottfried, C., Perry, I. S., & Riesgo, R. (2016). Feeding behavior and dietary intake of male children and adolescents with autism spectrum disorder: A case-control study. *International Journal of Developmental Neuroscience*, *53*, 68–74. https://doi.org/10.1016/j.ijdevneu.2016.07.003

Centers for Disease Control and Prevention. (2016, April 18). *Diagnostic Criteria | Autism Spectrum Disorder (ASD) | NCBDDD | CDC*. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/autism/hcp-dsm.html

Centers for Disease Control and Prevention. (2018). *Defining Childhood Obesity | Overweight & Obesity | CDC*. https://www.cdc.gov/obesity/childhood/defining.html

Cermak, S. A., Curtin, C., & Bandini, L. G. (2010). Food Selectivity and Sensory Sensitivity in Children with Autism Spectrum Disorders. *Journal of the American Dietetic Association*, *110*(2), 238–246. https://doi.org/10.1016/j.jada.2009.10.032

Chakraborti, C. K. (2015). New-found link between microbiota and obesity. *World Journal of Gastrointestinal Pathophysiology*, *6*(4), 110–119. https://doi.org/10.4291/wjgp.v6.i4.110

Chambers, E. S., Viardot, A., Psichas, A., Morrison, D. J., Murphy, K. G., Zac-Varghese, S. E. K., MacDougall, K., Preston, T., Tedford, C., Finlayson, G. S., Blundell, J. E., Bell, J. D., Thomas, E. L., Mt-Isa, S., Ashby, D., Gibson, G. R., Kolida, S., Dhillo, W. S., Bloom, S. R., … Frost, G. (2015). Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut*, *64*(11), 1744–1754. https://doi.org/10.1136/gutjnl-2014-307913

Chao, H.-C. (2018). Association of Picky Eating with Growth, Nutritional Status, Development, Physical Activity, and Health in Preschool Children. *Frontiers in Pediatrics*, *6*. https://doi.org/10.3389/fped.2018.00022

Chaput, J.-P., Lambert, M., Gray-Donald, K., McGrath, J. J., Tremblay, M. S., O'Loughlin, J., & Tremblay, A. (2011). Short Sleep Duration Is Independently Associated With Overweight and Obesity in Quebec Children. *Canadian Journal of Public Health = Revue Canadienne de Sante Publique*, *102*(5), 369–374.

Chawarska, K., Campbell, D., Chen, L., Shic, F., Klin, A., & Chang, J. (2011). Early Generalized Overgrowth in Boys With Autism. *Archives of General Psychiatry*, *68*(10), 1021–1031. https://doi.org/10.1001/archgenpsychiatry.2011.106

Chawner, L. R., Blundell-Birtill, P., & Hetherington, M. M. (2019). Interventions for Increasing Acceptance of New Foods Among Children and Adults with Developmental Disorders: A Systematic Review. *Journal of Autism and Developmental Disorders*, *49*(9), 3504–3525. https://doi.org/10.1007/s10803-019-04075-0

Chen, C., Zhang, Y., Sun, W., Chen, Y., Jiang, Y., Song, Y., Lin, Q., Zhu, L., Zhu, Q., Wang, X., Liu, S., & Jiang, F. (2017). Investigating the relationship between precocious puberty and obesity: A cross-sectional study in Shanghai, China. *BMJ Open*, *7*(4), e014004. https://doi.org/10.1136/bmjopen-2016-014004

Chen, Xiaoli, Beydoun, M. A., & Wang, Y. (2008). Is Sleep Duration Associated With Childhood Obesity? A Systematic Review and Meta-analysis. *Obesity*, *16*(2), 265–274. https://doi.org/10.1038/oby.2007.63

Chen, Xinhua, & Scholl, T. O. (2005). Oxidative stress: Changes in pregnancy and with gestational diabetes mellitus. *Current Diabetes Reports*, *5*(4), 282–288.

Chesi, A., & Grant, S. F. A. (2015). The genetics of pediatric obesity. *Trends in Endocrinology and Metabolism*, *26*(12), 711–721. https://doi.org/10.1016/j.tem.2015.08.008

Cheung, C. K., & Wu, J. C.-Y. (2013). Role of Ghrelin in the Pathophysiology of Gastrointestinal Disease. *Gut and Liver*, *7*(5), 505–512. https://doi.org/10.5009/gnl.2013.7.5.505

Child Mind Institute, Garey, J. (2020). *Autism and Picky Eating*. Child Mind Institute. Retrieved May 8, 2020, from https://childmind.org/article/autism-and-picky-eating/

Christensen, D. L., Baio, J., Van Naarden Braun, K., Bilder, D., Charles, J., Constantino, J. N., Daniels, J., Durkin, M. S., Fitzgerald, R. T., Kurzius-Spencer, M., Lee, L.-C., Pettygrove, S., Robinson, C., Schulz, E., Wells, C., Wingate, M. S., Zahorodny, W., Yeargin-Allsopp, M., & Centers for Disease Control and Prevention (CDC). (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.: 2002)*, *65*(3), 1–23. https://doi.org/10.15585/mmwr.ss6503a1

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*(1), 155–159. https://doi.org/10.1037/0033-2909.112.1.155

Constantino, J. N. (2013). Social Responsiveness Scale. In F. R. Volkmar (Ed.), *Encyclopedia of Autism Spectrum Disorders* (pp. 2919–2929). Springer. https://doi.org/10.1007/978-1-4419-1698-3_296

Constantino, J. N., Zhang, Y., Frazier, T., Abbacchi, A. M., & Law, P. (2010). Sibling recurrence and the genetic epidemiology of autism. *American Journal of Psychiatry*, *167*(11), 1349–1356. https://doi.org/10.1176/appi.ajp.2010.09101470

Conwell, L. S., Trost, S. G., Brown, W. J., & Batch, J. A. (2004). Indexes of insulin resistance and secretion in obese children and adolescents: a validation study. *Diabetes Care, 27*(2), 314-319. doi:10.2337/diacare.27.2.314

Corder K, van Sluijs EM, Wright A, Whincup P, Wareham NJ, Ekelund U. Is it possible to assess free-living physical activity and energy expenditure in young people by self-report? Am. J. Clin. Nutr. 89, 862–870, doi: 10.3945/ajcn.2008.26739 (2009).

Cortes, H. D., & Wevrick, R. (2018). Genetic analysis of very obese children with autism spectrum disorder. *Molecular Genetics and Genomics*, *293*(3), 725–736. https://doi.org/10.1007/s00438-018-1418-5

Coury, D. L., Anagnostou, E., Manning-Courtney, P., Reynolds, A., Cole, L., McCoy, R., Whitaker, A., & Perrin, J. M. (2012). Use of psychotropic medication in children and

adolescents with autism spectrum disorders. *Pediatrics*, *130*(Suppl 2), S69-76. https://doi.org/10.1542/peds.2012-0900D

Cowley, M. A., & Grove, K. L. (2004). Ghrelin—Satisfying a Hunger for the Mechanism. *Endocrinology*, *145*(6), 2604–2606. https://doi.org/10.1210/en.2004-0346

Cummings, D. E., & Shannon, M. H. (2003). Roles for Ghrelin in the Regulation of Appetite and Body Weight. *Archives of Surgery*, *138*(4), 389–396. https://doi.org/10.1001/archsurg.138.4.389

Cummings, D. E., Weigle, D. S., Frayo, R. S., Breen, P. A., Ma, M. K., Dellinger, E. P., & Purnell, J. Q. (2002). Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *The New England Journal of Medicine*, *346*(21), 1623–1630. https://doi.org/10.1056/NEJMoa012908

Curtin, C., Jojic, M., & Bandini, L. G. (2014). Obesity in Children with Autism Spectrum Disorder. *Harvard Review of Psychiatry*, *22*(2), 93. https://doi.org/10.1097/HRP.0000000000000031

Daniels, S. R., Hassink, S. G., & Nutrition, C. O. (2015). The Role of the Pediatrician in Primary Prevention of Obesity. *Pediatrics*. https://doi.org/10.1542/peds.2015-1558

Davis, C. D. (2016). The Gut Microbiome and Its Role in Obesity. *Nutrition Today*, *51*(4), 167–174. https://doi.org/10.1097/NT.0000000000000167

De Magistris, L., Familiari, V., Pascotto, A., Sapone, A., Frolli, A., Iardino, P., Carteni, M., De Rosa, M., Francavilla, R., Riegler, G., Militerni, R., & Bravaccio, C. (2010). Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. *Journal of Pediatric Gastroenterology and Nutrition*, *51*(4), 418–424. https://doi.org/10.1097/MPG.0b013e3181dcc4a5

De Silva, A., & Bloom, S. R. (2012). Gut Hormones and Appetite Control: A Focus on PYY and GLP-1 as Therapeutic Targets in Obesity. *Gut and Liver*, *6*(1), 10–20. https://doi.org/10.5009/gnl.2012.6.1.10

De Vadder, F., Kovatcheva-Datchary, P., Goncalves, D., Vinera, J., Zitoun, C., Duchampt, A., Bäckhed, F., & Mithieux, G. (2014). Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell*, *156*(1–2), 84–96. https://doi.org/10.1016/j.cell.2013.12.016

Dee, A., Kearns, K., O'Neill, C., Sharp, L., Staines, A., O'Dwyer, V., Fitzgerald, S., & Perry, I. J. (2014). The direct and indirect costs of both overweight and obesity: A systematic review. *BMC Research Notes*, *7*, 242. https://doi.org/10.1186/1756-0500-7-242

Deehan, E. C., & Walter, J. (2016). The Fiber Gap and the Disappearing Gut Microbiome: Implications for Human Nutrition. *Trends in Endocrinology and Metabolism: TEM*, *27*(5), 239–242. https://doi.org/10.1016/j.tem.2016.03.001

Deierlein, A. L., Siega-Riz, A. M., Chantala, K., & Herring, A. H. (2011). The Association Between Maternal Glucose Concentration and Child BMI at Age 3 Years. *Diabetes Care*, *34*(2), 480–484. https://doi.org/10.2337/dc10-1766

Delporte, C. (2013). Structure and Physiological Actions of Ghrelin. *Scientifica*, *2013*. https://doi.org/10.1155/2013/518909

DeMand, A., Johnson, C., & Foldes, E. (2015). Psychometric Properties of the Brief Autism Mealtime Behaviors Inventory. *Journal of Autism and Developmental Disorders*, *45*(9), 2667–2673. https://doi.org/10.1007/s10803-015-2435-4

Dhaliwal, K. K., Orsso, C. E., Richard, C., Haqq, A. M., & Zwaigenbaum, L. (2019). Risk Factors for Unhealthy Weight Gain and Obesity among Children with Autism Spectrum Disorder. *International Journal of Molecular Sciences*, *20*(13). https://doi.org/10.3390/ijms20133285

Diagnostic and Statistical Manual of Mental Disorders. (2018). In B. B. Frey, *The SAGE Encyclopedia of Educational Research, Measurement, and Evaluation*. SAGE Publications, Inc. https://doi.org/10.4135/9781506326139.n198

Dössegger, A., Ruch, N., Jimmy, G., Braun-Fahrländer, C., Mäder, U., Hänggi, J., Hofmann, H., Puder, J. J., Kriemler, S., & Bringolf-Isler, B. (2014). Reactivity to Accelerometer Measurement of Children and Adolescents. *Medicine and Science in Sports and Exercise*, *46*(6), 1140–1146. https://doi.org/10.1249/MSS.0000000000000215

Dubois, L., Farmer, A., Girard, M., Peterson, K., & Tatone-Tokuda, F. (2007). Problem eating behaviors related to social factors and body weight in preschool children: A longitudinal study. *International Journal of Behavioral Nutrition and Physical Activity*, *4*(1), 9. https://doi.org/10.1186/1479-5868-4-9

Dudova, I., Kocourkova, J., & Koutek, J. (2015). Early-onset anorexia nervosa in girls with Asperger syndrome. *Neuropsychiatric Disease and Treatment*, *11*, 1639–1643. https://doi.org/10.2147/NDT.S83831

Dunton, G. F., Liao, Y., Intille, S. S., Spruijt-Metz, D., & Pentz, M. (2011). Investigating Children's Physical Activity and Sedentary Behavior Using Ecological Momentary Assessment With Mobile Phones. *Obesity*, *19*(6), 1205–1212. https://doi.org/10.1038/oby.2010.302

Dykens, E. M., Lee, E., & Roof, E. (2011). Prader–Willi syndrome and autism spectrum disorders: An evolving story. *Journal of Neurodevelopmental Disorders*, *3*(3), 225–237. https://doi.org/10.1007/s11689-011-9092-5

Dykens, E. M., Maxwell, M. A., Pantino, E., Kossler, R., & Roof, E. (2007). Assessment of Hyperphagia in Prader-Willi Syndrome. *Obesity*, *15*(7), 1816–1826. https://doi.org/10.1038/oby.2007.216

Dykens, E. M., Roof, E., Hunt-Hawkins, H., Dankner, N., Lee, E. B., Shivers, C. M., Daniell, C., & Kim, S.-J. (2017). Diagnoses and characteristics of autism spectrum disorders in children with Prader-Willi syndrome. *Journal of Neurodevelopmental Disorders*, *9*(1), 18. https://doi.org/10.1186/s11689-017-9200-2

Eidelman, A. I., & Samueloff, A. (2002). The pathophysiology of the fetus of the diabetic mother. *Seminars in Perinatology*, *26*(3), 232–236.

