Evaluating the Relationships of Diet Quality with ADHD and Emotional Dysregulation Symptom Severities in a Pediatric Population

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in the Graduate School of The Ohio State University

By

Lisa M. Robinette, B.S.

Graduate Program in Human Nutrition

The Ohio State University

2021

Thesis Committee

Associate Professor Irene Hatsu, PhD RD, Advisor

Associate Professor Tonya Orchard, PhD RD

Assistant Professor James Odei, PhD

Abstract

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with a US pediatric prevalence of 10%. It presents with inattention and hyperactivity/impulsivity as well as emotional dysregulation (ED) symptoms such a s irritability and defiant behavior, typical of Oppositional Defiance Disorder (ODD) and Disruptive Mood Dysregulation Disorder (DMDD). The etiology of ADHD is multi-factorial with suggested effects related to diet.

Objectives: Building on prior studies, this study examines the association of diet quality with ADHD and emotional dysregulation symptoms among a pediatric population.

Methods: This cross-sectional study utilized baseline data for 134 children age 6-12 years old with symptoms of ADHD/ED enrolled in a randomized control trial of multi-nutrient supplementation. Diet quality was based on Healthy Eating Index-2015 (HEI-2015) determined from the Vioscreen food frequency questionnaire. ADHD, ODD and DMDD symptoms were assessed using the Child and Adolescent Symptom Inventory-5. Other ED symptoms were assessed using the Strengths and Difficulties Questionnaire. Analysis for association was conducted using linear regression models, adjusting for covariates when necessary.

Results: We found family income level to be significantly inversely associated with severity of hyperactivity ($p = 0.04$), emotional problems ($p=0.01$), conduct problems ($p=0.002$), along with ODD ($p=0.004$) and DMDD ($p=0.005$) symptoms. Mean HEI-2015 score was 63.4 (SD=8.8) and it was not significantly associated with any of the outcome symptoms. However, scores of HEI components vegetables (β= -0.118, p=0.016) and refined grains (β=0.052, p=0.017) were both associated with inattention even after adjusting for covariates. Similarly, total fruit (β= -0.423, p=0.037) was associated with conduct problems even after adjusting for covariates.

Conclusions: While better vegetable and total fruit scores were associated with better symptoms in aspects of ADHD and emotional dysregulation, overall diet quality was not associated with inattention, hyperactivity/impulsivity, and ED symptom severities among this cohort of children. Our findings could be explained by the fact that our study sample had a good diet quality and were only mildly impaired in their ADHD and emotional dysregulation symptoms.

Acknowledgments

First, I would like to express my gratitude for my advisor and mentor, Dr. Irene Hatsu, for providing me with the opportunity to participate in this research by taking a chance on me two years ago. Her direction throughout this research and writing of this thesis is invaluable and will serve me well as I continue my studies. Additionally, I would like to thank the rest of my thesis committee, Dr. Tonya Orchard and Dr. James Odei, for their insightful feedback and guidance as I proceeded through this project.

I would also like to thank the current and former members of the Hatsu Lab who contributed to this research. First, thanks to Dr. Leanna Eiterman and Madeline Stern who were instrumental in the clinical trial from which the data for this thesis was derived and were also great mentors and friends during my first year of graduate school. Thanks to my current lab mates: Maryan Dualle for providing me with fresh perspectives on my research, and Alethia Tefft and Marino Marko who made life better through their help, boundless energy, and friendship.

Finally, I would like to thank my family: my husband Clint Robinette for his selflessness and encouragement, and my children, Claire and Joseph, for being my inspiration to never stop learning and for giving me grace as I navigated this new role. And most of all, thanks to God for the many blessings in my life and for opening doors when it seemed impossible.

Vita

May 1997 ....Sycamore High School

May 2003..B.S. Chemical Engineering, University of Cincinnati

2003-2006..Chemical Engineer, BP Chemical Company

2006-2019..Chemical Engineer, Eastman Chemical Company

2019 to present ....Graduate Teaching Assistant, Department of Human Sciences, The Ohio State University

Fields of Study

Major Field: Human Nutrition

Table of Contents

List of Tables

List of Figures

Chapter 1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder affecting about 5% of children worldwide and up to 10% of children in the United States.[1, 2] ADHD is a significant public health concern since it is associated with poor social, academic, and economic outcomes as well as increased risk of hospital admissions and injuries.[2] It is clinically diagnosed as the presence of inattention and/ or hyperactivity/impulsivity that interferes with functioning in two or more settings.[3] ADHD is increasingly recognized as a disorder involving problems with self-regulation, which frequently includes emotional dysregulation. Clinical features of emotional dysregulation include irritability, inappropriately positive emotions, persistent anger for most of the day, argumentative/ defiant behavior and/or vindictiveness, and impulsive aggression.[4] These symptoms co-occur in conditions like Oppositional Defiant Disorder (ODD) and Disruptive Mood Dysregulation Disorder (DMDD).[3]

Conventional treatment for ADHD typically involves medication, behavior therapy, and educational accommodations. Stimulant medications are commonly used and effectively improve symptoms in most people with ADHD; however, as many as 20-30% of children do not respond to this class of drug or cannot tolerate it due to side effects.[5] The prevalence of side effects of medications combined with unknown effects of long-term use has necessitated investigation into alternative ADHD treatment options, which often includes dietary and nutrition interventions.

The etiology of ADHD is multi-factorial, involving genetic, environmental, social, and neurobiological factors.[6] Environmental factors that have shown an association with ADHD include pollution, exposure to toxins and contaminants such as lead, pesticides, and cigarette smoke, and dietary intake.[5] Several aspects of dietary habits have been linked to ADHD including sensitivity to artificial food additives, fatty acid imbalances, and vitamin and mineral deficiencies.[5]

With growing evidence linking dietary factors to ADHD, there has been increased interest in the relationship between dietary patterns and ADHD. Globally, studies have shown that ADHD is associated with Western dietary patterns[7, 8] and diets that are high in added sugars [9, 10] and refined carbohydrates.[11] While these studies provide useful findings, only one study was conducted in the United States. With high pediatric ADHD prevalence in the United States coupled with a dietary pattern that is different than those reported in other regions of the world, it is imperative to investigate how the American dietary pattern (particularly that of a pediatric population) relates to ADHD symptom severity. Most of the prior studies only examined the relationship of dietary pattern with a current ADHD diagnosis, but did not determine if diet quality was associated with severity of ADHD symptoms. In addition, there are limited studies on the relationship between diet quality and emotional dysregulation symptom severities. This study aims to fill these gaps by examining the association of dietary patterns with severity of ADHD and emotional dysregulation symptoms among a pediatric population in the United States.

Specific Aims and Hypotheses

Aim 1: Determine the relationship between dietary pattern (as measured by a diet quality score) and ADHD symptom severities among children.

Hypothesis 1: Diet quality score will be inversely associated with severity of inattention and hyperactivity/impulsiveness.

Aim 2: Determine the relationship between dietary pattern (as measured by a diet quality score) and emotional dysregulation symptom severities among children.

Hypothesis 2a: Diet quality score will be inversely associated with severity of ODD symptoms.

Hypothesis 2b: Diet quality score will be inversely associated with severity of DMDD symptoms.

Hypothesis 2c: Diet quality score will be inversely associated with severity of emotional and conduct problems.

Chapter 2. Literature Review

2.1 ADHD and Emotional Dysregulation in Children

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder diagnosed in childhood in the US. It is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity which interfere with functioning or development in two or more settings (e.g., at home, school, with friends, at other activities).[3] ADHD prevalence estimates vary based on methodology and age groups examined. Globally, a pooled prevalence rate of 5.29% is reported among children and adolescents 18 years of age and younger,[1] while in the U.S. an estimated 9.4% of children aged 2-17 have ever received an ADHD diagnosis.[2]

ADHD is generally recognized as a heterogeneous disorder due to the variety of clinical presentations plus the high prevalence of comorbidities. There are three recognized clinical presentations of ADHD: predominantly inattentive, predominantly hyperactive/impulsive, and combined presentation.[3] Most children diagnosed with ADHD will also be diagnosed with at least one comorbid condition, ranging from emotional, behavior, developmental, or physical conditions. The American Academy of Pediatrics recommends screening any child evaluated for ADHD for comorbid emotional or behavioral conditions, as these could alter ADHD treatment.[12] A study by Reale

(2017) determined that 66% of children with ADHD had at least one comorbid psychiatric disorder, and those with the combined type presentation and severe impairment were more likely to present comorbidity. The most prevalent psychiatric comorbidities in this study were learning disorders (56%), sleep disorders (23%), and ODD (20%).[13] Similarly, another large population-based study among children and adolescents between 6 and 18 years of age found that of those with ADHD, 61.5% had comorbid psychiatric disorders, with ODD as the most prevalent comorbid disorder (26.1%).[14]