Ekelund, U., Brage, S., Besson, H., Sharp, S., & Wareham, N. J. (2008). Time spent being sedentary and weight gain in healthy adults: Reverse or bidirectional causality? *The American Journal of Clinical Nutrition*, *88*(3), 612–617. https://doi.org/10.1093/ajcn/88.3.612

Elrod, M. G., Nylund, C. M., Susi, A. L., Gorman, G. H., Hisle-Gorman, E., Rogers, D. J., & Erdie-Lalena, C. (2016). Prevalence of diagnosed sleep disorders and related diagnostic and surgical procedures in children with autism spectrum disorders. *Journal of Developmental and Behavioral Pediatrics*, *37*(5), 377–384. https://doi.org/10.1097/DBP.0000000000000248

Emmer, C., Bosnjak, M., & Mata, J. (2020). The association between weight stigma and mental health: A meta-analysis. *Obesity Reviews*, *21*(1), e12935. https://doi.org/10.1111/obr.12935

English, P. J., Ghatei, M. A., Malik, I. A., Bloom, S. R., & Wilding, J. P. H. (2002). Food fails to suppress ghrelin levels in obese humans. *The Journal of Clinical Endocrinology and Metabolism*, *87*(6), 2984. https://doi.org/10.1210/jcem.87.6.8738

Enriori, P. J., Evans, A. E., Sinnayah, P., & Cowley, M. A. (2006). Leptin Resistance and Obesity. *Obesity*, *14*(S8), 254S-258S. https://doi.org/10.1038/oby.2006.319

Epstein, L. H., Robinson, J. L., Temple, J. L., Roemmich, J. N., Marusewski, A. L., & Nadbrzuch, R. L. (2009). Variety influences habituation of motivated behavior for food and energy intake in children. *The American Journal of Clinical Nutrition*, *89*(3), 746–754. https://doi.org/10.3945/ajcn.2008.26911

Esnafoglu, E., Cırrık, S., Ayyıldız, S. N., Erdil, A., Ertürk, E. Y., Daglı, A., & Noyan, T. (2017). Increased Serum Zonulin Levels as an Intestinal Permeability Marker in Autistic Subjects. *The Journal of Pediatrics*, *188*, 240–244. https://doi.org/10.1016/j.jpeds.2017.04.004

Esteban-Figuerola, P., Canals, J., Fernández-Cao, J. C., & Arija Val, V. (2018a). Differences in food consumption and nutritional intake between children with autism spectrum disorders and typically developing children: A meta-analysis. *Autism*, 1362361318794179. https://doi.org/10.1177/1362361318794179

Esteban-Figuerola, P., Canals, J., Fernández-Cao, J. C., & Arija Val, V. (2018b). Differences in food consumption and nutritional intake between children with autism spectrum disorders and typically developing children: A meta-analysis. *Autism: The International Journal of Research and Practice*, 1362361318794179. https://doi.org/10.1177/1362361318794179

Evans, E. W., Must, A., Anderson, S. E., Curtin, C., Scampini, R., Maslin, M., & Bandini, L. (2012). Dietary Patterns and Body Mass Index in Children with Autism and Typically Developing Children. *Research in Autism Spectrum Disorders*, *6*(1), 399–405. https://doi.org/10.1016/j.rasd.2011.06.014

Faith, M. S., & Kral, T. V. E. (2006). Social Environmental and Genetic Influences on Obesity and Obesity-Promoting Behaviors: Fostering Research Integration. In *Genes, Behavior, and the Social Environment: Moving Beyond the Nature/Nurture Debate*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK19935/

Fallah, M. S., Shaikh, M. R., Neupane, B., Rusiecki, D., Bennett, T. A., & Beyene, J. (2019). Atypical Antipsychotics for Irritability in Pediatric Autism: A Systematic Review and Network Meta-Analysis. *Journal of Child and Adolescent Psychopharmacology*, *29*(3), 168–180. https://doi.org/10.1089/cap.2018.0115

Farooqi, I. S. (2002). Leptin and the onset of puberty: Insights from rodent and human genetics. *Seminars in Reproductive Medicine*, *20*(2), 139–144. https://doi.org/10.1055/s-2002-32505

Fatima, Y., Doi, S. a. R., & Mamun, A. A. (2016). Sleep quality and obesity in young subjects: A meta-analysis. *Obesity Reviews*, *17*(11), 1154–1166. https://doi.org/10.1111/obr.12444

American Speech-Lanaguage-Hearing Association. (n.d.). *Feeding and Swallowing Disorders in Children*. Retrieved May 8, 2020, from https://www.asha.org/public/speech/swallowing/Feeding-and-Swallowing-Disorders-in-Children/

Ferguson, B. J., Marler, S., Altstein, L. L., Lee, E. B., Akers, J., Sohl, K., McLaughlin, A., Hartnett, K., Kille, B., Mazurek, M., Macklin, E. A., McDonnell, E., Barstow, M., Bauman, M. L., Margolis, K. G., Veenstra-VanderWeele, J., & Beversdorf, D. Q. (2017). Psychophysiological Associations with Gastrointestinal Symptomatology in Autism Spectrum Disorder. *Autism Research : Official Journal of the International Society for Autism Research*, *10*(2), 276–288. https://doi.org/10.1002/aur.1646

Ferreira, J. P., Ghiarone, T., Cabral Júnior, C. R., Furtado, G. E., Moreira Carvalho, H., Machado-Rodrigues, A. M., & Andrade Toscano, C. V. (2019). Effects of Physical Exercise on the Stereotyped Behavior of Children with Autism Spectrum Disorders. *Medicina*, *55*(10). https://doi.org/10.3390/medicina55100685

Fett-Conte A.G., Ana Luiza Bossolani-Martins and Dante Bruno Avanso Rosan (April 2nd 2015). Etiology of Autism the Complexity of Risk Factors in Autism Spectrum Disorder, Autism Spectrum Disorder - Recent Advances, *Michael Fitzgerald, IntechOpen,* DOI: 10.5772/59109.

Field, D., Garland, M., & Williams, K. (2003). Correlates of specific childhood feeding problems. *Journal of Paediatrics and Child Health*, *39*(4), 299–304. https://doi.org/10.1046/j.1440-1754.2003.00151.x

Fiorentino, M., Sapone, A., Senger, S., Camhi, S. S., Kadzielski, S. M., Buie, T. M., Kelly, D. L., Cascella, N., & Fasano, A. (2016). Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Molecular Autism*, *7*, 49. https://doi.org/10.1186/s13229-016-0110-z

Fleisch, A. F., Agarwal, N., Roberts, M. D., Han, J. C., Theim, K. R., Vexler, A., Troendle, J., Yanovski, S. Z., & Yanovski, J. A. (2007). Influence of Serum Leptin on Weight and Body Fat Growth in Children at High Risk for Adult Obesity. *The Journal of Clinical Endocrinology and Metabolism*, *92*(3), 948–954. https://doi.org/10.1210/jc.2006-1390

Frazier, P. A., Tix, A. P., & Barron, K. E. (2004). "Testing moderator and mediator effects in counseling psychology research": Correction to Frazier et al. (2004). *Journal of Counseling Psychology*, *51*(2), 157–157. https://doi.org/10.1037/0022-0167.51.2.157

Frazier, T. W., Ratliff, K. R., Gruber, C., Zhang, Y., Law, P. A., & Constantino, J. N. (2014). Confirmatory factor analytic structure and measurement invariance of quantitative autistic traits measured by the Social Responsiveness Scale-2. *Autism*, *18*(1), 31–44. https://doi.org/10.1177/1362361313500382

Frazier, T. W., Shattuck, P. T., Narendorf, S. C., Cooper, B. P., Wagner, M., & Spitznagel, E. L. (2011). Prevalence and Correlates of Psychotropic Medication Use in Adolescents with an Autism Spectrum Disorder with and without Caregiver-Reported Attention-Deficit/Hyperactivity Disorder. *Journal of Child and Adolescent Psychopharmacology*, *21*(6), 571–579. https://doi.org/10.1089/cap.2011.0057

Freemark, M. (2007). Pharmacotherapy of Childhood Obesity: An evidence-based, conceptual approach. *Diabetes Care*, *30*(2), 395–402. https://doi.org/10.2337/dc06-1569

Fujita-Shimizu, A., Suzuki, K., Nakamura, K., Miyachi, T., Matsuzaki, H., Kajizuka, M., Shinmura, C., Iwata, Y., Suda, S., Tsuchiya, K. J., Matsumoto, K., Sugihara, G., Iwata, K., Yamamoto, S., Tsujii, M., Sugiyama, T., Takei, N., & Mori, N. (2010). Decreased serum levels of adiponectin in subjects with autism. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*(3), 455–458. https://doi.org/10.1016/j.pnpbp.2009.12.020

Fung, L. K., Mahajan, R., Nozzolillo, A., Bernal, P., Krasner, A., Jo, B., Coury, D., Whitaker, A., Veenstra-Vanderweele, J., & Hardan, A. Y. (2016). Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. *Pediatrics*, *137 Suppl 2*, S124-135. https://doi.org/10.1542/peds.2015-2851K

Gallagher, E. J., & LeRoith, D. (2015). Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality. *Physiological Reviews*, *95*(3), 727–748. https://doi.org/10.1152/physrev.00030.2014

García, O. P., Long, K. Z., & Rosado, J. L. (2009). Impact of micronutrient deficiencies on obesity. *Nutrition Reviews*, *67*(10), 559–572. https://doi.org/10.1111/j.1753-4887.2009.00228.x

Garg, S. K., Maurer, H., Reed, K., & Selagamsetty, R. (2014). Diabetes and cancer: Two diseases with obesity as a common risk factor. *Diabetes, Obesity & Metabolism*, *16*(2), 97–110. https://doi.org/10.1111/dom.12124

Garza, J. C., Guo, M., Zhang, W., & Lu, X.-Y. (2008). Leptin increases adult hippocampal neurogenesis in vivo and in vitro. *The Journal of Biological Chemistry*, *283*(26), 18238–18247. https://doi.org/10.1074/jbc.M800053200

Ghaffari, M. A., Mousavinejad, E., Riahi, F., Mousavinejad, M., & Afsharmanesh, M. R. (2016). Increased Serum Levels of Tumor Necrosis Factor-Alpha, Resistin, and Visfatin in the Children with Autism Spectrum Disorders: A Case-Control Study. *Neurology Research International*, *2016*. https://doi.org/10.1155/2016/9060751

Goran, M. I., Reynolds, K. D., & Lindquist, C. H. (1999). Role of physical activity in the prevention of obesity in children. *International Journal of Obesity*, *23*(3), S18. https://doi.org/10.1038/sj.ijo.0800880

Gow, M. L., Ho, M., Burrows, T. L., Baur, L. A., Stewart, L., Hutchesson, M. J., Cowell, C. T., Collins, C. E., & Garnett, S. P. (2014). Impact of dietary macronutrient distribution on BMI and cardiometabolic outcomes in overweight and obese children and adolescents: A systematic review. *Nutrition Reviews*, *72*(7), 453–470. https://doi.org/10.1111/nure.12111

Graf-Myles, J., Farmer, C., Thurm, A., Royster, C., Kahn, P., Soskey, L., Rothschild, L., & Swedo, S. (2013). Dietary Adequacy of Children with Autism Compared to Controls and the Impact of Restricted Diet. *Journal of Developmental and Behavioral Pediatrics : JDBP*, *34*(7). https://doi.org/10.1097/DBP.0b013e3182a00d17

Griffiths, L. J., Cortina-Borja, M., Sera, F., Pouliou, T., Geraci, M., Rich, C., Cole, T. J., Law, C., Joshi, H., Ness, A. R., Jebb, S. A., & Dezateux, C. (2013). How active are our children? Findings from the Millennium Cohort Study. *BMJ Open*, *3*(8), e002893. https://doi.org/10.1136/bmjopen-2013-002893

Gruzdeva, O., Borodkina, D., Uchasova, E., Dyleva, Y., & Barbarash, O. (2019). Leptin resistance: Underlying mechanisms and diagnosis. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *12*, 191–198. https://doi.org/10.2147/DMSO.S182406

Guo, Y., Ma, L., Enriori, P. J., Koska, J., Franks, P. W., Brookshire, T., Cowley, M. A., Salbe, A. D., DelParigi, A., & Tataranni, P. A. (2006). Physiological Evidence for the Involvement of Peptide YY in the Regulation of Energy Homeostasis in Humans. *Obesity*, *14*(9), 1562–1570. https://doi.org/10.1038/oby.2006.180

Gutzwiller, J.-P., Göke, B., Drewe, J., Hildebrand, P., Ketterer, S., Handschin, D., Winterhalder, R., Conen, D., & Beglinger, C. (1999). Glucagon-like peptide-1: A potent regulator of food intake in humans. *Gut*, *44*(1), 81–86. https://doi.org/10.1136/gut.44.1.81

Hallioglu, O., Alehan, D., & Kandemir, N. (2003). Plasma leptin levels in children with cyanotic and acyanotic congenital heart disease and correlations with growth parameters. *International Journal of Cardiology*, *92*(1), 93–97. https://doi.org/10.1016/S0167-5273(03)00044-5

Han, J. C., Lawlor, D. A., & Kimm, S. Y. S. (2010). Childhood Obesity – 2010: Progress and Challenges. *Lancet*, *375*(9727), 1737–1748. https://doi.org/10.1016/S0140-6736(10)60171-7

Haqq, A. M., Grambow, S. C., Muehlbauer, M., Newgard, C. B., Svetkey, L. P., Carrel, A. L., Yanovski, J. A., Purnell, J. Q., & Freemark, M. (2008). Ghrelin concentrations in Prader-Willi syndrome (PWS) infants and children. *Clinical Endocrinology*, *69*(6), 911–920. https://doi.org/10.1111/j.1365-2265.2008.03385.x

Harold W. Kohl, I. I. I., Cook, H. D., Environment, C. on P. A. and P. E. in the S., Board, F. and N., & Medicine, I. of. (2013). Physical Activity and Physical Education: Relationship to Growth, Development, and Health. In *Educating the Student Body: Taking Physical Activity and Physical Education to School*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK201497/

Hasan, Z. A., Al-Kafaji, G., Al-Sherawi, M. I., Razzak, R. A., Eltayeb, D., Skrypnk, C., & Bakhiet, M. (2019). Investigation of serum levels of leptin, ghrelin and growth hormone in Bahraini children with autism. *International Archives of Translational Medicine*, *5*(1). https://doi.org/10.23937/2572-4142.1510007

Haye, K. de la, Dijkstra, J. K., Lubbers, M. J., Rijsewijk, L. van, & Stolk, R. (2017). The dual role of friendship and antipathy relations in the marginalization of overweight children in their peer networks: The TRAILS Study. *PLOS ONE*, *12*(6), e0178130. https://doi.org/10.1371/journal.pone.0178130

Hayes, A. F., & Little, T. D. (2018). Introduction to mediation, moderation, and conditional process analysis : a regression-based approach (Second edition.). The Guilford Press.