ADHD and common behavioral comorbidities such as ODD and conduct disorder (CD) are considered externalizing disorders characterized by the propensity to express distress outwards, with shared vulnerability from a general inability to regulate impulses.[15] ODD is defined by diagnostic criteria of angry/ irritable mood, argumentative/ defiant behavior, and vindictiveness, which can be differentiated from typical normative behavior by both the frequency and persistence of the behavior.[3] Diagnostically ODD and CD are grouped in DSM-5 as “Disruptive, Impulse-Control, and Conduct Disorders” and lie along a continuum of symptoms; however, CD is distinct from ODD in that it involves impingement of other’s rights and violating social norms.[3]ODD diagnosis is a risk factor for the development of CD, but they remain two distinct disorders.[16] DMDD is characterized by severe recurrent temper outbursts that are disproportionate to the situation and occur three or more times per week.[3] Like ODD, it presents with a persistently irritable and angry mood for most of the day nearly every day.[3] The symptoms of DMDD and ODD have been shown to overlap considerably. One study found that 92% of children with DMDD symptoms had ODD symptoms, and 66% of children with ODD had DMDD symptoms, which suggests that DMDD cannot be differentiated from ODD based on symptomology.[17]

Emotional dysregulation is increasingly recognized as a core feature of ADHD. Emotional dysregulation is defined as an "inability to modulate emotional responses, resulting in extreme responses of internalizing or externalizing behavior that would be considered inappropriate for the developmental age of the person."[18] Clinical features of emotional dysregulation include irritability, inappropriately positive emotions, persistent anger for most of the day, argumentative/ defiant behavior and/or vindictiveness, and impulsive aggression.[4] Dysregulation may also be characterized by severe outbursts in children under age 13, which includes behaviors such wrecking property, throwing things, hitting/kicking/spitting during the outburst, threatening others, hurting themselves, and requiring physical restraint by parent.[19] ADHD is a disorder of self-regulation with deficits in the regulation of attention, impulses, activity and emotion.[20] Irritability is a common clinical feature among several diagnoses including ADHD, ODD, and DMDD. Even among individuals with ADHD but no comorbid mood disorders, 71.5% displayed irritability; and overall, 40-50% of children with ADHD have impairments that stem from rages or irritability.[4] Persistent irritability in children is more prevalent in the combined-type presentation of ADHD and is associated with increased severity of ADHD symptoms and poorer functioning in multiple domains.[4]

Among elementary and middle-school aged children, ADHD is frequently treated with either stimulant or non-stimulant medications, with strong evidence supporting the use of stimulant medications such as methylphenidate, and sufficient but weaker support for the use of non-stimulant medications such as atomoxetine, guanfacine, and clonidine.[12] However, stimulant medication either causes side effects or is not effective in as many as 20-30% of children.[5] Short-term and long-term side effects may include loss of appetite, mood swings, insomnia, increased blood pressure, tics, paranoid psychoses, suppression of growth, and can lead to physical and/or psychological dependence.[5] Concerns about side effects and long-term safety of these medications cause many parents to explore complimentary or alternative treatment of ADHD, with about 12% of children with ADHD using alternate therapies including nutrition-based therapies like nutritional supplements.[6]

2.2 Nutrients and Nervous System Function in ADHD

There is a large body of evidence linking ADHD to dysfunction in neurotransmitter pathways pertaining to moderation of executive function, working memory, emotional regulation, and reward processing.[21] The etiology of ADHD is theorized to be related to low levels of serotonin and catecholamines (epinephrine, norepinephrine, and dopamine), and abnormalities in glutamate/glutamine in the brain.[5] Several ADHD pharmaceutical treatments including methylphenidate work by inhibiting the dopamine transporter [22] and thus mimicking the action of norepinephrine and dopamine.[5]

Several vitamins and minerals serve key roles in the central nervous system and brain function, notably iron, magnesium, zinc, and vitamin B6 for neurotransmitter synthesis and function. The neurotransmitter dopamine cannot cross the blood/brain barrier and is synthesized in the brain from precursors phenylalanine and tyrosine via an intermediate structure L-DOPA. Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme which converts tyrosine to L-DOPA; therefore iron modulates dopamine and subsequent norepinephrine and epinephrine production.[23] Zinc directly regulates the dopamine transporter, which carries dopamine from the synaptic cleft back into the neuron, by acting as a potent non-competitive blocker.[22] Vitamin B6 (Pyridoxal 5′-Phosphate) is a cofactor in several enzymes in neurotransmitter synthesis, including in the conversion of 5-Hydroxytryptophan (5-HTP) to serotonin, and in the conversion of dopa to dopamine.[24] Iron is a component of monooxygenase which is integral for the transformation of tryptophan to serotonin.[25] The glutamatergic system is the major excitatory neurotransmitter in the nervous system, and there are many types of glutamate receptors involved in neurotransmission with the most important being the N-methyl D-aspartate (NMDA) receptor pathway.[26] Magnesium is an antagonist of the NMDA receptor, and magnesium deficiency has been related to symptoms such as agitation, anxiety, irritability, and hyperexcitability.[27] Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter which plays a role in behavior control, motor function and motor learning.[26] GABA is synthesized in the GABAergic nerve endings from glutamate via glutamic acid decarboxylase (GAD) enzyme, which requires vitamin B6 as a cofactor.[24] Zinc can inhibit both the GABA and NMDA receptors in the glutamatergic pathway.[27]

Long-chain polyunsaturated fatty acids (LC PUFAs), including omega-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and omega-6 arachidonic acid (AA) also play a critical role in brain and central nervous system development and functioning. Due to LC PUFAs' flexible structure, they impart membrane fluidity in neuronal membrane phospholipids and can influence signaling processes by changing the binding or release of neurotransmitters.[28] In addition to the structural importance, the PUFAs are also precursors of eicosanoids which have hormone-like actions that effect metabolic processes. Eicosanoids derived from omega-3 PUFAs tend to have more favorable anti-inflammatory effects than those derived from omega-6 PUFAs, thus illustrating one aspect why the ratio of omega-3 to omega-6 is critical to optimum body functioning.[28] Foods commonly consumed in industrialized countries such as vegetable oils, seeds, nuts, and margarines are typically high in omega-6 fatty acids and low in omega-3 fatty acids which are usually found in coldwater fish, canola oil, walnuts, eggs, and some meats. The imbalance in omega-3 to omega-6 intake associated with the Western diet has been linked to neurodevelopmental disorders including ADHD and autism spectrum disorder.[28]

A small but diverse body of research has investigated the effect of supplementation of various vitamins, minerals, and fatty acids, individually and in combinations, on ADHD. The effect of magnesium on ADHD has been studied in combination with other nutrients, including Vitamin B6,[29] Vitamin D,[30] zinc and PUFAs.[31] Supplementation with Vitamin D and magnesium significantly improved conduct problem, social problem, and anxiety scores in children with ADHD.[30] Higher dietary magnesium intake was associated with reduced externalizing behavior problems such as attention problems, aggressive behavior, and rule-breaking in adolescents, with a similar trend for zinc though findings were not statistically significant.[27] A supplement of PUFA plus magnesium and zinc provided a beneficial effect on attention, behavior, and emotional problems in children and adolescents.[31] A trial of zinc supplementation as treatment for ADHD found that the supplemented group had significantly improved hyperactivity, impulsivity, and socialization subscale scores, though no improvement on the attention deficit subscale.[32] Iron supplementation improved ADHD symptoms in non-anemic children with low serum ferritin levels with effectiveness comparable to stimulants.[23] A combination of omega-3 and omega-6 fatty acids plus magnesium and zinc had a beneficial effect on attention, behavior, and emotion in children and adolescents.[31] A high dose of omega-3 EPA/DHA supplementation in a small open-label pilot study showed significant improvements in behavior categories of inattention, hyperactivity, oppositional behavior, and conduct disorder.[33]

2.3 Dietary Patterns

Over the past three decades, the nutrition science field began to move forward from single nutrient theories that inadequately explained numerous diet-chronic disease links, towards a focus on the complex biological effects of food and diet patterns on chronic disease.[34] For example, dietary patterns have shown to be helpful when studied in relation to chronic diseases such as high blood pressure and diabetes in which there are several known dietary associations.[35] The potential advantage of dietary patterns over single nutrients reflects the interactions between carbohydrate quality, fatty acid profiles, protein types, micronutrients, phytochemicals, food structure, preparation and processing methods, and additives.[34]

The 2015 Dietary Guidelines Advisory Committee defines dietary patterns as "the quantities, proportions, variety or combination of different foods, drinks and nutrients (when available) in diets and the frequency which they are consumed."[36] The Mediterranean dietary pattern, for example, is a well-balanced diet consisting of high consumption of fruits, vegetables, nuts, whole grains, fish, and olive oil as the primary source of added fat, and has been shown to reduce the risk of chronic diseases such as Type 2 Diabetes, cardiovascular disease, and depression.[37] Dietary Approaches to Stop Hypertension (DASH) diet is another dietary pattern rich in fruits and vegetables, low-fat dairy, and reduced saturated and total fat, and is proven to substantially lower blood pressure.[38] In contrast, a Western dietary pattern or the Standard American Diet (SAD) is characterized by excess consumption of refined carbohydrates, fatty meats, added sodium, and added fats, while low in intake and nutrients from whole grains, fruits, and vegetables.[39] This dietary pattern is frequently linked to diet-related diseases such as type 2 diabetes, hypertension, and heart disease.[39]