Hayes, A. F., & Matthes, J. (2009). Computational procedures for probing interactions in OLS and logistic regression: SPSS and SAS implementations. *Behavior Research Methods*, *41*(3), 924–936. https://doi.org/10.3758/BRM.41.3.924

Healy, S., Haegele, J. A., Grenier, M., & Garcia, J. M. (2017). Physical Activity, Screen-Time Behavior, and Obesity Among 13-Year Olds in Ireland with and without Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *47*(1), 49–57. https://doi.org/10.1007/s10803-016-2920-4

Heck, A. M., Yanovski, J. A., & Calis, K. A. (2000). Orlistat, a new lipase inhibitor for the management of obesity. *Pharmacotherapy*, *20*(3), 270–279.

Henauw, S. D., Huybrechts, I., Bourdeaudhuij, I. D., Bammann, K., Barba, G., Lissner, L., Mårild, S., Molnár, D., Moreno, L. A., Pigeot, I., Tornaritis, M., Veidebaum, T., Verbestel, V., & Ahrens, W. (2015). Effects of a community-oriented obesity prevention programme on indicators of body fatness in preschool and primary school children. Main results from the IDEFICS study. *Obesity Reviews*, *16*(S2), 16–29. https://doi.org/10.1111/obr.12346

Herndon, A. C., DiGuiseppi, C., Johnson, S. L., Leiferman, J., & Reynolds, A. (2009). Does nutritional intake differ between children with autism spectrum disorders and children with typical development? *Journal of Autism and Developmental Disorders*, *39*(2), 212–222. https://doi.org/10.1007/s10803-008-0606-2

Hill, A. P., Zuckerman, K. E., & Fombonne, E. (2015). Obesity and Autism. *Pediatrics*, *136*(6), 1051–1061. https://doi.org/10.1542/peds.2015-1437

Hira, T., Pinyo, J., & Hara, H. (2020). What Is GLP-1 Really Doing in Obesity? *Trends in Endocrinology & Metabolism*, *31*(2), 71–80. https://doi.org/10.1016/j.tem.2019.09.003

Hirsch, L. E., & Pringsheim, T. (2016). Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews*, *6*. https://doi.org/10.1002/14651858.CD009043.pub3

Hjorth, M. F., Ritz, C., Blaak, E. E., Saris, W. H., Langin, D., Poulsen, S. K., Larsen, T. M., Sørensen, T. I., Zohar, Y., & Astrup, A. (2017). Pretreatment fasting plasma glucose and insulin modify dietary weight loss success: Results from 3 randomized clinical trials. *The American Journal of Clinical Nutrition*, *106*(2), 499–505. https://doi.org/10.3945/ajcn.117.155200

Hollander, E., Soorya, L., Chaplin, W., Anagnostou, E., Taylor, B. P., Ferretti, C. J., Wasserman, S., Swanson, E., & Settipani, C. (2012). A Double-Blind Placebo-Controlled Trial of Fluoxetine for Repetitive Behaviors and Global Severity in Adult Autism Spectrum Disorders. *American Journal of Psychiatry*, *169*(3), 292–299. https://doi.org/10.1176/appi.ajp.2011.10050764

Hrafnkelsson, H., Magnusson, K. TH., Sigurdsson, E. L., & Johannsson, E. (2009). Association of BMI and fasting insulin with cardiovascular disease risk factors in seven-year-old Icelandic children. *Scandinavian Journal of Primary Health Care*, *27*(3), 186–191. https://doi.org/10.1080/02813430903155028

Hsia, Y., Wong, A. Y. S., Murphy, D. G. M., Simonoff, E., Buitelaar, J. K., & Wong, I. C. K. (2014). Psychopharmacological prescriptions for people with autism spectrum disorder (ASD): A multinational study. *Psychopharmacology*, *231*(6), 999–1009. https://doi.org/10.1007/s00213-013-3263-x

Hyman, S. L., Stewart, P. A., Foley, J., Cain, U., Peck, R., Morris, D. D., Wang, H., & Smith, T. (2016). The Gluten-Free/Casein-Free Diet: A Double-Blind Challenge Trial in Children with Autism. *Journal of Autism and Developmental Disorders*, *46*(1), 205–220. https://doi.org/10.1007/s10803-015-2564-9

Hyman, S. L., Stewart, P. A., Schmidt, B., Cain, U., Lemcke, N., Foley, J. T., Peck, R., Clemons, T., Reynolds, A., Johnson, C., Handen, B., James, S. J., Courtney, P. M., Molloy, C., & Ng, P. K. (2012). Nutrient intake from food in children with autism. *Pediatrics*, *130 Suppl 2*, S145-153. https://doi.org/10.1542/peds.2012-0900L

Indiani, C. M. D. S. P., Rizzardi, K. F., Castelo, P. M., Ferraz, L. F. C., Darrieux, M., & Parisotto, T. M. (2018). Childhood Obesity and Firmicutes/Bacteroidetes Ratio in the Gut Microbiota: A Systematic Review. *Childhood Obesity (Print)*, *14*(8), 501–509. https://doi.org/10.1089/chi.2018.0040

Inge, T. H., Courcoulas, A. P., Jenkins, T. M., Michalsky, M. P., Brandt, M. L., Xanthakos, S. A., Dixon, J. B., Harmon, C. M., Chen, M. K., Xie, C., Evans, M. E., Helmrath, M. A., & Teen–LABS Consortium. (2019). Five-Year Outcomes of Gastric Bypass in Adolescents as Compared with Adults. *The New England Journal of Medicine*, *380*(22), 2136–2145. https://doi.org/10.1056/NEJMoa1813909

Inui, A. (2001). Ghrelin: An orexigenic and somatotrophic signal from the stomach. *Nature Reviews Neuroscience*, *2*(8), 551–560. https://doi.org/10.1038/35086018

Ip, A., Zwaigenbaum, L., Brian, J. A., Candian Pediatric Society (2019). Post-diagnostic management and follow-up care for autism spectrum disorder. *Paediatrics & Child Health*, *24*(7), 461–468. https://doi.org/10.1093/pch/pxz121

Jazani, N. H., Savoj, J., Lustgarten, M., Lau, W. L., & Vaziri, N. D. (2019). Impact of gut dysbiosis on neurohormonal pathways in chronic kidney disease. *Diseases*, *7*(1), 21. https://doi.org/10.3390/diseases7010021

Jobski, K., Höfer, J., Hoffmann, F., & Bachmann, C. (2017). Use of psychotropic drugs in patients with autism spectrum disorders: A systematic review. *Acta Psychiatrica Scandinavica*, *135*(1), 8–28. https://doi.org/10.1111/acps.12644

Johnson, F., & Wardle, J. (2014). Variety, Palatability, and Obesity1234. *Advances in Nutrition*, *5*(6), 851–859. https://doi.org/10.3945/an.114.007120

Jones, R. A., Downing, K., Rinehart, N. J., Barnett, L. M., May, T., McGillivray, J. A., Papadopoulos, N. V., Skouteris, H., Timperio, A., & Hinkley, T. (2017). Physical activity, sedentary behavior and their correlates in children with Autism Spectrum Disorder: A systematic review. *PLOS ONE*, *12*(2), e0172482. https://doi.org/10.1371/journal.pone.0172482

Joseph, P. V., Reed, D. R., & Mennella, J. A. (2016). Individual Differences Among Children in Sucrose Detection Thresholds: Relationship With Age, Gender, and Bitter Taste Genotype. *Nursing Research*, *65*(1), 3–12. https://doi.org/10.1097/NNR.0000000000000138

Kahathuduwa, C. N., West, B. D., Blume, J., Dharavath, N., Moustaid-Moussa, N., & Mastergeorge, A. (2019). The risk of overweight and obesity in children with autism spectrum disorders: A systematic review and meta-analysis. *Obesity Reviews*, *20*(12), 1667–1679. https://doi.org/10.1111/obr.12933

Kahn, B. B., & Flier, J. S. (2000). Obesity and insulin resistance. *Journal of Clinical Investigation*, *106*(4), 473–481.

Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*, *444*(7121), 840–846. https://doi.org/10.1038/nature05482

Kamal Nor, N., Ghozali, A. H., & Ismail, J. (2019). Prevalence of Overweight and Obesity Among Children and Adolescents With Autism Spectrum Disorder and Associated Risk Factors. *Frontiers in Pediatrics*, *7*, 38. https://doi.org/10.3389/fped.2019.00038

Kang, D.W., Park, J. G., Ilhan, Z. E., Wallstrom, G., Labaer, J., Adams, J. B., & Krajmalnik-Brown, R. (2013). Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. *PloS One*, *8*(7), e68322. https://doi.org/10.1371/journal.pone.0068322

Kang, Y., & Cai, Y. (2017). Gut microbiota and obesity: Implications for fecal microbiota transplantation therapy. *Hormones (Athens, Greece)*, *16*(3), 223–234. https://doi.org/10.14310/horm.2002.1742

Kawano, J., & Arora, R. (2009). The role of adiponectin in obesity, diabetes, and cardiovascular disease. *Journal of the Cardiometabolic Syndrome*, *4*(1), 44–49. https://doi.org/10.1111/j.1559-4572.2008.00030.x

Kawasaki, M., Arata, N., Miyazaki, C., Mori, R., Kikuchi, T., Ogawa, Y., & Ota, E. (2018). Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. *PloS One*, *13*(1), e0190676. https://doi.org/10.1371/journal.pone.0190676

Kern, J. K., Trivedi, M. H., Garver, C. R., Grannemann, B. D., Andrews, A. A., Savla, J. S., Johnson, D. G., Mehta, J. A., & Schroeder, J. L. (2006). The pattern of sensory processing abnormalities in autism. *Autism*, *10*(5), 480–494. https://doi.org/10.1177/1362361306066564

Khan, F. U. F., Khan, K. U. Z., & Singh, S. K. (2018). Is Group Means Imputation Any Better Than Mean Imputation: A Study Using C5.0 Classifier. *Journal of Physics: Conference Series*, *1060*, 012014. https://doi.org/10.1088/1742-6596/1060/1/012014

Khodaverdi, F., Alhani, F., Kazemnejad, A., & Khodaverdi, Z. (2011). The Relationship between Obesity and Quality Of Life in School Children. *Iranian Journal of Public Health*, *40*(2), 96–101.

King, B. H., Hollander, E., Sikich, L., McCracken, J. T., Scahill, L., Bregman, J. D., Donnelly, C. L., Anagnostou, E., Dukes, K., Sullivan, L., Hirtz, D., Wagner, A., & Ritz, L. (2009). Lack of Efficacy of Citalopram in Children With Autism Spectrum Disorders and High Levels of Repetitive Behavior: Citalopram Ineffective in Children With Autism. *Archives of General Psychiatry*, *66*(6), 583–590. https://doi.org/10.1001/archgenpsychiatry.2009.30

Kirk, S. L., Samuelsson, A.-M., Argenton, M., Dhonye, H., Kalamatianos, T., Poston, L., Taylor, P. D., & Coen, C. W. (2009). Maternal Obesity Induced by Diet in Rats Permanently Influences Central Processes Regulating Food Intake in Offspring. *PLoS ONE*, *4*(6). https://doi.org/10.1371/journal.pone.0005870

Kirkovski, M., Enticott, P. G., & Fitzgerald, P. B. (2013). A Review of the Role of Female Gender in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *43*(11), 2584–2603. https://doi.org/10.1007/s10803-013-1811-1

Klein, S., Coppack, S. W., Mohamed-Ali, V., & Landt, M. (1996). Adipose tissue leptin production and plasma leptin kinetics in humans. *Diabetes*, *45*(7), 984–987. https://doi.org/10.2337/diab.45.7.984

Knight, Z. A., Hannan, K. S., Greenberg, M. L., & Friedman, J. M. (2010). Hyperleptinemia Is Required for the Development of Leptin Resistance. *PLoS ONE*, *5*(6). https://doi.org/10.1371/journal.pone.0011376

Knutson, K. L. (2012). Does inadequate sleep play a role in vulnerability to obesity? *American Journal of Human Biology: The Official Journal of the Human Biology Council*, *24*(3), 361–371. https://doi.org/10.1002/ajhb.22219

Kolevzon, A., Gross, R., & Reichenberg, A. (2007). Prenatal and Perinatal Risk Factors for Autism: A Review and Integration of Findings. *Archives of Pediatrics & Adolescent Medicine*, *161*(4), 326–333. https://doi.org/10.1001/archpedi.161.4.326