Three methods used to determine dietary patterns in the literature are factor analysis, cluster analysis, and dietary indices.[35] The Healthy Eating Index (HEI) is an example of a dietary index measuring the degree to which a dietary pattern meets the requirements of the Dietary Guidelines for Americans (DGA) set forth by the US Department of Agriculture.[35, 40] The HEI-2015 consists of thirteen components, of which 9 are categorized as adequacy components and 4 as moderation components. The adequacy components of HEI-2015 are total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids (ratio of unsaturated to saturated fatty acids). The 4 moderation components are refined grains, sodium, added sugars, and saturated fat. The HEI provides an overall diet quality score ranging from 0 to 100, with each component worth 5 or 10 points. Higher scores represent closer alignment to the DGA; the adequacy components receive higher scores for higher consumption, while moderation components receive higher scores for lower consumption.[40]

In addition to overall dietary scores, further insights can be derived by distinguishing between the healthy and unhealthy components that make up the dietary score. A systematic review of global dietary patterns of adults by Imamura (2015) found that while high-income countries (including the U.S.) had the highest scores based on greater consumption of healthy dietary items, these same countries also had substantially poorer diets based on consumption of unhealthy dietary items. Although the high-income nations showed some improvements at reducing consumption of unhealthy foods from 1990-2010, the dietary scores for unhealthy items remained among the worst in the world in 2010.[41] Another study compared dietary patterns of 9–11-year-old children from 12 countries using principal component analysis and identified 2 dietary patterns, ‘healthy’ and ‘unhealthy’, with the healthy diet characterized by higher consumption of vegetables, fruits, and whole grains, while the unhealthy diet had higher consumption of fast foods, ice cream, fried foods, and sugary drinks and desserts.[42] Children in the United States ranked near the top of the unhealthy diet pattern score, indicating higher consumption of unhealthy factors compared to other countries in the world.[42] A study by Banfield (2016) using National Health and Nutrition Examination Survey (NHANES) data for children 4-

18 years old measured adherence to the U.S. DGA using HEI-2010. Overall diet scores for the group (43.6-52.1) were significantly lower than the benchmark score of 80 considered to indicate a healthy diet. The results were compared across age groups (4-8, 9-13, and 14-18 years old) and determined the lowest age group was associated with higher overall HEI scores.[43] A more recent study found that the general U.S. child population aged 6-11 had a mean HEI-2015 score of 53.9 (95% CI: 52.5-55.1) based on 2009-2014 NHANES data.[44]

2.4 Dietary Patterns Associated with ADHD and Emotional Dysregulation

With mounting evidence that essential nutrients are critical to brain function and that supplementation can improve symptoms of ADHD, it is important to investigate more broadly how ADHD is associated with overall diet quality given that diet is the primary source of essential nutrient intake. Such studies can quantify any differences in dietary pattern by ADHD diagnosis and by disease severity. Additionally, these studies can reveal if any general dietary patterns or habits such as eating certain types of foods or minimizing others may have a harmful or protective effect on ADHD symptoms.

Several studies have compared the dietary patterns of children and adolescents with and without an ADHD diagnosis and ADHD symptom severity (Table 1). In a study among 375 school-aged Iranian children, four major dietary patterns were identified: healthy, Western, sweet, and fast food.[45] The researchers found that both the sweet and the fast-food dietary pattern were associated with higher risk or odds for ADHD, but no significant associations between the healthy or Western dietary pattern and ADHD.[45] For specific nutrients, this study identified that iron, zinc, calcium, vitamin B1 and vitamin

B2 intakes were significantly lower in children with ADHD.[45] Similarly, among Iranian preschool children, researchers found that those adhering to the Western dietary pattern had greater odds of having ADHD than those with lowest adherence, and the healthy dietary patterns was inversely associated with ADHD.[8] In another study among children and adolescents in Spain found a positive relationship between lower adherence to the Mediterranean diet and ADHD diagnosis.[9] Lower frequency of consuming fruits, vegetables, pasta, and rice was associated with higher prevalence of ADHD diagnosis.[9] Higher frequency of skipping breakfast, eating at fast-food restaurants, and high consumption of sugar, candy, colas, and soft drinks was associated with ADHD diagnosis.[9] Among a cohort of adolescents in Australia, it was found that ADHD diagnosis was associated with the western dietary pattern but not with the healthy dietary pattern.[7] In a study conducted on children aged 7-12 in Korea, four major dietary patterns were identified by PCA: traditional, seaweed-egg, traditional-healthy, and snack. The traditional-healthy dietary pattern, which consisted of high intake of kimchi, grains, bonefish, and low intake of fast food and beverage, was significantly associated with lower odds of having ADHD.[46] A recent study among Taiwanese children found that those with ADHD consumed more refined grains and less dairy compared to healthy controls; they also had lower intake of calcium and vitamin B2 compared to the healthy controls.[11] This study also found that a composite diet/nutrient score derived from these four factors was significantly correlated with the severity of ADHD symptoms.[11] Similarly, another study of children in Taiwan showed that children with ADHD consumed more nutrient poor food such as high sugar and high fat foods, and less intake of vegetables, fruit, and protein-rich foods than the control group.[10] Among children in the Netherlands, Mian et al. assessed the bidirectional association between ADHD symptoms and diet quality scores reflecting adherence to Dutch dietary guidelines.[47] The authors concluded that children with more severe emotional symptoms may be at higher risk of subsequent unhealthy diets, but overall diet quality does not affect ADHD risk.[47] A study of adolescents aged 6-17 years in Germany found a negative correlation between hyperactivity/ impulsivity scores and nutrition quality scores.[48]

Finally, in a study focused on children and college-aged young adults in United States, Holton et al., found no difference in overall diet quality (measured by Healthy Eating Index scores) between those with and without ADHD diagnosis.[49] The mean HEI scores for all groups in this study ranged from 54.5-57.8 out of a maximum of 100,[49] which are well-below the benchmark score of 80 representing a healthy diet. No data was reported on the scores for individual components of the HEI, so it is undetermined if there are any differences in the consumption of the healthy items (adequacy components) or unhealthy items (moderation components) between the groups. The study did identify lower vitamin B12, D, and K intakes among children with the ADHD diagnosis.[49]

A smaller body of research within the past decade has examined the relationship between dietary pattern and severity of emotional symptoms, which are summarized in Table 2. Five of these studies examined causal relationships between emotional dysregulation symptom severity and dietary patterns. In a large study among children from eight European countries, Arvidsson et al., found that a higher adherence to healthy dietary guidelines at baseline was associated with fewer emotional and peer problems two years later.[50] Two studies of a cohort of children in the UK investigated the causal relationship between dietary components and behavioral problems. The first study found increased junk food intake at age 4.5 to be associated with increased hyperactivity at age 7; but found no significant relationship with overall behavior score.[51] The second study, however, found no evidence to support an association between a junk food diet at 6.75 years of age and behavior problems at 8 years.[52] A limitation of both studies was the exclusion of children categorized with behavioral problems at the baseline age to create a "disease-free" cohort, potentially excluding many children if their behaviors at the baseline age were caused by junk food intake at earlier age.[51, 52] In a prospective cohort study of adolescents in Australia, two dietary patterns were identified using factor analysis: Western and healthy. They found that a higher score for Western dietary pattern at 14 years old was associated with increases in externalizing behaviors at age 17, but only in females.[53] In a study among German children, higher diet quality scores were found to be associated with lower likelihood of emotional symptoms, plus increased consumption of high-sugar products was associated with increased odds of emotional symptoms.[54] A study among Iranian female adolescents showed that high scores in unhealthy eating patterns of "snacking and convenience," "planning ahead," and "meal skipping" were associated with increased risk of emotional disorders.[55] Another study of 14-year-old children in Australia found that increased intake of foods in the Western dietary pattern was associated with poorer internalizing and externalizing behavior scores.[56] This study also found that higher intakes of leafy green vegetables and fruit were associated with improved behavior scores, but not the overall healthy dietary pattern.[56]

Table 1. Key studies of dietary patterns and ADHD

Author/ Year/ Country	**Study Design/ Population**	**Dietary Index or Dietary Pattern/Factors**	**Findings**
Azadbakht 2012 Iran	cross-sectional/ 375 school-age children	Four major dietary patterns identified by factor analysis: *healthy: high in fruits, vegetable, vegetable oil, whole grains, legumes, and dairy *Western: high in processed meat, red meat, butter, eggs, pizza, snacks *sweet: high in ice cream, refined grains, sweet desserts, sugar, and soft drinks *fast food: high in processed meat, commercial fruit juices, pizza, snacks, sauces, soft drinks	*Children in the top quintile of the sweet dietary pattern score had greater odds for having ADHD compared with those in the lowest quintile *Greater adherence to the fast-food dietary pattern was significantly associated with a higher risk of having ADHD *No overall significant associations were seen between the healthy or Western dietary pattern and ADHD.
Abbasi 2019 Iran	case-control/ 500 preschool- and school-aged children (4-12 years old) matched by age and sex	Two major dietary patterns identified by factor analysis: *Healthy: high in fruits, vegetables, vegetable oils, whole grains, legumes, and dairy products *Western: high in processed meat, red meat, pizza, eggs, snacks, animal fat, hydrogenated fat, and salt	*Children in the top quintile of the Western dietary pattern score had greater odds having ADHD, compared with those in the lowest quintile *The healthy pattern was inversely associated with ADHD
Holton 2019 United States	case-control/ children age 7-12 with ADHD (n=23) and without (n=22) and young adults with ADHD (n=21) and without ADHD (n=30)	Healthy Eating Index-2010 diet quality score reflecting adherence to 2010 Dietary Guidelines for Americans	*No difference in overall HEI score between groups in either the school-age children or young adults
Rios-Hernandez 2017 Spain	case-control/ 60 children (age 6-16) with ADHD and 60 matched controls	KIDMED test scores reflecting adherence to Mediterranean diet	*Positive relationship between lower adherence to Mediterranean diet and ADHD diagnoses. *Lower frequency of consuming fruits, vegetables, pasta, and rice; high frequency of skipping breakfast and eating at fast food restaurants; and high consumption of sugar, candy, colas, and non-cola soft drinks were all associated with higher prevalence of ADHD diagnosis.

Continued

Table 1 Continued

Howard 2011 Australia	cross-sectional/ 1,799 adolescents age 14 years old (115 adolescents had an ADHD diagnosis)	Two dietary patterns identified by factor analysis: *Western: high in take-away food, confectionary, red meat, refined grains, process meat, chips, soft drinks, etc. *Healthy: high in vegetables, fresh fruit, legumes, and whole grains	*A higher score for the Western dietary pattern was associated with ADHD diagnosis after adjusting for known confounding factors from pregnancy to 14 years. *ADHD diagnosis was not associated with the "Healthy" dietary pattern.
Woo 2014 Korea	case-control/ 192 elementary school students aged 7-12 years (96 ADHD, 96 case-matched controls)	Four major dietary patterns identified by PCA: *traditional: condiments, vegetables, tofu/soymilk, and mushrooms *seaweed-egg: high intakes of seaweeds, fats/oils/ sweets, and eggs *traditional-healthy: kimchi, grains, bonefish, low intake of fast food and beverages *snack: snacks, processed meat, low intake of noodles.	*Traditional-healthy dietary pattern was associated with lower odds having ADHD.
Chou 2018 Taiwan	case-control/ 42 children with ADHD (no medication) and 36 healthy control children, Age 6-16	Two dietary indices that differentiated ADHD from controls derived by ROC: *refined grain *dairy Two nutrient Indices that differentiated ADHD from controls derived by ROC: *Calcium *Vitamin B2	*ADHD children and healthy controls have different dietary patterns and that dietary and nutrient factors may play a role in the pathophysiology of ADHD. *Children with ADHD tend to intake more refined grain and less intake of dairy. *The composite dietary/nutrient score demonstrated a significant correlation with the severity of ADHD clinical symptoms.
Wang/ Yu 2019 Taiwan	case-control/ 216 children with ADHD and 216 age-, height- and gender-matched controls	Four dietary factors derived by PCA: *nutrient poor foods *vegetable-fruit *flesh foods *soymilk-egg	*Children with ADHD had more intake of nutrient-poor foods such as high sugar and high fat foods, and had less intake of vegetable, fruit, protein-rich foods than their counterpart. *Conclusion: an unhealthy dietary pattern may be a predecessor of the poor nutritional biochemistry status and managing diet and nutrition conditions should be considered to improve ADHD symptoms in children.
van Egmond-Fröhlich 2012 Germany	cross-sectional/ 9428 children and adolescents aged 6-17 years	Healthy Nutrition Score for Kids and Youth (HuSKY) diet quality score	*Hyperactivity/impulsivity scores correlated negatively with the nutritional quality score
Mian 2019 Netherlands	prospective cohort/ 3680 children ages 6-10 years	Predefined diet quality score reflecting adherence to Dutch dietary recommendations for children	*Significant inverse association between ADHD symptoms at age 6y and dietary patterns at age 8y *no association between dietary pattern at 8y and ADHD symptoms at 10y.

Table 2. Key studies of dietary patterns and emotional symptoms

Author/ Year/ Country	**Study Design/ Population**	**Dietary Index or Dietary Pattern/Factors**	**Findings**
Abbasalizad Farhangi 2018 Iran	cross-section/ 107 adolescent girls aged 15-17 years old	Six eating patterns as assessed by eating behavioral pattern questionnaire (EBPQ): *snacking and convenience *planning ahead *meal skipping *low fat *emotional *cultural and lifestyle behavior	*unhealthy eating patterns of "snacking and convenience," "planning ahead," and "meal skipping" were associated with increased risk of emotional disorders
Arvidsson 2017 Europe	prospective cohort/ 7,675 children aged 2-9 years old	Healthy Dietary Adherence Score (HDAS) reflecting adherence to healthy dietary guidelines common for all 8 countries in this study	*Higher adherence to healthy dietary guidelines at baseline was associated with fewer emotional and peer problems 2 years later.
Kohlboeck 2012 Germany	cross-section/ 3,361 children at 11 years of age	Diet quality score reflecting adherence to German optimized mixed diet (OMD)	*increased consumption of high-sugar products was associated with increased odds of emotional symptoms *higher OMD diet quality score (reflects a diet low in fat but with adequate amount of plant foods) was associated with lower likelihood of emotional symptoms
Peacock 2011 UK	cohort/ ~7,500 children at ages 6.75 years and then 8 years old	PCA generated components: *junk food: increased consumption of high-fat processed foods, snack foods high in fat and/or sugar *health-conscious: vegetarian style foods, rice, pasta, salad, and fruit *traditional: meat, potatoes, and vegetables	*Association between junk food score at 6.75 years and total difficulties and pro-social behaviors at 8 years, but after adjusting for baseline SDQ scores attenuated the association. *no evidence to support an association with a junk food diet at 6.75 years of age and behavior problems 16 months later.
Wiles 2009 UK	cohort/ ~4000 children at age 4.5 and then age 7	PCA generated components: *junk food: increased consumption of high-fat processed foods, snack foods high in fat and/or sugar *health-conscious: vegetarian style foods, rice, pasta, salad, and fruit *traditional: meat, potatoes, and vegetables	*An increase in junk food intake at age 4.5 was associated with increased hyperactivity at age 7 *No association between the junk food eating pattern and overall behavior score or the other SDQ subscales

Continued

Table 2 Continued

Oddy 2009 Australia	prospective cohort study/ 1324 children at age 14	Two dietary patterns identified using factor analysis: *Western: components of takeaway foods, confectionary, red meat, refined grains *Healthy: components of vegetables, fresh fruit, legumes, whole grains, and fish	*poorer behavior scores, both internalizing and externalizing behaviors, were associated with an increased intake of the Western dietary pattern, particularly takeaway foods, red meat and confectionary *improved behavioral scores were associated with higher intakes of leafy green vegetables and fruit, but not with an overall Healthy dietary pattern
Trapp 2016 Australia	prospective cohort study/ 746 adolescents at 14 and 17 years old	Two dietary patterns identified using factor analysis: *Western: components of takeaway foods, confectionary, red meat, refined grains *Healthy: components of vegetables, fresh fruit, legumes, whole grains, and fish	*higher score for a Western dietary pattern at 14 years was associated with a significant increase in externalizing behaviors and a greater odds of having clinically concerning externalizing behaviors at 17, but only in females

Chapter 3. Methods

3.1 Study Population and Eligibility

The data for this analysis was obtained from the Multinutrients for ADHD in Youth (MADDY) Study, an 8-week randomized double-blind placebo-controlled trial that examined the efficacy of a 36-ingredient vitamin/mineral supplement as treatment for children with ADHD and irritability.[57] Participants were recruited from three sites: in Oregon through the Oregon Health & Science University (OHSU), in Ohio through The Ohio State University and Nationwide Children's Hospital, and in Canada through the University of Lethbridge in Southern Alberta. Additional details on study design, recruitment, and enrollment are described elsewhere.[57] The MADDY Study *inclusion criteria* were:

1. being between ages of 6 and 12, inclusive
2. meeting the DSM-5 criteria for ADHD as assessed by parent reports on the Child and Adolescent Symptom Inventory-5 (CASI-5) ADHD scales using a clinical cutoff of 6+ questions scored as "often" or "very often" (scored as 2 or 3), or sufficient "sometimes" responses scored as 0.5 to meet a score of 6.0
3. demonstrating at least one symptom of irritability or anger scored as "often" or "very often" or 2 "sometimes" responses from the CASI-5 ODD or DMDD subscales

4. being psychotropic medication free or having washed-out for at least 2 weeks prior to the study.