Koliada, A., Syzenko, G., Moseiko, V., Budovska, L., Puchkov, K., Perederiy, V., Gavalko, Y., Dorofeyev, A., Romanenko, M., Tkach, S., Sineok, L., Lushchak, O., & Vaiserman, A. (2017). Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population. *BMC Microbiology*, *17*(1), 120. https://doi.org/10.1186/s12866-017-1027-1

Koning, M., de Jong, A., de Jong, E., Visscher, T. L. S., Seidell, J. C., & Renders, C. M. (2018). Agreement between parent and child report of physical activity, sedentary and dietary behaviours in 9-12-year-old children and associations with children's weight status. *BMC Psychology*, *6*(1), 14. https://doi.org/10.1186/s40359-018-0227-2

Koutouratsas, T., Kalli, T., Karamanolis, G., & Gazouli, M. (2019). Contribution of ghrelin to functional gastrointestinal disorders' pathogenesis. *World Journal of Gastroenterology*, *25*(5), 539–551. https://doi.org/10.3748/wjg.v25.i5.539

Krakowiak, P., Walker, C. K., Bremer, A. A., Baker, A. S., Ozonoff, S., Hansen, R. L., & Hertz-Picciotto, I. (2012). Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics*, *129*(5), e1121-1128. https://doi.org/10.1542/peds.2011-2583

Kushak, R. I., Buie, T. M., Murray, K. F., Newburg, D. S., Chen, C., Nestoridi, E., & Winter, H. S. (2016). Evaluation of Intestinal Function in Children With Autism and Gastrointestinal Symptoms. *Journal of Pediatric Gastroenterology and Nutrition*, *62*(5), 687–691. https://doi.org/10.1097/MPG.0000000000001174

Lake, A., & Townshend, T. (2006). Obesogenic environments: Exploring the built and food environments. *The Journal of the Royal Society for the Promotion of Health*, *126*(6), 262–267. https://doi.org/10.1177/1466424006070487

Larraufie, P., Martin-Gallausiaux, C., Lapaque, N., Dore, J., Gribble, F. M., Reimann, F., & Blottiere, H. M. (2018). SCFAs strongly stimulate PYY production in human enteroendocrine cells. *Scientific Reports*, *8*(1), 74. https://doi.org/10.1038/s41598-017-18259-0

Lawlor, D. A., Lichtenstein, P., & Långström, N. (2011). Association of maternal diabetes mellitus in pregnancy with offspring adiposity into early adulthood: Sibling study in a prospective cohort of 280,866 men from 248,293 families. *Circulation*, *123*(3), 258–265. https://doi.org/10.1161/CIRCULATIONAHA.110.980169

Lebenthal, Y., Gat-Yablonski, G., Shtaif, B., Padoa, A., Phillip, M., & Lazar, L. (2006). Effect of sex hormone administration on circulating ghrelin levels in peripubertal children. *The Journal of Clinical Endocrinology and Metabolism*, *91*(1), 328–331. https://doi.org/10.1210/jc.2005-0204

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the Sensory Abnormalities of Children and Adults with Autism. *Journal of Autism and*

Developmental Disorders, *37*(5), 894–910. https://doi.org/10.1007/s10803-006-0218-7

Levy, S. E., Pinto-Martin, J. A., Bradley, C. B., Chittams, J., Johnson, S. L., Pandey, J., Pomykacz, A., Ramirez, A., Reynolds, A., Rubenstein, E., Schieve, L. A., Shapira, S. K., Thompson, A., Young, L., & Kral, T. V. E. (2019). Relationship of Weight Outcomes, Co-Occurring Conditions, and Severity of Autism Spectrum Disorder in the Study to Explore Early Development. *The Journal of Pediatrics*, *205*, 202–209. https://doi.org/10.1016/j.jpeds.2018.09.003

Ley, R. E., Bäckhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut microbial ecology. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(31), 11070–11075. https://doi.org/10.1073/pnas.0504978102

Li, Y.-M., Ou, J.-J., Liu, L., Zhang, D., Zhao, J.-P., & Tang, S.-Y. (2016). Association Between Maternal Obesity and Autism Spectrum Disorder in Offspring: A Meta-analysis. *Journal of Autism and Developmental Disorders*, *46*(1), 95–102. https://doi.org/10.1007/s10803-015-2549-8

Lihn, A. S., Pedersen, S. B., & Richelsen, B. (2005). Adiponectin: Action, regulation and association to insulin sensitivity. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*, *6*(1), 13–21. https://doi.org/10.1111/j.1467-789X.2005.00159.x

Lin, S., Thomas, T. C., Storlien, L. H., & Huang, X. F. (2000). Development of high fat diet-induced obesity and leptin resistance in C57Bl/6J mice. *International Journal of Obesity*, *24*(5), 639–646. https://doi.org/10.1038/sj.ijo.0801209

Linke, A. C., Olson, L., Gao, Y., Fishman, I., & Müller, R.-A. (2017). Psychotropic medication use in autism spectrum disorders may affect functional brain connectivity. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, *2*(6), 518–527. https://doi.org/10.1016/j.bpsc.2017.06.008

Lipek, T., Igel, U., Gausche, R., Kiess, W., & Grande, G. (2015). Obesogenic environments: Environmental approaches to obesity prevention. *Journal of Pediatric Endocrinology and Metabolism*, *28*(5–6), 485–495. https://doi.org/10.1515/jpem-2015-0127

Liu, F., Li, J., Wu, F., Zheng, H., Peng, Q., & Zhou, H. (2019). Altered composition and function of intestinal microbiota in autism spectrum disorders: A systematic review. *Translational Psychiatry*, *9*(1), 43. https://doi.org/10.1038/s41398-019-0389-6

Liu, X., Liu, J., Xiong, X., Yang, T., Hou, N., Liang, X., Chen, J., Cheng, Q., & Li, T. (2016). Correlation between Nutrition and Symptoms: Nutritional Survey of Children with Autism Spectrum Disorder in Chongqing, China. *Nutrients*, *8*(5). https://doi.org/10.3390/nu8050294

Llewellyn, A., Simmonds, M., Owen, C. G., & Woolacott, N. (2016). Childhood obesity as a predictor of morbidity in adulthood: A systematic review and meta-analysis. *Obesity Reviews*, *17*(1), 56–67. https://doi.org/10.1111/obr.12316

Lloyd, M., MacDonald, M., & Lord, C. (2013). Motor skills of toddlers with autism spectrum disorders. *Autism: The International Journal of Research and Practice*, *17*(2), 133–146. https://doi.org/10.1177/1362361311402230

Lucas, R. F., & Cutler, A. (2015). Dysregulated Breastfeeding Behaviors in Children Later Diagnosed With Autism. *The Journal of Perinatal Education*, *24*(3), 171–180. https://doi.org/10.1891/1058-1243.24.3.171

Lukens, C. T., & Linscheid, T. R. (2008). Development and validation of an inventory to assess mealtime behavior problems in children with autism. *Journal of Autism and Developmental Disorders*, *38*(2), 342–352. https://doi.org/10.1007/s10803-007-0401-5

Macdiarmid, J., & Blundell, J. (1998). Assessing dietary intake: Who, what and why of under-reporting. *Nutrition Research Reviews*, *11*(02), 231. https://doi.org/10.1079/NRR19980017

MacDonald, M., Lord, C., & Ulrich, D. A. (2014). Motor skills and calibrated autism severity in young children with autism spectrum disorder. *Adapted Physical Activity Quarterly: APAQ*, *31*(2), 95–105. https://doi.org/10.1123/apaq.2013-0068

MacDonald, P. E., El-kholy, W., Riedel, M. J., Salapatek, A. M. F., Light, P. E., & Wheeler, M. B. (2002). The Multiple Actions of GLP-1 on the Process of Glucose-Stimulated Insulin Secretion. *Diabetes*, *51*(suppl 3), S434–S442. https://doi.org/10.2337/diabetes.51.2007.S434

Macia, L., Tan, J., Vieira, A. T., Leach, K., Stanley, D., Luong, S., Maruya, M., Ian McKenzie, C., Hijikata, A., Wong, C., Binge, L., Thorburn, A. N., Chevalier, N., Ang, C., Marino, E., Robert, R., Offermanns, S., Teixeira, M. M., Moore, R. J., … Mackay, C. R. (2015). Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. *Nature Communications*, *6*, 6734. https://doi.org/10.1038/ncomms7734

Maïano, C., Normand, C. L., Aimé, A., & Bégarie, J. (2014). Lifestyle interventions targeting changes in body weight and composition among youth with an intellectual disability: A systematic review. *Research in Developmental Disabilities*, *35*(8), 1914–1926. https://doi.org/10.1016/j.ridd.2014.04.014

Makris, C. M., Alexendrou, A., Pasatsoutsos, G. E., Maetzis, G., Tslimigras, I. D., Guerron, D. A., & Moris, D. (2017). Ghrelin and Obesity: Identifying Gaps and Dispelling Myths. A Reappraisal. *In Vivo*, *31*(6), 1047–1050. https://doi.org/10.21873/invivo.11168

Malik, S., McGlone, F., Bedrossian, D., & Dagher, A. (2008). Ghrelin Modulates Brain Activity in Areas that Control Appetitive Behavior. *Cell Metabolism*, *7*(5), 400–409. https://doi.org/10.1016/j.cmet.2008.03.007

Maneeton, N., Maneeton, B., Putthisri, S., Woottiluk, P., Narkpongphun, A., & Srisurapanont, M. (2018). Risperidone for children and adolescents with autism spectrum disorder: A systematic review. *Neuropsychiatric Disease and Treatment*, *14*, 1811–1820. https://doi.org/10.2147/NDT.S151802

Martins, Y., Young, R. L., & Robson, D. C. (2008). Feeding and Eating Behaviors in Children with Autism and Typically Developing Children. *Journal of Autism and Developmental Disorders*, *38*(10), 1878–1887. https://doi.org/10.1007/s10803-008-0583-5

Matarese, G., Moschos, S., & Mantzoros, C. S. (2005). Leptin in Immunology. *The Journal of Immunology*, *174*(6), 3137–3142. https://doi.org/10.4049/jimmunol.174.6.3137

Matthews, C. E., Chen, K. Y., Freedson, P. S., Buchowski, M. S., Beech, B. M., Pate, R. R., & Troiano, R. P. (2008). Amount of time spent in sedentary behaviors in the United States,

2003-2004. *American Journal of Epidemiology*, *167*(7), 875–881. https://doi.org/10.1093/aje/kwm390

Maxwell-Horn, A., & Malow, B. A. (2017). Sleep in Autism. *Seminars in Neurology*, *37*(04), 413–418. https://doi.org/10.1055/s-0037-1604353

Mayer, E. A., Padua, D., & Tillisch, K. (2014). Altered brain-gut axis in autism: Comorbidity or causative mechanisms? *BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology*, *36*(10), 933–939. https://doi.org/10.1002/bies.201400075

Mayes, S. D., & Zickgraf, H. (2019). Atypical eating behaviors in children and adolescents with autism, ADHD, other disorders, and typical development. *Research in Autism Spectrum Disorders*, *64*, 76–83. https://doi.org/10.1016/j.rasd.2019.04.002

Mazefsky, C. A., Borue, X., Day, T. N., & Minshew, N. J. (2014). Emotion Regulation Patterns in Adolescents With High-Functioning Autism Spectrum Disorder: Comparison to Typically Developing Adolescents and Association With Psychiatric Symptoms. *Autism Research : Official Journal of the International Society for Autism Research*, *7*(3), 344–354. https://doi.org/10.1002/aur.1366

Mazor, R., Friedmann-Morvinski, D., Alsaigh, T., Kleifeld, O., Kistler, E. B., Rousso-Noori, L., Huang, C., Li, J. B., Verma, I. M., & Schmid-Schönbein, G. W. (2018). Cleavage of the leptin receptor by matrix metalloproteinase-2 promotes leptin resistance and obesity in mice. *Science Translational Medicine*, *10*(455). https://doi.org/10.1126/scitranslmed.aah6324

Mazurek, M. O., Shattuck, P. T., Wagner, M., & Cooper, B. P. (2012). Prevalence and correlates of screen-based media use among youths with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *42*(8), 1757–1767. https://doi.org/10.1007/s10803-011-1413-8

Mazurek, M. O., & Wenstrup, C. (2013). Television, Video Game and Social Media Use Among Children with ASD and Typically Developing Siblings. *Journal of Autism and Developmental Disorders*, *43*(6), 1258–1271. https://doi.org/10.1007/s10803-012-1659-9

McCoy, S. M., Jakicic, J. M., & Gibbs, B. B. (2016). Comparison of Obesity, Physical Activity, and Sedentary Behaviors Between Adolescents With Autism Spectrum Disorders and Without. *Journal of Autism and Developmental Disorders*, *46*(7), 2317–2326. https://doi.org/10.1007/s10803-016-2762-0

McCrory, M. A., Burke, A., & Roberts, S. B. (2012). Dietary (sensory) variety and energy balance. *Physiology & Behavior*, *107*(4), 576–583. https://doi.org/10.1016/j.physbeh.2012.06.012

McElhanon, B. O., McCracken, C., Karpen, S., & Sharp, W. G. (2014). Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis. *PEDIATRICS*, *133*(5), 872–883. https://doi.org/10.1542/peds.2013-3995

McPhillips, M., Finlay, J., Bejerot, S., & Hanley, M. (2014). Motor deficits in children with autism spectrum disorder: A cross-syndrome study. *Autism Research: Official Journal of the International Society for Autism Research*, *7*(6), 664–676. https://doi.org/10.1002/aur.1408

Meltzer, H. Y., & Massey, B. W. (2011). The role of serotonin receptors in the action of atypical antipsychotic drugs. *Current Opinion in Pharmacology*, *11*(1), 59–67. https://doi.org/10.1016/j.coph.2011.02.007