The study's e*xclusion criteria* were:

1. having neurological disorder involving brain or other central function (e.g., history of or suspected intellectual disability, autism spectrum disorder, epilepsy, multiple sclerosis, narcolepsy) or other major psychiatric condition requiring hospitalization (e.g. significant mood disorder, active suicidal ideation, or psychosis)
2. having any serious medical condition, including inflammatory bowel disease, history of cancer, kidney or liver disease, hyperthyroidism, diabetes Type I or II.
3. taking any other medication with primarily central nervous system activity, including stimulants, within the last 2 weeks prior to in-person assessment.

For the current analysis, the inclusion and exclusion criteria were:

Inclusion criteria: Children aged 6-12 who completed the baseline visit of the MADDY study.

Exclusion criteria: Children missing baseline assessments of dependent or independent variables.

3.2 Design and Procedures

The current analysis was a cross-sectional observational study using information from the baseline visits of the MADDY study. All participants who attended a baseline visit and completed a food frequency questionnaire assessment were included, resulting in a sample size of 134 participants for this study.

Participants for the MADDY Study were recruited using a flyer, by word of mouth, and through social media, specifically Facebook and Twitter. Written and informed consent and assent was completed at the baseline visit, prior to any study procedures. All study protocols and materials were approved by the Institutional Review Board (IRB) / Research Ethics Board (REB) at each site. Overall, 135 participants were enrolled in the MADDY study.

At the two U.S. sites, the child and parent received compensation for participating in the MADDY Study in the form of a gift card for completing study visits, biological samples, and required questionnaires. All of the information used in this analysis was acquired at the baseline visit, for which parent/guardians were paid $20 for completion of the in-person visit including questionnaires, while child participants were paid $10 per in-person assessment. At the Canadian site, payment to participants was not expected or customary; parents were reimbursed for cost of travel, including parking and mileage per onsite visit.

3.3 Measures

Sociodemographic measures

Demographic information was collected at the baseline visit using a Demographics and History questionnaire and recorded in REDCap, an electronic data capture tool used in clinical and translational research.[58] Questions included gender, ethnicity, race, parent/guardians' occupation, parent/guardians' level of education, and family income used in estimating socioeconomic status (SES).

Nutrient intake and diet quality

Dietary intake was collected using a digital food frequency questionnaire (FFQ) called Vioscreen. VioScreen is a validated dietary analysis software that provides the equivalent of 90 days of nutrition tracking in about 20 minutes.[59] VioScreen's dietary analysis offers over 1,200 food images and various portion sizes developed from the Nutrition Coordinating Center (NCC) Food and Nutrient Database located at the University of Minnesota Division of Epidemiology and Community Health in Minneapolis.[59] Data is provided for both macro and micronutrient intakes. The dietary data collected using the FFQs were used to calculate diet quality using a predefined diet quality index, Healthy Eating Index-2015 (HEI-2015), which reflects adherence to the Dietary Guidelines for Americans. Dietary quality was analyzed as an HEI-2015 Total Score created from 13 dietary components which encompass specific healthy and unhealthy eating patterns including total fruit, whole fruit, vegetables, greens and beans, whole grains, dairy, protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, saturated fat, and added sugars.[40] Each component has a minimum score of 0, and a maximum score between 5 and 10. Each component is scored such that a higher value indicates better adherence to the dietary guideline. The healthy components are scored such that higher intake corresponds with higher scores, while the "moderation components" which include sodium, saturated fat, and added sugars, are scored with a lower intake corresponding to a higher score. Each component score is summed to create the total HEI score, ranging from 0 to 100.[40]

Behavioral and overall health assessments

At the baseline visit, each parent and child completed multiple questionnaires to assess the current mental health and behavior of the participant. Questionnaires were administered with a research assistant present by providing a handheld electronic tablet to the parent to complete the questions as a survey in REDCap. The parent-administered questionnaires included the CASI-5 and Strengths and Difficulties Questionnaire (SDQ). ADHD symptoms were assessed using subscales of CASI-5; emotional dysregulation symptoms were assessed using subscales of CASI-5 and SDQ measures.

CASI-5 is a validated behavior rating scale for DSM-5-defined emotional and behavioral disorders in youths between 5 and 18 years old.[60] The CASI-5 includes questions assessing symptoms of ADHD (2 subscales: inattention and hyperactivity), 1 subscale for symptoms of Disruptive Mood Dysregulation Disorder (DMDD), and 1 subscale for symptoms of Oppositional Defiant Disorder (ODD). There are 2 to 9 Likert-style questions for each subscale, with raw scores of 0=never, 1=sometimes, 2=often, 3=very often. A symptom severity score is calculated for each subscale as the sum of the raw scores for each question in a subscale. A mean score with a value from 0 to 3 is calculated for each subscale, with 3 being the highest possible symptom severity mean score.[60] ADHD symptom severity is measured using the symptom severity mean scores for both inattention and hyperactivity/impulsiveness subscale on the CASI-5. A mean item score of 2 or greater is considered clinically impairing. Emotional dysregulation symptoms are measured using the symptom severity mean scores from the ODD and DMDD subscales on the CASI-5.

The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire designed to measure positive and negative attributes, divided between 5 scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationships, and prosocial behaviors.[61] Each problem has a maximum score of 10, with higher scores denoting more severe problems, except on the prosocial subscale which is reverse scored. Cut-points are provided to differentiate between scores that are "close to average," defined such that 80% of the population would score in that range, and elevated scores. The "close to average" ranges are 0-3 for emotional problems, 0-2 for conduct problems, 0-5 for hyperactivity/impulsivity, 0-2 for peer problems, and 8-10 for prosocial scores; anything above that range (or below the range for prosocial) is considered elevated.[62]

3.4 Statistical Analysis

Demographic variables and diet quality scores were analyzed using descriptive statistics. These were reported as means (standard deviations) for normally distributed data or medians (interquartile ranges) for non-normal data, and proportions where appropriate. For non-parametric data, p-values comparing data across 2 categories were calculated using Mann-Whitney test and Kruskal-Wallis test was used for 3+ categories. One-sample t-test and Wilcoxon Signed-rank test were used to compare total HEI score and HEI category scores, respectively, to the national average. ADHD and emotional symptom scores and diet quality scores were analyzed as continuous variables. Linear regression models were used to examine the relation of diet quality scores and severity of ADHD and emotional symptoms, adjusting for covariates when necessary. Statistical analyses were conducted using Stata Version 16 statistical software package (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Chapter 4. Results

4.1 Sample Population Characteristics

The study included 134 children aged 6 to 12 (median age = 9.9 years, IQR= 8.4-11.1) presenting with symptoms of ADHD and emotional dysregulation, 71% of whom were male. Approximately 79% of the sample identified as White/Caucasian. Over half of the sample (57%) had family income greater than $80,000/year, while about 34% had incomes between $30,000-80,000/year, and the remaining 9% had incomes below $30,000/year. A complete description of the sociodemographic characteristics and symptom scores of the study population are shown in Table 3. The characteristics of the study participants as related to symptoms of ADHD are shown in Table 4, and characteristics as related to symptoms of emotional dysregulation are shown in Tables 5 and 6. Tables 4-6 show an inverse relationship between family income and symptom severity scores for all outcome conditions [hyperactivity ($p = 0.04$), Emotional Problems ($p = 0.01$), Conduct Problems ($p = 0.002$), ODD ($p = 0.004$), and DMDD ($p = 0.005$)], except inattention ($p =0.91$). Correlation coefficients were calculated to find associations between age, BMI, and symptom severity scores. There was a significant association between age and the CASI-5 Inattention score ($r = 0.19$, $p=0.03$) and between BMI and SDQ Emotional Problems score ($r = 0.176$, $p=0.05$); the rest of the relationships were not significant. The characteristics of the study participants as related to HEI scores are shown in Table 7. There were no significant associations between the demographic variables and HEI scores.

The average total HEI-2015 score for the study sample was 63.4 [(SD =8.8); range (40.8-81.2)], which is significantly higher than the mean of 53.9 (95% CI: 52.5-55.1) ($p < 0.0001$) reported among the general U.S. child population aged 6-11 based on 2009-2014 NHANES data.[44] This sample of children with ADHD symptoms also had significantly better scores than the national average for all the HEI component scores, except for Whole Fruit, Dairy, Sodium, and Saturated Fat which were all significantly below the national average. The mean score for Fatty Acids was not significantly different between the two populations (Table 8). A radar plot comparing the dietary patterns for the study sample compared to the national average is shown in Figure 1.

Table 3. Characteristics of the study sample.

Characteristic	Median	IQR
Child's age	9.9	8.4-11.1
BMI	16.6	15.3-18.6
CASI-5 Item Mean Scores		
Inattention	2.2	1.9-2.7
Hyperactivity	1.9	1.3-2.3
Oppositional Defiant Disorder (ODD)	1.8	1.1-2.3
Disruptive Mood Dysregulation Disorder (DMDD)	1.0	0.5-2.0
SDQ scores		
Emotional Problems	3.0	2.0-5.0
Conduct Problems	3.0	2.0-5.0
	N	%
Child's sex		
male	95	70.9
female	39	29.1
Family Income		
Less than $30,000	12	9.0
$30,001 - 60,000	28	20.9
$60,001 - 80,000	18	13.4
$80,001 or more	76	56.7
Parent Marital Status		
married	101	75.4
divorced	25	18.7
single	8	6.0
Parent Educational Level		
high school	21	15.7
technical college/ trade school	32	23.9
university or higher	81	60.4
Ethnicity [a]		
Not Hispanic or Latino	92	68.7
Hispanic or Latino	8	6.0
Other	7	5.2
Race [a]		
Asian	5	3.7
Black	8	6.0
White	106	79.1
Other	7	5.2

[a] 27 participants did not report ethnicity, 8 participants did not report race

Table 4. Characteristics of participants as related to symptoms of ADHD

Characteristic	CASI-5 Inattention Mean (SD)	CASI-5 Inattention Median (IQR)	CASI-5 Inattention p-value[a]	CASI-5 Hyperactivity/ Impulsivity Mean (SD)	CASI-5 Hyperactivity/ Impulsivity Median (IQR)	CASI-5 Hyperactivity/ Impulsivity p-value[a]
Child's sex			0.119			0.058
male	2.26 (0.47)	2.33 (1.89-2.67)		1.84 (0.67)	2.00 (1.40-2.30)	
female	2.10 (0.52)	2.11 (1.78-2.44)		1.62 (0.66)	1.60 (1.20-2.10)	
Family Income			0.908			0.040
Less than $30,000	2.25 (0.59)	2.28 (1.95-2.73)		2.03 (0.53)	2.10 (1.55-2.40)	
$30,001 - 60,000	2.27 (0.43)	2.33 (1.89-2.62)		2.00 (0.49)	1.90 (1.65-2.45)	
$60,001 - 80,000	2.18 (0.49)	2.22 (1.78-2.44)		1.96 (0.72)	1.95 (1.30-2.60)	
$80,001 or more	2.20 (0.50)	2.22 (1.89-2.62)		1.61 (0.70)	1.75 (1.05-2.20)	
Parent Marital Status			0.978			0.782
married	2.21 (0.50)	2.33 (1.89-2.67)		1.78 (0.64)	1.80 (1.30-2.20)	
divorced	2.24 (0.42)	2.22 (2.00-2.56)		1.73 (0.83)	2.00 (1.10-2.30)	
single	2.15 (0.64)	2.22 (1.61-2.73)		1.94 (0.57)	2.05 (1.50-2.40)	
Parent Educational Level			0.299			0.001
high school	2.09 (0.56)	2.00 (1.67-2.44)		2.13 (0.59)	2.30 (1.80-2.60)	
technical college/ trade school	2.18 (0.45)	2.22 (1.95-2.44)		2.00 (0.54)	2.00 (1.70-2.30)	
university or higher	2.26 (0.49)	2.33 (1.89-2.67)		1.60 (0.68)	1.70 (1.10-2.20)	
Ethnicity			0.112			0.849
Not Hispanic or Latino	2.23 (0.53)	2.28 (1.89-2.67)		1.83 (0.68)	1.95 (1.30-2.35)	
Hispanic or Latino	2.38 (0.32)	2.33 (2.17-2.67)		1.86 (0.70)	1.95 (1.60-2.40)	
Other	1.84 (0.47)	1.67 (1.56-2.44)		1.79 (0.61)	1.60 (1.30-2.10)	
Race			0.441			0.879
Asian	1.96 (0.59)	1.89 (1.67-2.22)		1.90 (0.63)	2.00 (1.30-2.40)	
Black	2.37 (0.42)	2.39 (2.06-2.67)		1.75 (0.88)	2.05 (0.95-2.40)	
White	2.21 (0.50)	2.22 (1.89-2.67)		1.80 (0.66)	1.90 (1.30-2.30)	
Other	2.40 (0.49)	2.44 (2.00-2.78)		2.03 (0.67)	1.90 (1.30-2.80)	

a. p-value comparing 2 categories is calculated using Mann-Whitney test and for 3+ categories is calculated using Kruskal-Wallis test

Table 5. Characteristics of participants as related to symptoms of emotional dysregulation based on CASI-5 measures

	CASI-5 ODD			CASI-5 DMDD		
Characteristic	**Mean (SD)**	**Median (IQR)**	**p-value [a]**	**Mean (SD)**	**Median (IQR)**	**p-value [a]**
Child's sex			0.123			0.226
male	1.73 (0.69)	1.88 (1.25-2.25)		1.30 (0.85)	1.00 (0.50-2.00)	
female	1.53 (0.69)	1.50 (1.00-2.13)		1.09 (0.79)	1.00 (0.50-1.50)	
Family Income			0.004			0.005
Less than $30,000	2.21 (0.61)	2.44 (2.00-2.63)		1.88 (0.80)	2.00 (1.25-2.50)	
$30,001 - 60,000	1.76 (0.61)	1.88 (1.25-2.19)		1.25 (0.83)	1.00 (0.50-2.00)	
$60,001 - 80,000	1.80 (0.70)	1.88 (1.38-2.38)		1.58 (0.84)	1.50 (1.00-2.00)	
$80,001 or more	1.52 (0.69)	1.50 (1.07-1.94)		1.05 (0.78)	1.00 (0.50-1.50)	
Parent Marital Status			0.117			0.128
married	1.66 (0.66)	1.75 (1.25-2.13)		1.20 (0.76)	1.00 (0.50-1.50)	
divorced	1.57 (0.78)	1.50 (1.00-2.25)		1.18 (1.01)	1.00 (0.50-2.00)	
single	2.11 (0.69)	2.19 (1.94-2.57)		1.88 (1.03)	2.00 (1.25-2.75)	
Parent Educational Level			0.513			0.191
high school	1.56 (0.73)	1.75 (1.00-2.00)		0.95 (0.69)	1.00 (0.50-1.25)	
technical college/ trade school	1.76 (0.74)	1.88 (1.19-2.38)		1.39 (0.98)	1.50 (0.50-2.00)	
university or higher	1.66 (0.67)	1.75 (1.25-2.25)		1.25 (0.80)	1.50 (0.50-2.00)	
Ethnicity			0.599			0.825
Not Hispanic or Latino	1.69 (0.71)	1.75 (1.13-2.25)		1.21 (0.80)	1.00 (0.50-1.50)	
Hispanic or Latino	1.89 (0.52)	1.94 (1.44-2.32)		1.50 (1.07)	1.25 (0.50-2.50)	
Other	1.52 (0.60)	1.50 (1.25-1.88)		1.29 (1.07)	1.00 (0.50-2.50)	
Race			0.193			0.133
Asian	1.70 (0.24)	1.88 (1.50-1.88)		1.50 (0.94)	1.00 (1.00-2.50)	
Black	2.18 (0.46)	2.19 (1.94-2.44)		1.88 (0.64)	1.75 (1.50-2.25)	
White	1.65 (0.70)	1.75 (1.13-2.25)		1.21 (0.83)	1.00 (0.50-2.00)	
Other	1.75 (0.54)	1.75 (1.25-2.00)		1.07 (0.84)	1.00 (0.50-1.50)	

a. p-value comparing 2 categories is calculated using Mann-Whitney test and for 3+ categories is calculated using Kruskal-Wallis test

Table 6. Characteristics of participants as related to symptoms of emotional dysregulation based on SDQ measures

Characteristic	SDQ Emotional Problems			SDQ Conduct Problems		
	Mean (SD)	Median (IQR)	p-value [a]	Mean (SD)	Median (IQR)	p-value [a]
Child's sex			0.394			0.562
male	3.25 (2.44)	3.00 (1.00-5.00)		3.67 (1.97)	4.00 (2.00-5.00)	
female	3.56 (2.23)	4.00 (2.00-5.00)		3.49 (1.75)	3.00 (2.00-5.00)	
Family Income			0.011			0.002
Less than $30,000	5.00 (2.73)	4.00 (3.00-8.00)		4.92 (1.73)	5.00 (4.00-6.00)	
$30,001 - 60,000	3.86 (2.21)	4.00 (2.00-5.00)		4.32 (2.07)	4.00 (3.00-5.50)	
$60,001 - 80,000	3.83 (2.36)	4.00 (2.00-5.00)		3.72 (1.78)	4.00 (2.00-5.00)	
$80,001 or more	2.78 (2.23)	2.00 (1.00-4.00)		3.13 (1.74)	3.00 (2.00-4.00)	
Parent Marital Status			0.442			0.513
married	3.32 (2.37)	3.00 (1.00-5.00)		3.63 (1.92)	3.00 (2.00-5.00)	
divorced	3.04 (2.11)	3.00 (2.00-4.00)		3.40 (1.96)	3.00 (2.00-5.00)	
single	4.63 (3.07)	3.50 (2.50-7.50)		4.13 (1.55)	4.50 (3.50-5.00)	
Parent Educational Level			0.161			0.857
high school	3.24 (1.58)	3.00 (2.00-4.00)		3.48 (2.20)	3.00 (1.00-5.00)	
technical college/ trade school	3.94 (2.34)	4.00 (2.00-6.00)		3.75 (1.85)	3.50 (2.50-5.00)	
university or higher	3.14 (2.54)	3.00 (1.00-5.00)		3.60 (1.86)	3.00 (2.00-5.00)	
Ethnicity			0.702			0.266
Not Hispanic or Latino	3.32 (2.34)	3.00 (2.00-5.00)		3.73 (1.92)	4.00 (2.00-5.00)	
Hispanic or Latino	3.63 (3.34)	2.00 (1.50-6.50)		4.13 (2.17)	4.00 (2.50-6.00)	
Other	3.86 (1.77)	4.00 (2.00-5.00)		2.71 (1.11)	3.00 (2.00-4.00)	
Race			0.554			0.314
Asian	3.00 (1.00)	3.00 (2.00-4.00)		4.20 (2.28)	4.00 (2.00-6.00)	
Black	4.00 (1.93)	4.00 (2.00-5.50)		4.63 (1.19)	5.00 (3.50-5.50)	
White	3.15 (2.34)	3.00 (1.00-5.00)		3.61 (1.96)	3.00 (2.00-5.00)	
Other	4.29 (3.09)	4.00 (2.00-6.00)		3.29 (1.25)	3.00 (3.00-4.00)	

a. p-value comparing 2 categories is calculated using Mann-Whitney test and for 3+ categories is calculated using Kruskal-Wallis test