Mennella, J. A., & Bobowski, N. K. (2015). The sweetness and bitterness of childhood: Insights from basic research on taste preferences. *Physiology & Behavior*, *152*(0 0), 502–507. https://doi.org/10.1016/j.physbeh.2015.05.015

Miller, G. D. (2017). Appetite Regulation: Hormones, Peptides, and Neurotransmitters and Their Role in Obesity. *American Journal of Lifestyle Medicine*, *13*(6), 586–601. https://doi.org/10.1177/1559827617716376

Ming, X., Stein, T. P., Brimacombe, M., Johnson, W. G., Lambert, G. H., & Wagner, G. C. (2005). Increased excretion of a lipid peroxidation biomarker in autism. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *73*(5), 379–384. https://doi.org/10.1016/j.plefa.2005.06.002

Mirmonsef, P., Zariffard, M. R., Gilbert, D., Makinde, H., Landay, A. L., & Spear, G. T. (2012). Short Chain Fatty Acids Induce Pro-Inflammatory Cytokine Production Alone And In Combination With Toll-like Receptor Ligands. *American Journal of Reproductive Immunology*, *67*(5), 391–400. https://doi.org/10.1111/j.1600-0897.2011.01089.x

Mittelman, S. D., Klier, K., Braun, S., Azen, C., Geffner, M. E., & Buchanan, T. A. (2010). Obese Adolescents Show Impaired Meal Responses of the Appetite-Regulating Hormones Ghrelin and PYY. *Obesity*, *18*(5), 918–925. https://doi.org/10.1038/oby.2009.499

Mohammed, M. A., Moles, R. J., & Chen, T. F. (2016). Medication-related burden and patients' lived experience with medicine: A systematic review and metasynthesis of qualitative studies. *BMJ Open*, *6*(2), e010035. https://doi.org/10.1136/bmjopen-2015-010035

Morrison, D. J., & Preston, T. (2016). Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*, *7*(3), 189–200. https://doi.org/10.1080/19490976.2015.1134082

Morton, G. J., Blevins, J. E., Williams, D. L., Niswender, K. D., Gelling, R. W., Rhodes, C. J., Baskin, D. G., & Schwartz, M. W. (2005). Leptin action in the forebrain regulates the hindbrain response to satiety signals. *The Journal of Clinical Investigation*, *115*(3), 703–710. https://doi.org/10.1172/JCI22081

Mughal, S., Faizy, R. M., & Saadabadi, A. (2020). Autism Spectrum Disorder (Regressive Autism, Child Disintegrative Disorder). In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK525976/

Munk, D. D., & Repp, A. C. (1994). Behavioral Assessment of Feeding Problems of Individuals with Severe Disabilities. *Journal of Applied Behavior Analysis*, *27*(2), 241–250. https://doi.org/10.1901/jaba.1994.27-241

Murphy, E. F., Cotter, P. D., Healy, S., Marques, T. M., O'Sullivan, O., Fouhy, F., Clarke, S. F., O'Toole, P. W., Quigley, E. M., Stanton, C., Ross, P. R., O'Doherty, R. M., & Shanahan, F. (2010). Composition and energy harvesting capacity of the gut microbiota: Relationship to diet, obesity and time in mouse models. *Gut*, *59*(12), 1635–1642. https://doi.org/10.1136/gut.2010.215665

Murray, M. L., Hsia, Y., Glaser, K., Simonoff, E., Murphy, D. G. M., Asherson, P. J., Eklund, H., & Wong, I. C. K. (2014). Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology*, *231*(6), 1011–1021. https://doi.org/10.1007/s00213-013-3140-7

Must, A., Phillips, S., Curtin, C., & Bandini, L. G. (2015). Barriers to Physical Activity in Children With Autism Spectrum Disorders: Relationship to Physical Activity and Screen Time. *Journal of Physical Activity & Health*, *12*(4), 529–534. https://doi.org/10.1123/jpah.2013-0271

My Health Alberta & Healthwise Staff. (2018). *Routine Checkups*. Retrieved May 1, 2020, from https://myhealth.alberta.ca:443/Health/Pages/conditions.aspx?hwid=ue5162

Myers, M. G., Leibel, R. L., Seeley, R. J., & Schwartz, M. W. (2010). Obesity and Leptin Resistance: Distinguishing Cause from Effect. *Trends in Endocrinology and Metabolism: TEM*, *21*(11), 643–651. https://doi.org/10.1016/j.tem.2010.08.002

Nakazato, M., Murakami, N., Date, Y., Kojima, M., Matsuo, H., Kangawa, K., & Matsukura, S. (2001). A role for ghrelin in the central regulation of feeding. *Nature*, *409*(6817), 194–198. https://doi.org/10.1038/35051587

Narang, I., & Mathew, J. L. (2012). Childhood obesity and obstructive sleep apnea. *Journal of Nutrition and Metabolism*, *2012*, 134202. https://doi.org/10.1155/2012/134202

Naska, A., Lagiou, A., & Lagiou, P. (2017). Dietary assessment methods in epidemiological research: Current state of the art and future prospects. *F1000Research*, *6*. https://doi.org/10.12688/f1000research.10703.1

National Institute of Mental Health. (2019, May 6). Autism spectrum disorder. *US Department of Health and Human Services*. https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml

Nauck, M. A., Niedereichholz, U., Ettler, R., Holst, J. J., Ørskov, C., Ritzel, R., & Schmiegel, W. H. (1997). Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *American Journal of Physiology-Endocrinology and Metabolism*, *273*(5), E981–E988. https://doi.org/10.1152/ajpendo.1997.273.5.E981

Nihalani, N., Schwartz, T. L., Siddiqui, U. A., & Megna, J. L. (2011). Weight gain, obesity, and psychotropic prescribing. *Journal of Obesity*, *2011*, 893629. https://doi.org/10.1155/2011/893629

Ofner, M., Coles, A., Decou, M. L., Do, M. T., Bienek, A., Snider, J., & Ugnat, A.M. Public Healthy Agency of Canada (2018, March 29). *Autism spectrum disorder among children and youth in Canada 2018: A report of the National Autism Spectrum Disorder Surveillance System.* Aem. https://www.canada.ca/en/public-health/services/publications/diseases-conditions/autism-spectrum-disorder-children-youth-canada-2018.html

Ohman-Hanson, R. A., Cree-Green, M., Kelsey, M. M., Bessesen, D. H., Sharp, T. A., Pyle, L., Pereira, R. I., & Nadeau, K. J. (2016). Ethnic and Sex Differences in Adiponectin: From Childhood to Adulthood. *The Journal of Clinical Endocrinology and Metabolism*, *101*(12), 4808–4815. https://doi.org/10.1210/jc.2016-1137

Olukotun, O., & Seal, N. (2015). A Systematic Review of Dietary Assessment Tools for Children Age 11 Years and Younger. *ICAN: Infant, Child, & Adolescent Nutrition*, *7*(3), 139–147. https://doi.org/10.1177/1941406415584819

Onore, C., Careaga, M., & Ashwood, P. (2012). The role of immune dysfunction in the pathophysiology of autism. *Brain, Behavior, and Immunity*, *26*(3), 383–392. https://doi.org/10.1016/j.bbi.2011.08.007

Ortega-García, J. A., Kloosterman, N., Alvarez, L., Tobarra-Sánchez, E., Cárceles-Álvarez, A., Pastor-Valero, R., López-Hernández, F. A., Sánchez-Solis, M., & Claudio, L. (2018). Full Breastfeeding and Obesity in Children: A Prospective Study from Birth to 6 Years. *Childhood Obesity*, *14*(5), 327–337. https://doi.org/10.1089/chi.2017.0335

Ouchi, N., & Walsh, K. (2007). Adiponectin as an anti-inflammatory factor. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, *380*(1–2), 24–30. https://doi.org/10.1016/j.cca.2007.01.026

Owen, N., Sparling, P. B., Healy, G. N., Dunstan, D. W., & Matthews, C. E. (2010). Sedentary Behavior: Emerging Evidence for a New Health Risk. *Mayo Clinic Proceedings*, *85*(12), 1138–1141. https://doi.org/10.4065/mcp.2010.0444

Park, H. S., Lee, K.-U., Kim, Y. S., & Park, C. Y. (2005). Relationships between fasting plasma ghrelin levels and metabolic parameters in children and adolescents. *Metabolism*, *54*(7), 925–929. https://doi.org/10.1016/j.metabol.2005.02.007

Park, H.-K., & Ahima, R. S. (2015). Physiology of leptin: Energy homeostasis, neuroendocrine function and metabolism. *Metabolism: Clinical and Experimental*, *64*(1), 24–34. https://doi.org/10.1016/j.metabol.2014.08.004

Park, S. Y., Cervesi, C., Galling, B., Molteni, S., Walyzada, F., Ameis, S. H., Gerhard, T., Olfson, M., & Correll, C. U. (2016). Antipsychotic Use Trends in Youth With Autism Spectrum Disorder and/or Intellectual Disability: A Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(6), 456-468.e4. https://doi.org/10.1016/j.jaac.2016.03.012

Patel, S. R., & Hu, F. B. (2008). Short sleep duration and weight gain: A systematic review. *Obesity (Silver Spring, Md.)*, *16*(3), 643–653. https://doi.org/10.1038/oby.2007.118

Paz-Filho, G., Mastronardi, C., Wong, M.-L., & Licinio, J. (2012). Leptin therapy, insulin sensitivity, and glucose homeostasis. *Indian Journal of Endocrinology and Metabolism*, *16*(Suppl 3), S549–S555. https://doi.org/10.4103/2230-8210.105571

Perelló, M., & Zigman, J. M. (2012). The role of ghrelin in reward-based eating. *Biological Psychiatry*, *72*(5), 347–353. https://doi.org/10.1016/j.biopsych.2012.02.016

Perry, B., & Wang, Y. (2012). Appetite regulation and weight control: The role of gut hormones. *Nutrition & Diabetes*, *2*(1), e26. https://doi.org/10.1038/nutd.2011.21

Pietiläinen, K. H., Kaprio, J., Borg, P., Plasqui, G., Yki-Järvinen, H., Kujala, U. M., Rose, R. J., Westerterp, K. R., & Rissanen, A. (2008). Physical inactivity and obesity: A vicious circle. *Obesity (Silver Spring, Md.)*, *16*(2), 409–414. https://doi.org/10.1038/oby.2007.72

Plum, L., Belgardt, B. F., & Brüning, J. C. (2006). Central insulin action in energy and glucose homeostasis. *The Journal of Clinical Investigation*, *116*(7), 1761–1766. https://doi.org/10.1172/JCI29063

Pringsheim, T., Panagiotopoulos, C., Davidson, J., & Ho, J. (2011). Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth. *Paediatrics & Child Health*, *16*(9), 581–589.

Prosperi, M., Santocchi, E., Balboni, G., Narzisi, A., Bozza, M., Fulceri, F., Apicella, F., Igliozzi, R., Cosenza, A., Tancredi, R., Calderoni, S., & Muratori, F. (2017). Behavioral Phenotype of ASD Preschoolers with Gastrointestinal Symptoms or Food Selectivity. *Journal of Autism and Developmental Disorders*, *47*(11), 3574–3588. https://doi.org/10.1007/s10803-017-3271-5

Puglisi, L. M., Okely, A. D., Pearson, P., & Vialle, W. (2010). Barriers to increasing physical activity and limiting small screen recreation among obese children. *Obesity Research & Clinical Practice*, *4*(1), e33–e40. https://doi.org/10.1016/j.orcp.2009.07.004

Puhl, R. M., Luedicke, J., & Heuer, C. (2011). Weight-Based Victimization Toward Overweight Adolescents: Observations and Reactions of Peers. *Journal of School Health*, *81*(11), 696–703. https://doi.org/10.1111/j.1746-1561.2011.00646.x

Raghavan, R., Fallin, M. D., Hong, X., Wang, G., Ji, Y., Stuart, E. A., Paige, D., & Wang, X. (2019). Cord and Early Childhood Plasma Adiponectin Levels and Autism Risk: A Prospective Birth Cohort Study. *Journal of Autism and Developmental Disorders*, *49*(1), 173–184. https://doi.org/10.1007/s10803-018-3688-5

Raghavan, R., Zuckerman, B., Hong, X., Wang, G., Yuelong, Ji, Paige, D., DiBari, J., Zhang, C., Fallin, M. D., & Wang, X. (2018). Fetal and infancy growth pattern, cord and early childhood plasma leptin, and development of autism spectrum disorder in the Boston birth cohort. *Autism Research*, *11*(10), 1416–1431. https://doi.org/10.1002/aur.2011

Ramos-Molina, B., Molina-Vega, M., Fernández-García, J. C., & Creemers, J. W. (2018). Hyperphagia and Obesity in Prader–Willi Syndrome: PCSK1 Deficiency and Beyond? *Genes*, *9*(6). https://doi.org/10.3390/genes9060288

Reekie, J., Hosking, S. P. M., Prakash, C., Kao, K.-T., Juonala, M., & Sabin, M. A. (2015). The effect of antidepressants and antipsychotics on weight gain in children and adolescents: Antidepressants/psychotics and weight in youth. *Obesity Reviews*, *16*(7), 566–580. https://doi.org/10.1111/obr.12284

Reynolds, L. C., Inder, T. E., Neil, J. J., Pineda, R. G., & Rogers, C. E. (2014). Maternal obesity and increased risk for autism and developmental delay among very preterm infants. *Journal of Perinatology*, *34*(9), 688–692. https://doi.org/10.1038/jp.2014.80