Table 7. Characteristics of participants as related to HEI scores

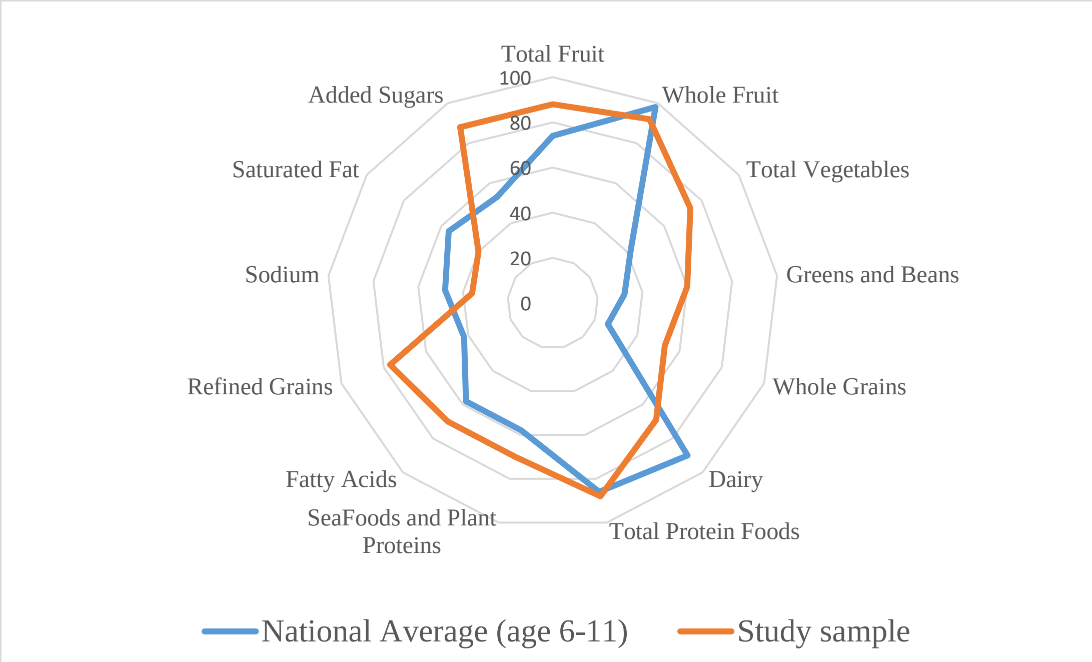
	HEI-2015 Total Score		
Characteristic	**Mean (SD)**	**Median (IQR)**	**p-value [a]**
Child's sex			0.793
male	63.2 (8.7)	63.3 (58.8-68.8)	
female	63.9 (9.1)	65.2 (57.1-71.1)	
Family Income			0.439
Less than $30,000	61.4 (9.6)	59.3 (57.5-62.5)	
$30,001 - 60,000	62.3 (8.8)	63.9 (57.0-68.3)	
$60,001 - 80,000	65.4 (6.7)	67.0 (60.5-69.8)	
$80,001 or more	63.6 (9.2)	64.9 (58.3-70.1)	
Parent Marital Status			0.414
married	63.1 (9.1)	63.5 (57.7-69.8)	
divorced	63.2 (7.7)	65.4 (58.8-67.9)	
single	68.0 (8.2)	65.2 (62.5-73.7)	
Parent Educational Level			0.162
high school	62.8 (9.0)	62.6 (57.2-69.8)	
technical college/ trade school	60.9 (7.7)	61.8 (57.0-67.1)	
university or higher	64.5 (9.1)	65.2 (58.7-70.8)	
Ethnicity			0.450
Not Hispanic or Latino	63.1 (8.9)	63.4 (57.7-69.2)	
Hispanic or Latino	67.2 (6.9)	65.7 (62.1-70.4)	
Other	66.3 (13.4)	66.9 (54.4-79.4)	
Race			0.456
Asian	68.4 (9.2)	69.7 (66.6-71.4)	
Black	65.9 (11.6)	67.8 (62.8-73.3)	
White	63.0 (8.8)	62.9 (57.2-69.0)	
Other	63.4 (10.0)	66.0 (58.2-71.1)	

Table 8. Diet quality of the study sample

	National Average[a]	Study Sample		p-value [b]
	mean	mean (SD)	median (IQR)	
Total HEI-2015 Score (max 100)	53.9	63.4 (8.8)	63.6 (58.2-69.2)	<0.0001
Adequacy components[c]:				
Total Fruit (max 5)	3.7	4.4 (1.1)	5.0 (4.1-5.0)	<0.0001
Whole Fruit (max 5)	4.9	4.6 (0.9)	5.0 (5.0-5.0)	0.001
Total Vegetables (max 5)	2.1	3.7 (1.2)	3.8 (2.9-5.0)	<0.0001
Greens and Beans (max 5)	1.6	3.0 (1.8)	3.2 (1.7-5.0)	<0.0001
Whole Grains (max 10)	2.6	5.3 (3.2)	5.1 (2.5-7.8)	<0.0001
Dairy (max 10)	9.0	6.9 (2.8)	7.2 (4.7-10.0)	<0.0001
Total Protein Foods (max 5)	4.3	4.4 (1.0)	5.0 (4.1-5.0)	0.007
SeaFoods and Plant Proteins (max 5)	2.9	3.5 (1.6)	4.0 (2.4-5.0)	<0.0001
Fatty Acids (max 10)	2.9	3.5 (2.6)	3.0 (1.5-5.1)	0.125
Moderation Components[d]:				
Refined Grains (max 10)	4.2	7.7 (2.5)	8.5 (6.3-10.0)	<0.0001
Sodium (max 10)	4.8	3.6 (2.3)	3.8 (2.0-5.4)	<0.0001
Saturated Fat (max 10)	5.6	4.0 (2.8)	3.8 (1.7-6.0)	<0.0001
Added Sugars (max 10)	5.3	8.8 (1.5)	9.4 (7.9-10.0)	<0.0001

[a] National Average HEI scores for ages 6-11 (Thomson et al. 2018)
[b] p-value calculated by one-sample t-test for Total HEI score and by Wilcoxon signed-rank test for category scores
[c] Adequacy components are scored where higher scores mean higher consumption
[d] Moderation components are scored where higher scores mean lower consumption

Figure 1. Radar plot of HEI category scores for study sample



4.2 Relationship between ADHD Symptom Severity and Diet Quality in Children

The median CASI-5 symptom score for inattention was 2.2 (IQR: 1.9-2.7) and for hyperactivity/ impulsivity was 1.9 (IQR: 1.3-2.3). For most items on the CASI-5, symptom scores above 2, which includes symptoms marked as occurring "often" (score=2) or "very often" (score=3) are considered clinically significant. The study sample had high levels of inattentive symptoms that would be considered clinically significant based on the median CASI-5 item mean scores.

The results of the regression analysis between diet quality scores and ADHD symptom severities are shown in Table 9. Neither the severity of inattention nor hyperactivity-impulsivity symptoms were associated with the HEI-2015 Total Score

(Table 9). In further analysis using the dietary component scores, both vegetables (β = -0.118, p =0.016) and refined grains (β = 0.052, p =0.017) were found to be associated with inattention (Table 9). The statistically significant relationship remained even after adjusting for potential covariates of gender, household income level, and parent education level. Refined grains (β = 0.057, p =0.054) neared a significant association with hyperactivity/impulsivity symptoms, but that relationship was attenuated after controlling for covariates (Table 9).