Riccio, M. P., Franco, C., Negri, R., Ferrentino, R. I., Maresca, R., D'alterio, E., Greco, L., & Bravaccio, C. (2018). Is food refusal in autistic children related to TAS2R38 genotype? *Autism Research*, *11*(3), 531–538. https://doi.org/10.1002/aur.1912

Rodrigues, D. H., Rocha, N. P., Sousa, L. F. da C., Barbosa, I. G., Kummer, A., & Teixeira, A. L. (2014). Changes in adipokine levels in autism spectrum disorders. *Neuropsychobiology*, *69*(1), 6–10. https://doi.org/10.1159/000356234

Rodriguez, J. A., Bruggeman, E. C., Mani, B. K., Osborne-Lawrence, S., Lord, C. C., Roseman, H. F., Viroslav, H. L., Vijayaraghavan, P., Metzger, N. P., Gupta, D., Shankar, K., Pietra, C., Liu, C., & Zigman, J. M. (2018). Ghrelin Receptor Agonist Rescues Excess Neonatal Mortality in a Prader-Willi Syndrome Mouse Model. *Endocrinology*, *159*(12), 4006–4022. https://doi.org/10.1210/en.2018-00801

Roerig, J. L., Steffen, K. J., & Mitchell, J. E. (2011). Atypical Antipsychotic-Induced Weight Gain. *CNS Drugs*, *25*(12), 1035–1059. https://doi.org/10.2165/11596300-000000000-00000

Romero, M., Aguilar, J. M., Del-Rey-Mejías, Á., Mayoral, F., Rapado, M., Peciña, M., Barbancho, M. Á., Ruiz-Veguilla, M., & Lara, J. P. (2016). Psychiatric comorbidities in autism spectrum disorder: A comparative study between DSM-IV-TR and DSM-5 diagnosis. *International Journal of Clinical and Health Psychology*, *16*(3), 266–275. https://doi.org/10.1016/j.ijchp.2016.03.001

Rueda-Clausen, C. F., Lahera, V., Calderón, J., Bolivar, I. C., Castillo, V. R., Gutiérrez, M., Carreño, M., Oubiña, M. del P., Cachofeiro, V., & López-Jaramillo, P. (2010). The presence of abdominal obesity is associated with changes in vascular function independently of other cardiovascular risk factors. *International Journal of Cardiology*, *139*(1), 32–41. https://doi.org/10.1016/j.ijcard.2008.09.005

Sahu, A. (2003). Leptin signaling in the hypothalamus: Emphasis on energy homeostasis and leptin resistance. *Frontiers in Neuroendocrinology*, *24*(4), 225–253. https://doi.org/10.1016/j.yfrne.2003.10.001

Sanchez, C. E., Barry, C., Sabhlok, A., Russell, K., Majors, A., Kollins, S. H., & Fuemmeler, B. F. (2018). Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: A meta-analysis. *Obesity Reviews*, *19*(4), 464–484. https://doi.org/10.1111/obr.12643

Sanchez-Garrido, M. A., & Tena-Sempere, M. (2013). Metabolic control of puberty: Roles of leptin and kisspeptins. *Hormones and Behavior*, *64*(2), 187–194. https://doi.org/10.1016/j.yhbeh.2013.01.014

Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Hultman, C., Larsson, H., & Reichenberg, A. (2017). The Heritability of Autism Spectrum Disorder. *JAMA*, *318*(12), 1182–1184. https://doi.org/10.1001/jama.2017.12141

Santos, V. V. dos, Rodrigues, A. L. S., Lima, T. C. D., Barioglio, S. R. de, & Prediger, R. R.-V. and R. D. (2013, October 31). *Ghrelin as a Neuroprotective and Palliative Agent in Alzheimer's and Parkinson's Disease*. Current Pharmaceutical Design. http://www.eurekaselect.com/111530/article

Sarker, H., Anderson, L. N., Borkhoff, C. M., Abreo, K., Tremblay, M. S., Lebovic, G., Maguire, J. L., Parkin, P. C., & Birken, C. S. (2015). Validation of parent-reported physical activity and sedentary time by accelerometry in young children. *BMC Research Notes*, *8*. https://doi.org/10.1186/s13104-015-1648-0

Sathe, N., Andrews, J. C., McPheeters, M. L., & Warren, Z. E. (2017). Nutritional and Dietary Interventions for Autism Spectrum Disorder: A Systematic Review. *Pediatrics*, *139*(6), e20170346. https://doi.org/10.1542/peds.2017-0346

Schuit, F. C., Huypens, P., Heimberg, H., & Pipeleers, D. G. (2001). Glucose Sensing in Pancreatic β-Cells: A Model for the Study of Other Glucose-Regulated Cells in Gut, Pancreas, and Hypothalamus. *Diabetes*, *50*(1), 1–11. https://doi.org/10.2337/diabetes.50.1.1

Sea, M. M.-M., Woo, J., Tong, P. C.-Y., Chow, C.-C., & Chan, J. C.-N. (2004). Associations between Food Variety and Body Fatness in Hong Kong Chinese Adults. *Journal of the American College of Nutrition*, *23*(5), 404–413. https://doi.org/10.1080/07315724.2004.10719385

Serdarevic, F., Ghassabian, A., van Batenburg-Eddes, T., White, T., Blanken, L. M. E., Jaddoe, V. W. V., Verhulst, F. C., & Tiemeier, H. (2017). Infant muscle tone and childhood autistic traits: A longitudinal study in the general population. *Autism Research: Official Journal of the International Society for Autism Research*, *10*(5), 757–768. https://doi.org/10.1002/aur.1739

Shafai, T., Mustafa, M., Hild, T., Mulari, J., & Curtis, A. (2014). The association of early weaning and formula feeding with autism spectrum disorders. *Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine*, *9*(5), 275–276. https://doi.org/10.1089/bfm.2013.0104

Sharma, J. R., Arieff, Z., Sagar, S., & Kaur, M. (2012). Autism and obesity: Prevalence, molecular basis and potential therapies. *Autism Insights*, 1. https://doi.org/10.4137/AUI.S9138

Sharon, G., Cruz, N. J., Kang, D.-W., Gandal, M. J., Wang, B., Kim, Y.-M., Zink, E. M., Casey, C. P., Taylor, B. C., Lane, C. J., Bramer, L. M., Isern, N. G., Hoyt, D. W., Noecker, C., Sweredoski, M. J., Moradian, A., Borenstein, E., Jansson, J. K., Knight, R., … Mazmanian, S. K. (2019). Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. *Cell*, *177*(6), 1600-1618.e17. https://doi.org/10.1016/j.cell.2019.05.004

Sharp, W. G., Berry, R. C., McCracken, C., Nuhu, N. N., Marvel, E., Saulnier, C. A., Klin, A., Jones, W., & Jaquess, D. L. (2013). Feeding Problems and Nutrient Intake in Children with Autism Spectrum Disorders: A Meta-analysis and Comprehensive Review of the Literature. *Journal of Autism and Developmental Disorders*, *43*(9), 2159–2173. https://doi.org/10.1007/s10803-013-1771-5

Shiiya, T., Nakazato, M., Mizuta, M., Date, Y., Mondal, M. S., Tanaka, M., Nozoe, S.-I., Hosoda, H., Kangawa, K., & Matsukura, S. (2002). Plasma Ghrelin Levels in Lean and Obese Humans and the Effect of Glucose on Ghrelin Secretion. *The Journal of Clinical Endocrinology & Metabolism*, *87*(1), 240–244. https://doi.org/10.1210/jcem.87.1.8129

Shimizu, H., Shimomura, Y., Hayashi, R., Ohtani, K., Sato, N., Futawatari, T., & Mori, M. (1997). Serum leptin concentration is associated with total body fat mass, but not abdominal fat distribution. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity*, *21*(7), 536–541.

Shinawi, M., Sahoo, T., Maranda, B., Skinner, S. A., Skinner, C., Chinault, C., Zascavage, R., Peters, S. U., Patel, A., Stevenson, R. E., & Beaudet, A. L. (2011). 11p14.1 microdeletions associated with ADHD, autism, developmental delay, and obesity. *American Journal of Medical Genetics. Part A*, *155A*(6), 1272–1280. https://doi.org/10.1002/ajmg.a.33878

Shmaya, Y., Eilat-Adar, S., Leitner, Y., Reif, S., & Gabis, L. (2015). Nutritional deficiencies and overweight prevalence among children with autism spectrum disorder. *Research in Developmental Disabilities*, *38*, 1–6. https://doi.org/10.1016/j.ridd.2014.11.020

Siniscalco, D., Brigida, A. L., & Antonucci, N. (2018). Autism and neuro-immune-gut link. *Molecular 2018, Vol. 5, Pages 166-172*. https://doi.org/10.3934/molsci.2018.2.166

Siniscalco, D., Schultz, S., Brigida, A. L., & Antonucci, N. (2018). Inflammation and Neuro-Immune Dysregulations in Autism Spectrum Disorders. *Pharmaceuticals*, *11*(2). https://doi.org/10.3390/ph11020056

Soliman, A. T., Yasin, M., & Kassem, A. (2012). Leptin in pediatrics: A hormone from adipocyte that wheels several functions in children. *Indian Journal of Endocrinology and Metabolism*, *16*(Suppl 3), S577–S587. https://doi.org/10.4103/2230-8210.105575

Song, H. J., Oh, S., Quan, S., Ryu, O.-H., Jeong, J.-Y., Hong, K.-S., & Kim, D.-H. (2014). Gender differences in adiponectin levels and body composition in older adults: Hallym aging study. *BMC Geriatrics*, *14*, 8. https://doi.org/10.1186/1471-2318-14-8

Sørensen, T. I., & Stunkard, A. J. (1993). Does obesity run in families because of genes? An adoption study using silhouettes as a measure of obesity. *Acta Psychiatrica Scandinavica. Supplementum*, *370*, 67–72.

Spencer, D., Marshall, J., Post, B., Kulakodlu, M., Newschaffer, C., Dennen, T., Azocar, F., & Jain, A. (2013). Psychotropic Medication Use and Polypharmacy in Children With Autism Spectrum Disorders. *Pediatrics*, *132*(5), 833–840. https://doi.org/10.1542/peds.2012-3774

Srisawasdi, P., Vanwong, N., Hongkaew, Y., Puangpetch, A., Vanavanan, S., Intachak, B., Ngamsamut, N., Limsila, P., Sukasem, C., & Kroll, M. H. (2017). Impact of risperidone on leptin and insulin in children and adolescents with autistic spectrum disorders. *Clinical Biochemistry*, *50*(12), 678–685. https://doi.org/10.1016/j.clinbiochem.2017.02.003

Stanish, H. I., Curtin, C., Must, A., Phillips, S., Maslin, M., & Bandini, L. G. (2017). Physical Activity Levels, Frequency, and Type Among Adolescents with and Without Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *47*(3), 785–794. https://doi.org/10.1007/s10803-016-3001-4

Steinberger Julia, & Daniels Stephen R. (2003). Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children. *Circulation*, *107*(10), 1448–1453. https://doi.org/10.1161/01.CIR.0000060923.07573.F2

Steinman, G. (2006). Can the chance of having twins be modified by diet. *Lancet*, *367*(9521), 1461–1462. https://doi.org/10.1016/S0140-6736(06)68623-6

Stolzer, J. M. (2011). Breastfeeding and obesity: A meta-analysis. *Open Journal of Preventive Medicine*, *01*, 88. https://doi.org/10.4236/ojpm.2011.13013

Stough, C. O., Dreyer Gillette, M. L., Roberts, M. C., Jorgensen, T. D., & Patton, S. R. (2015). Mealtime Behaviors Associated with Consumption of Unfamiliar Foods by Young Children with Autism Spectrum Disorder. *Appetite*, *95*, 324–333. https://doi.org/10.1016/j.appet.2015.07.019

Strati, F., Cavalieri, D., Albanese, D., De Felice, C., Donati, C., Hayek, J., Jousson, O., Leoncini, S., Renzi, D., Calabrò, A., & De Filippo, C. (2017). New evidences on the altered gut microbiota in autism spectrum disorders. *Microbiome*, *5*(1), 24. https://doi.org/10.1186/s40168-017-0242-1

Stylianou, C., Galli-Tsinopoulou, A., Farmakiotis, D., Rousso, I., Karamouzis, M., Koliakos, G., & Nousia-Arvanitakis, S. (2007). Ghrelin and leptin levels in obese adolescents. Relationship with body fat and insulin resistance. *Hormones (Athens, Greece)*, *6*(4), 295–303. https://doi.org/10.14310/horm.2002.1111025

Styne, D. M., Arslanian, S. A., Connor, E. L., Farooqi, I. S., Murad, M. H., Silverstein, J. H., & Yanovski, J. A. (2017). Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism*, *102*(3), 709–757. https://doi.org/10.1210/jc.2016-2573

Subar, A. F., Freedman, L. S., Tooze, J. A., Kirkpatrick, S. I., Boushey, C., Neuhouser, M. L., Thompson, F. E., Potischman, N., Guenther, P. M., Tarasuk, V., Reedy, J., & Krebs-Smith, S. M. (2015). Addressing current criticism regarding the value of self-report dietary data. *Journal of Nutrition*, *145*(12), 2639–2645. https://doi.org/10.3945/jn.115.219634

Tang-Christensen, M., Larsen, P. J., Goke, R., Fink-Jensen, A., Jessop, D. S., Moller, M., & Sheikh, S. P. (1996). Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *271*(4), R848–R856. https://doi.org/10.1152/ajpregu.1996.271.4.R848

Tareen, R. S., & Kamboj, M. K. (2012). Role of endocrine factors in autistic spectrum disorders. *Pediatric Clinics of North America*, *59*(1), 75–88, x. https://doi.org/10.1016/j.pcl.2011.10.013

Taylor, V. H. (2008). Implementing antiobesity treatment in a patient with a mood disorder. *Journal of Psychiatry & Neuroscience : JPN*, *33*(6), E1–E2.

Thivel, D., Tremblay, A., Genin, P. M., Panahi, S., Rivière, D., & Duclos, M. (2018). Physical Activity, Inactivity, and Sedentary Behaviors: Definitions and Implications in Occupational Health. *Frontiers in Public Health*, *6*. https://doi.org/10.3389/fpubh.2018.00288

Thomas, P., Zahorodny, W., Peng, B., Kim, S., Jani, N., Halperin, W., & Brimacombe, M. (2012). The association of autism diagnosis with socioeconomic status. *Autism: The International Journal of Research and Practice*, *16*(2), 201–213. https://doi.org/10.1177/1362361311413397

Tomiyama, A. J., Carr, D., Granberg, E. M., Major, B., Robinson, E., Sutin, A. R., & Brewis, A. (2018). How and why weight stigma drives the obesity 'epidemic' and harms health. *BMC Medicine*, *16*(1), 123. https://doi.org/10.1186/s12916-018-1116-5

Tonhajzerova, I., Ondrejka, I., Mestanik, M., Mikolka, P., Hrtanek, I., Mestanikova, A., Bujnakova, I., & Mokra, D. (2015). Inflammatory Activity in Autism Spectrum Disorder. *Advances in Experimental Medicine and Biology*, *861*, 93–98. https://doi.org/10.1007/5584_2015_145

Tschöp, M., Smiley, D. L., & Heiman, M. L. (2000). Ghrelin induces adiposity in rodents. *Nature*, *407*(6806), 908–913. https://doi.org/10.1038/35038090

Tschöp, M., Weyer, C., Tataranni, P. A., Devanarayan, V., Ravussin, E., & Heiman, M. L. (2001). Circulating Ghrelin Levels Are Decreased in Human Obesity. *Diabetes*, *50*(4), 707–709. https://doi.org/10.2337/diabetes.50.4.707

Tseng, P.-T., Chen, Y.-W., Stubbs, B., Carvalho, A. F., Whiteley, P., Tang, C.-H., Yang, W.-C., Chen, T.-Y., Li, D.-J., Chu, C.-S., Yang, W.-C., Liang, H.-Y., Wu, C.-K., Yen, C.-F., & Lin, P.-Y. (2019). Maternal breastfeeding and autism spectrum disorder in

children: A systematic review and meta-analysis. *Nutritional Neuroscience*, *22*(5), 354–362. https://doi.org/10.1080/1028415X.2017.1388598

Tsilioni, I., Patel, A. B., Pantazopoulos, H., Berretta, S., Conti, P., Leeman, S. E., & Theoharides, T. C. (2019). IL-37 is increased in brains of children with autism spectrum disorder and inhibits human microglia stimulated by neurotensin. *Proceedings of the National Academy of Sciences*, *116*(43), 21659–21665. https://doi.org/10.1073/pnas.1906817116

Umer, A., Hamilton, C., Britton, C. M., Mullett, M. D., John, C., Neal, W., & Lilly, C. L. (2015). Association between Breastfeeding and Childhood Obesity: Analysis of a Linked Longitudinal Study of Rural Appalachian Fifth-Grade Children. *Childhood Obesity*, *11*(4), 449–455. https://doi.org/10.1089/chi.2015.0026

U.S. Department of Health and Human Services. (2019, May 28). *Current guidelines.* https://health.gov/paguidelines/second-edition/

Valdes, A. M., Walter, J., Segal, E., & Spector, T. D. (2018). Role of the gut microbiota in nutrition and health. *BMJ*, *361*, k2179. https://doi.org/10.1136/bmj.k2179

Van der Klaauw, A. A., Keogh, J. M., Henning, E., Trowse, V. M., Dhillo, W. S., Ghatei, M. A., & Farooqi, I. S. (2013). High protein intake stimulates postprandial GLP1 and PYY release. Obesity (19307381), 21(8), 1602–1607. https://doi-org.login.ezproxy.library.ualberta.ca/10.1002/oby.20154

Via, M. (2012). The Malnutrition of Obesity: Micronutrient Deficiencies That Promote Diabetes. *ISRN Endocrinology*, *2012*. https://doi.org/10.5402/2012/103472

Vrang, N., Madsen, A. N., Tang-Christensen, M., Hansen, G., & Larsen, P. J. (2006). PYY(3–36) reduces food intake and body weight and improves insulin sensitivity in rodent models of diet-induced obesity. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *291*(2), R367–R375. https://doi.org/10.1152/ajpregu.00726.2005

Walls, M., Broder-Fingert, S., Feinberg, E., Drainoni, M.-L., & Bair-Merritt, M. (2018). Prevention and Management of Obesity in Children with Autism Spectrum Disorder among Primary Care Pediatricians. *Journal of Autism and Developmental Disorders*, *48*(7), 2408–2417. https://doi.org/10.1007/s10803-018-3494-0

Walters, R. G., Jacquemont, S., Valsesia, A., de Smith, A. J., Martinet, D., Andersson, J., Falchi, M., Chen, F., Andrieux, J., Lobbens, S., Delobel, B., Stutzmann, F., El-Sayed Moustafa, J. S., Chèvre, J.-C., Lecoeur, C., Vatin, V., Bouquillon, S., Buxton, J. L., Boute, O., … Beckmann, J. S. (2010). A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. *Nature*, *463*(7281), 671–675. https://doi.org/10.1038/nature08727

Wan, H., Zhang, C., Li, H., Luan, S., & Liu, C. (2018). Association of maternal diabetes with autism spectrum disorders in offspring. *Medicine*, *97*(2). https://doi.org/10.1097/MD.0000000000009438

Wan, Y., Wang, F., Yuan, J., Li, J., Jiang, D., Zhang, J., Huang, T., Zheng, J., Mann, J., & Li, D. (2017). Effects of Macronutrient Distribution on Weight and Related Cardiometabolic Profile in Healthy Non-Obese Chinese: A 6-month, Randomized Controlled-Feeding Trial. *EBioMedicine*, *22*, 200–207. https://doi.org/10.1016/j.ebiom.2017.06.017

Wang, L. W., Tancredi, D. J., & Thomas, D. W. (2011). The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members. *Journal of Developmental and Behavioral Pediatrics: JDBP*, *32*(5), 351–360. https://doi.org/10.1097/DBP.0b013e31821bd06a

Wang, Y., Min, J., Khuri, J., & Li, M. (2017). A Systematic Examination of the Association between Parental and Child Obesity across Countries123. *Advances in Nutrition*, *8*(3), 436–448. https://doi.org/10.3945/an.116.013235

Weihrauch-Blüher, S., Schwarz, P., & Klusmann, J.-H. (2019). Childhood obesity: Increased risk for cardiometabolic disease and cancer in adulthood. *Metabolism: Clinical and Experimental*, *92*, 147–152. https://doi.org/10.1016/j.metabol.2018.12.001

Westerterp, K. R. (2017). Doubly labelled water assessment of energy expenditure: Principle, practice, and promise. *European Journal of Applied Physiology*, *117*(7), 1277–1285. https://doi.org/10.1007/s00421-017-3641-x

Whatmore, A. J., Hall, C. M., Jones, J., Westwood, M., & Clayton, P. E. (2003). Ghrelin concentrations in healthy children and adolescents. *Clinical Endocrinology*, *59*(5), 649–654. https://doi.org/10.1046/j.1365-2265.2003.01903.x

World Health Organization (2020). WHO Physical activity and young people. Retrieved June 2, 2019, from https://www.who.int/dietphysicalactivity/factsheet_young_people/en/

World Health Organization (2003). Controlling the Global Obesity Pandemic. WHO; World Health Organization, https://www.who.int/nutrition/topics/obesity/en/

Wilasco, M. I. A., Goldani, H. A. S., Dornelles, C. T. L., Maurer, R. L., Kieling, C. O., Porowski, M., & Silveira, T. R. (2012). Ghrelin, leptin and insulin in healthy children: Relationship with anthropometry, gender, and age distribution. *Regulatory Peptides*, *173*(1), 21–26. https://doi.org/10.1016/j.regpep.2011.08.013

Willemsen, L. E. M., Koetsier, M. A., van Deventer, S. J. H., & van Tol, E. a. F. (2003). Short chain fatty acids stimulate epithelial mucin 2 expression through differential effects on prostaglandin E(1) and E(2) production by intestinal myofibroblasts. *Gut*, *52*(10), 1442–1447. https://doi.org/10.1136/gut.52.10.1442

Williams, B. L., Hornig, M., Buie, T., Bauman, M. L., Paik, M. C., Wick, I., Bennett, A., Jabado, O., Hirschberg, D. L., & Lipkin, W. I. (2011). Impaired Carbohydrate Digestion and Transport and Mucosal Dysbiosis in the Intestines of Children with Autism and Gastrointestinal Disturbances. *PLOS ONE*, *6*(9), e24585. https://doi.org/10.1371/journal.pone.0024585

Williams, D. L., Baskin, D. G., & Schwartz, M. W. (2006). Leptin Regulation of the Anorexic Response to Glucagon-Like Peptide-1 Receptor Stimulation. *Diabetes*, *55*(12), 3387–3393. https://doi.org/10.2337/db06-0558

Williams, K., Wheeler, D. M., Silove, N., & Hazell, P. (2010). Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *The Cochrane Database of Systematic Reviews*, *8*, CD004677. https://doi.org/10.1002/14651858.CD004677.pub2

World Health Organization. (2018, April 2). *Autism spectrum disorders.* https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders

Xiang, A. H., Wang, X., Martinez, M. P., Walthall, J. C., Curry, E. S., Page, K., Buchanan, T. A., Coleman, K. J., & Getahun, D. (2015). Association of Maternal Diabetes With

Autism in Offspring. *JAMA*, *313*(14), 1425–1434. https://doi.org/10.1001/jama.2015.2707

Xu, G., Jing, J., Bowers, K., Liu, B., & Bao, W. (2014). Maternal Diabetes and the Risk of Autism Spectrum Disorders in the Offspring: A Systematic Review and Meta-Analysis. *Journal of Autism and Developmental Disorders*, *44*(4), 766. https://doi.org/10.1007/s10803-013-1928-2

Yamashita, Y., Makinodan, M., Toritsuka, M., Yamauchi, T., Ikawa, D., Kimoto, S., Komori, T., Takada, R., Kayashima, Y., Hamano-Iwasa, K., Tsujii, M., Matsuzaki, H., & Kishimoto, T. (2019). Anti-inflammatory Effect of Ghrelin in Lymphoblastoid Cell Lines From Children With Autism Spectrum Disorder. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00152

Yan, J., Liu, L., Zhu, Y., Huang, G., & Wang, P. P. (2014). The association between breastfeeding and childhood obesity: A meta-analysis. *BMC Public Health*, *14*. https://doi.org/10.1186/1471-2458-14-1267

Yang, J., Wang, H.-P., Zhou, L., & Xu, C.-F. (2012). Effect of dietary fiber on constipation: A meta-analysis. *World Journal of Gastroenterology : WJG*, *18*(48), 7378–7383. https://doi.org/10.3748/wjg.v18.i48.7378

Yang, Y. J., Kim, M. K., Hwang, S. H., Ahn, Y., Shim, J. E., & Kim, D. H. (2010). Relative validities of 3-day food records and the food frequency questionnaire. *Nutrition Research and Practice*, *4*(2), 142–148. https://doi.org/10.4162/nrp.2010.4.2.142

Yu, Z. M., DeClercq, V., Cui, Y., Forbes, C., Grandy, S., Keats, M., Parker, L., Sweeney, E., & Dummer, T. J. B. (2018). Fruit and vegetable intake and body adiposity among populations in Eastern Canada: The Atlantic Partnership for Tomorrow's Health Study. *BMJ Open*, *8*(4), e018060. https://doi.org/10.1136/bmjopen-2017-018060

Zhang, F., Basinski, M. B., Beals, J. M., Briggs, S. L., Churgay, L. M., Clawson, D. K., DiMarchi, R. D., Furman, T. C., Hale, J. E., Hsiung, H. M., Schoner, B. E., Smith, D. P., Zhang, X. Y., Wery, J. P., & Schevitz, R. W. (1997). Crystal structure of the obese protein leptin-E100. *Nature*, *387*(6629), 206–209. https://doi.org/10.1038/387206a0

Zhang, M., Ma, W., Zhang, J., He, Y., & Wang, J. (2018). Analysis of gut microbiota profiles and microbe-disease associations in children with autism spectrum disorders in China. *Scientific Reports*, *8*(1), 13981. https://doi.org/10.1038/s41598-018-32219-2

Zheng, Z., Zhang, L., Li, S., Zhao, F., Wang, Y., Huang, L., Huang, J., Zou, R., Qu, Y., & Mu, D. (2017). Association among obesity, overweight and autism spectrum disorder: A systematic review and meta-analysis. *Scientific Reports*, *7*(1), 11697. https://doi.org/10.1038/s41598-017-12003-4

Zimmer, M. H., Hart, L. C., Manning-Courtney, P., Murray, D. S., Bing, N. M., & Summer, S. (2012). Food variety as a predictor of nutritional status among children with autism. *Journal of Autism and Developmental Disorders*, *42*(4), 549–556. https://doi.org/10.1007/s10803-011-1268-z

Zimmet, P., Boyko, E. J., Collier, G. R., & Courten, M. (1999). Etiology of the Metabolic Syndrome: Potential Role of Insulin Resistance, Leptin Resistance, and Other Players. *Annals of the New York Academy of Sciences*, *892*(1 THE METABOLIC), 25–44. https://doi.org/10.1111/j.1749-6632.1999.tb07783.x

Zmora, N., Soffer, E., & Elinav, E. (2019). Transforming medicine with the microbiome. *Science Translational Medicine*, *11*(477), eaaw1815. https://doi.org/10.1126/scitranslmed.aaw1815

Zou, J., Chassaing, B., Singh, V., Pellizzon, M., Ricci, M., Fythe, M. D., Kumar, M. V., & Gewirtz, A. T. (2018). Fiber-Mediated Nourishment of Gut Microbiota Protects against Diet-Induced Obesity by Restoring IL-22-Mediated Colonic Health. *Cell Host & Microbe*, *23*(1), 41-53.e4. https://doi.org/10.1016/j.chom.2017.11.003

Zuckerman, K. E., Hill, A. P., Guion, K., Voltolina, L., & Fombonne, E. (2014). Overweight and Obesity: Prevalence and Correlates in a Large Clinical Sample of Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *44*(7), 1708–1719. https://doi.org/10.1007/s10803-014-2050-9

Zuo, H., Shi, Z., Yuan, B., Dai, Y., Wu, G., & Hussain, A. (2013). Association between Serum Leptin Concentrations and Insulin Resistance: A Population-Based Study from China. *PLoS ONE*, *8*(1). https://doi.org/10.1371/journal.pone.0054615

Zwaigenbaum, L., Brian, J. A., & Ip, A. (2019). Early detection for autism spectrum disorder in young children. *Paediatrics & Child Health*, *24*(7), 424–432. https://doi.org/10.1093/pch/pxz119

Appendices

Appendix A. Example for the puberty assessment

Girls Tanner Scale
At your age, girls usually begin to experience many physical changes. Please mark any changes you have experienced.

	Breast	Pubic Hair
Stage 1	Small nipples. No breast. 	No pubic hair. 
Stage 2	Breast and nipples have just started to grow. The areola has become larger. Breast tissue bud feels firm behind the nipple. 	Initial growth of long pubic hairs. These are straight, without curls, and of light color. 
Stage 3	Breast and nipples have grown additionally. The areola has become darker. The breast tissue bud is larger. 	The pubic hair is more widespread. The hair is darker, and curls may have appeared. 
Stage 4	Nipples and areolas are elevated and form an edge towards the breast. The breast has also grown a little larger. 	More dense hair growth with curls and dark hair. Still not entirely as an adult woman. 
Stage 5	Fully developed breast. Nipples are protruding, and the edge between areola and breast has disappeared. 	Adult hair growth. Dense, curly hair extending towards the inner thighs. 

Boys Tanner Scale

At your age, boys usually begin to experience many physical changes. Please mark any changes you have experienced. Please choose only ONE answer for each stage.

	Genitals	Pubic Hair
Stage 1	No signs of puberty. Scrotum, testes, and penis as in childhood. 	No pubic hair. 
Stage 2	Initial growth of scrotum and testes. The skin on the scrotum has become redder, thinner, and more wrinkled. The penis may have grown a little in length. 	Few hairs around the root of the penis. The hairs are straight, without curls, an of light color. 
Stage 3	The penis has now grown in length. Scrotum and testes have grown. The skin of the scrotum has become darker and more wrinkled. 	Hairs are darker and curlier and still sparse, mostly located at the penis root. 
Stage 4	The penis has grown in both length and width. The head of the penis has become larger. The scrotum and testes have grown. 	More dense, curly, and dark hair. The hair growth is reaching the inner thighs. 
Stage 5	Penis and scrotum as an adult. 	Pubic hair extends upwards to the umbilicus. It is dense and curly. 

Girls and boys tanner scales adapted from "Validity of self-assessment of pubertal maturation," by Rasmussen, A. R., Wohlfahrt-Veje, C., Tefre de Renzy-Martin, K., Hagen, C. P., Tinggaard, J., Mouritsen, A., Main, K. M. (2015), Pediatrics, 135(1), 86-93. doi:10.1542/peds.2014-0793. Adapted with permission

Appendix B. Children's Physical Activity Questionnaire (C-PAQ)

CHILDREN'S PHYSICAL ACTIVITY QUESTIONNAIRE (C-PAQ)

Parent Questionnaire

Your child's name: .....

Your child's date of birth (dd/mm/yy): ..... / ..... / .....

Are you the child's: mother / father / guardian / other

Please note: - this questionnaire will take approximately 10 minutes to complete
- please answer the questions in relation to the child named above
- please **complete every line** in the questionnaire

For further information, please contact:

Which of the following PHYSICAL activities did your child do in the PAST 7 DAYS?

Please complete this questionnaire for the following days: ..... to .....

Did your CHILD do the following activities in the **past 7 days?**			**MONDAY – FRIDAY**		**SATURDAY – SUNDAY**	
			How many times **Mon–Fri**?	**Total** hours/minutes **Mon-Fri**?	How many times **Sat-Sun**?	**Total** hours/minutes **Sat-Sun**?
EXAMPLE: **Bike riding**	**No**	**Yes**	**2**	**40 mins**	**1**	**15 mins**
SPORTS ACTIVITIES Aerobics	No	Yes				
Baseball/softball	No	Yes				
Basketball/volleyball	No	Yes				
Cricket	No	Yes				
Dancing	No	Yes				
Football	No	Yes				
Gymnastics	No	Yes				
Hockey (field or ice)	No	Yes				
Martial arts	No	Yes				
Netball	No	Yes				
Rugby	No	Yes				

Did your CHILD do the following activities in the **past 7 days?**		MONDAY – FRIDAY		SATURDAY – SUNDAY	
		How many times **Mon–Fri**?	**Total** hours/minutes **Mon-Fri**?	How many times **Sat-Sun**?	**Total** hours/minutes **Sat-Sun**?
Running or jogging	No Yes				
Swimming lessons	No Yes				
Swimming for fun	No Yes				
Tennis/badminton/squash/ other racquet sport	No Yes				
LEISURE TIME ACTIVITIES Bike riding (not school travel)	No Yes				
Bounce on the trampoline	No Yes				
Bowling	No Yes				
Household chores	No Yes				
Play in a play house	No Yes				
Play on playground equipment	No Yes				
Play with pets	No Yes				
Rollerblading/roller-skating	No Yes				
Scooter	No Yes				

Did your CHILD do the following activities in the **past 7 days?**		MONDAY – FRIDAY		SATURDAY – SUNDAY	
		How many times **Mon–Fri**?	**Total** hours/minutes **Mon-Fri**?	How many times **Sat-Sun**?	**Total** hours/minutes **Sat-Sun**?
Skateboarding	No Yes				
Skiing, snowboarding, sledging	No Yes				
Skipping rope	No Yes				
Tag	No Yes				
Walk the dog	No Yes				
Walk for exercise/hiking	No Yes				
ACTIVITIES AT SCHOOL Physical education class	No Yes				
Travel by walking to school (to and from school = 2 times)	No Yes				
Travel by cycling to school (to and from school = 2 times)	No Yes				
OTHER please state:	No Yes				

Did your CHILD do the following activities in the **past 7 days?**			**MONDAY-FRIDAY** **Total** hours/minutes	**SATURDAY-SUNDAY** **Total** hours/minutes
EXAMPLE: **Watching TV/videos**	**No**	**Yes**	**15hrs**	**6hrs 30mins**
Art & craft (eg. pottery, sewing, drawing, painting)	No	Yes		
Doing homework	No	Yes		
Imaginary play	No	Yes		
Listen to music	No	Yes		
Play indoors with toys	No	Yes		
Playing board games / cards	No	Yes		
Playing computer games (e.g. playstation / gameboy)	No	Yes		
Playing musical instrument	No	Yes		
Reading	No	Yes		
Sitting talking	No	Yes		
Talk on the phone	No	Yes		
Travel by car / bus to school (to and from school)	No	Yes		

Did your CHILD do the following activities in the **past 7 days?**			**MONDAY-FRIDAY** **Total** hours/minutes	**SATURDAY-SUNDAY** **Total** hours/minutes
Using computer / internet	No	Yes		
Watching TV/videos	No	Yes		
Other (please state):	No	Yes		

Corder K, van Sluijs EM, Wright A, Whincup P, Wareham NJ, Ekelund U. Is it possible to assess free-living physical activity and energy expenditure in young people by self-report? Am. J. Clin. Nutr. 89, 862–870, doi: 10.3945/ajcn.2008.26739 (2009).

Appendix C. Medical History Questionnaire

Patient ID: _____ Date: _____

UNIVERSITY OF ALBERTA
MEDICAL HISTORY QUESTIONAIRE

For person filling out this form

Relationship to participant: _____

Please list the current and recent medications that the participant is/has been on

MEDICATIONS (current and recent):

Drug Name	Strength (e.g. 50 mg)	How many times per day?

Any recent changes in the medications:

Other medications your child has been on for the last year:

BIRTH HISTORY

How much weight did mother gain during the pregnancy? _____(circle: lbs/kg)
How many months was the pregnancy? _____
What was the birth weight? _____ (circle: lbs/kg)
Was the birth ___vaginal ___c-section?
If vaginal, was the baby ___head first ___legs first?

Any complications during the labour or delivery?

Were there any problems during the first month, such as jaundice or feeding problems?

___Breast fed or ___Bottle fed? Age at weaning: _____

Patient ID: _____ Date: _____

MEDICAL HISTORY

Has the participant been diagnosed with or treated for any disease/disorders affecting these organ/body systems? *Check all that apply. If yes to any please specific in comments below.*

➲ Diabetes Mellitus	❑ Yes or ❑ No	➲ Digestive / GI	❑ Yes or ❑ No
➲ Cardiovascular	❑ Yes or ❑ No	➲ Kidney / Renal / Liver	❑ Yes or ❑ No
➲ Immune / Lymphatic	❑ Yes or ❑ No	➲ Thyroid / Endocrine	❑ Yes or ❑ No
➲ Lungs / Respiratory	❑ Yes or ❑ No	➲ Nervous System	❑ Yes or ❑ No
➲ Musculoskeletal	❑ Yes or ❑ No	➲ Allergies	❑ Yes or ❑ No
➲ Psychiatric / Neurologic	❑ Yes or ❑ No	➲ Injuries:_____	❑ Yes or ❑ No

➲ Other:_____ ❑ Yes or ❑ No

↳ *Please provide details, type, date of occurrence, interventions if any.*

Comments:

❑ **Surgeries or Surgical Interventions in the past 2 years?** ❑ Yes ⇨ *(Please comment)* ❑ No

↳ *Please comment on date, type etc.*

Comments:

- Has medical history of IBD or other GI disorder. ❑ Yes ❑ No
- Has history of GI surgical interventions. ❑ Yes ❑ No

Has your child had any teenage development? ___Y ___N If yes, when did you note:

Breast: _____Pubic Hair: _____Acne: _____

Vaginal Discharge: _____ Menstrual periods: _____

Other signs of puberty: _____

Patient ID: _____ Date: _____

FAMILY HISTORY: Does anyone in the family have (if YES, who is it?):

Overweight/Obesity	___Y ___N	_____
Bariatric Surgery	___Y ___N	_____
Type 2 diabetes	___Y ___N	_____

Thank you for answering this questionnaire.

Appendix D. Brief Autism Mealtime Behavior Inventory (BAMBI)

The Brief Autism Mealtime Behaviour Inventory (BAMBI)

Think about mealtimes with your child over the past 6 months. Rate the following items according to how often each occurs, using the following scale:

Never/Rarely	Seldom	Occasionally	Often	At Almost Every Meal
1	2	3	4	5

Circle YES if you think an item is a problem for you or NO if you think it is not a problem

1. My child cries or screams during mealtimes	1	2	3	4	5	YES	NO
2. My child turns his/her face or body away from food	1	2	3	4	5	YES	NO
3. My child remains seated at the table until the meal is finished	1	2	3	4	5	YES	NO
4. My child expels (spits out) food that he/she has eaten	1	2	3	4	5	YES	NO
5. My child is aggressive during mealtimes (hitting, kicking, scratching others)	1	2	3	4	5	YES	NO
6. My child displays self-injurious behavior during mealtimes (hitting self, biting self)	1	2	3	4	5	YES	NO
7. My child is disruptive during mealtimes (pushing/throwing utensils, food).	1	2	3	4	5	YES	NO
8. My child closes his/her mouth tightly when food is presented	1	2	3	4	5	YES	NO
9. My child is flexible about mealtime routines (e.g. times for meals, seating arrangements, place settings)	1	2	3	4	5	YES	NO
10. My child is willing to try new foods	1	2	3	4	5	YES	NO
11. My child dislikes certain foods and won't eat them	1	2	3	4	5	YES	NO
12. My child refuses to eat foods that require a lot of chewing (e.g. eats only soft or pureed foods)	1	2	3	4	5	YES	NO
13. My child prefers the same foods at each meal	1	2	3	4	5	YES	NO
14. My child prefers "crunchy" foods (snacks, crackers)	1	2	3	4	5	YES	NO
15. My child accepts or prefers a variety of foods	1	2	3	4	5	YES	NO
16. My child prefers to have food served in a particular way	1	2	3	4	5	YES	NO
17. My child prefers only sweet foods (e.g. candy, sugary cereals)	1	2	3	4	5	YES	NO
18. My child prefers food prepared in a particular way (e.g. eats mostly fried foods, cold cereals, raw vegetables)	1	2	3	4	5	YES	NO

LUKENS, Colleen Taylor, and Thomas R. LINSCHEID. "Development and Validation of an Inventory to Assess Mealtime Behavior Problems in Children with Autism." Journal of Autism and Developmental Disorders, no. 2, 2008, p. 342.