Table 9. Associations between diet quality score and ADHD symptoms

	CASI-5 Inattention				CASI-5 Hyp/ Imp			
	β	**p-value**	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**
Analysis 1: Total Diet Quality	**Model 0**		**Model 1**		**Model 0**		**Model 1**	
HEI-2015 Total Score	0.001	0.806	0.001	0.856	0.005	0.413	0.010	0.113
Analysis 2: Dietary components*	**Model 0**		**Model 1**		**Model 0**		**Model 1**	
Total Fruit	-0.058	0.256	-0.063	0.228	-0.105	0.133	-0.091	0.169
Vegetables	-0.118	**0.016**	-0.120	**0.015**	-0.087	0.188	-0.077	0.211
Whole Grains	-0.001	0.973	0.002	0.887	0.010	0.614	0.025	0.208
Dairy	-0.024	0.271	-0.015	0.491	0.019	0.512	0.004	0.885
Protein Foods	-0.012	0.820	-0.012	0.831	-0.038	0.610	-0.074	0.292
SeaFoods and Plant Proteins	-0.002	0.943	-0.005	0.873	0.030	0.475	0.036	0.358
Fatty Acids	-0.007	0.798	-0.001	0.973	0.033	0.345	0.032	0.333
Refined Grains	0.052	**0.017**	0.050	**0.022**	0.057	0.054	0.039	0.155
Sodium	-0.024	0.353	-0.031	0.267	-0.030	0.410	-0.005	0.888
Saturated Fat	0.025	0.280	0.025	0.305	0.039	0.229	0.031	0.303
Added Sugars	0.049	0.165	0.033	0.391	-0.030	0.531	0.007	0.892

Model 0: unadjusted model

Model 1: includes model 0 plus gender, household income level, and parental education level as covariates
*components Whole Fruit & Greens and Beans were removed from the regression analysis due to multicollinearity with Total Fruits and Total Vegetables, respectively

4.3 Relationship between Emotional Dysregulation Symptom Severities and Diet Quality in Children

The median SDQ Emotional Problems subscale score for the study sample was 3.0 (IQR: 1.8-5.0) which is considered a “slightly raised” score according to the four-band categorization of SDQ scores for 4–17-year-olds [62] (Table 3). The median Conduct Problems subscale score was 3.0 (IQR: 2.0-5.0) which falls within the “close to average” category [62] (Table 3). The median ODD symptom mean score for the sample population was 1.8 (IQR: 1.1-2.3) and the median DMDD mean symptom score was 1.0 (IQR: 0.5-2.0); neither of these scores are considered clinically significant.

Table 10 includes the results of the regression analysis between diet quality scores and emotional dysregulation symptoms. In the unadjusted models (model 0), HEI-2015 Total Score was not associated with conduct problems, emotional problems, ODD symptoms, or DMDD symptoms. In the unadjusted model examining the relationship between dietary component scores and emotional dysregulation outcomes, the only significant relationship was the Total Fruit score with conduct problems ($\beta = -0.423$, $p = 0.037$). This relationship remained significant after the model was adjusted for covariates of gender, household income level, and parent education level (model 1).

Table 10. Associations between diet quality scores and emotional dysregulation symptoms severities

	SDQ Emotional Problems				SDQ Conduct Problems				CASI ODD Symptom Score				CASI DMDD Symptom Score			
	β	**p-value**	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**
Analysis 1: Total diet quality	**Model 0**		**Model 1**		**Model 0**		**Model 1**		**Model 0**		**Model 1**		**Model 0**		**Model 1**	
HEI-2015 Total Score	-0.040	0.086	-0.036	0.119	0.002	0.924	0.005	0.791	0.004	0.554	0.005	0.412	0.010	0.218	0.011	0.165
Analysis 2: Dietary components*	**Model 0**		**Model 1**		**Model 0**		**Model 1**		**Model 0**		**Model 1**		**Model 0**		**Model 1**	
Total Fruit	-0.174	0.491	-0.162	0.520	-0.423	0.037	-0.400	**0.043**	-0.037	0.618	-0.048	0.506	-0.051	0.572	-0.084	0.330
Vegetables	-0.018	0.942	0.051	0.828	0.213	0.264	0.245	0.179	0.037	0.596	0.052	0.442	0.070	0.410	0.097	0.226
Whole Grains	-0.003	0.966	0.011	0.877	0.061	0.301	0.093	0.110	0.021	0.335	0.034	0.113	0.029	0.271	0.040	0.119
Dairy	-0.006	0.957	-0.017	0.872	0.016	0.854	0.025	0.769	-0.024	0.447	-0.024	0.439	0.018	0.641	0.022	0.551
Protein Foods	0.179	0.507	0.168	0.529	0.198	0.357	0.176	0.397	-0.040	0.611	-0.054	0.478	-0.036	0.709	-0.043	0.636
SeaFoods and Plant Proteins	0.108	0.475	0.102	0.489	-0.109	0.363	-0.119	0.298	-0.002	0.958	-0.004	0.924	0.028	0.606	0.024	0.639
Fatty Acids	-0.067	0.599	-0.042	0.739	0.070	0.495	0.106	0.277	-0.001	0.988	0.012	0.733	-0.012	0.797	0.006	0.881
Refined Grains	-0.065	0.537	-0.116	0.271	0.092	0.279	0.050	0.541	0.041	0.191	0.023	0.443	0.032	0.400	0.008	0.813
Sodium	-0.134	0.302	-0.062	0.639	0.046	0.656	0.074	0.473	-0.015	0.694	0.003	0.928	-0.020	0.658	0.008	0.851
Saturated Fat	-0.082	0.481	-0.084	0.465	-0.009	0.920	-0.027	0.761	-0.019	0.579	-0.024	0.465	-0.008	0.851	-0.007	0.851
Added Sugars	-0.134	0.441	-0.097	0.603	-0.136	0.328	-0.232	0.113	-0.073	0.155	-0.092	0.090	-0.027	0.664	-0.021	0.739

Model 0: unadjusted model

Model 1: includes model 0 plus gender, household income level, and parental education level as covariates

*components Whole Fruit & Greens and Beans were removed from the regression analysis due to multicollinearity with Total Fruits and Total Vegetables, respectively

Chapter 5. Discussion

Summary of Main Findings

This cross-sectional study sought to determine the relationships between diet quality and ADHD and emotional dysregulation symptom severity among youth. We did not find a relationship between overall diet quality and severity of ADHD symptoms of inattention nor hyperactivity/impulsivity. This finding is aligned with a prior study in the United States by Holton et al. (2019) which found no significant difference in HEI scores between those with and without ADHD among both children and college student populations.[49] However, the finding also contrasts with results from several other studies that used other *a priori* defined diet quality indices and found significant associations between ADHD and diet quality. Using a diet quality index reflecting adherence to the Dutch dietary recommendations for children, a significant inverse relationship was found between ADHD symptoms at 6 years of age and diet quality score at age 8.[47] In a study utilizing a diet quality score reflecting adherence to the Mediterranean diet, researchers found a positive relationship between lower diet quality and ADHD diagnosis in children and adolescents.[9] In a study among German children, hyperactivity/impulsivity scores were negatively correlated with diet quality scores based on Healthy Nutrition Score for Kids and Youth guidelines.[48]

Similarly, our study did not find a relationship between overall diet quality and symptoms of emotional dysregulation as measured by ODD symptoms, DMDD symptoms, emotional problems and conduct problems. This finding also contrasts with several studies using *a priori* defined diet quality scores which found that better diet quality was associated with less emotional symptoms. In Germany, a higher diet quality score reflecting adherence to the German Optimized Mixed Diet was associated with lower likelihood of emotional symptoms in 11-year-old children.[54] Additionally, a study of children aged 2-9 in Europe found that higher adherence to healthy dietary guidelines at baseline was associated with fewer emotional and peer problems 2 years later.[50]

There are several plausible explanations for the different findings between the two North American studies and the set of studies from Europe. First, the two North American studies had smaller sample sizes compared with most of the other above cited studies, except for the study by Rios-Hernandez et al., which may make it hard to detect smaller effect sizes. Second, it is possible that the other dietary guidelines/ diet quality indices (Dutch, German, Mediterranean diet, etc.) may more directly reflect dietary factors expected to affect ADHD than the HEI-2015, such as consumption of seafoods, red meat, legumes, nuts, and seeds specifically since these foods are typically high in omega-3 fatty acids, iron, zinc, magnesium, and B-vitamins.

While many of the studies used *a priori* defined dietary indices to measure diet quality, several studies used factor analysis to generate *a posteriori* defined "healthy" dietary patterns, which were consistently defined as high in fruits, vegetables, and whole grains, though other factors were slightly different among the studies. [7, 8, 45, 53, 56] The findings from these studies, as they related ADHD and emotional dysregulation symptoms, were less conclusive. Only one study found an inverse association between the “healthy” dietary pattern and ADHD,[8] while four other studies found that ADHD diagnosis or behavior scores were not associated with the overall “healthy” dietary pattern.[7, 45, 53, 56] Instead, most of these studies found stronger relationships between unhealthy dietary patterns such as “sweet” and “Western” and either ADHD or emotional/behavior problems.

Our study also examined associations between the HEI-2015 dietary component scores and symptom severities. We found the HEI-2015 vegetable component scores to be inversely associated with inattention even after adjusting for covariates, while refined grains showed a direct association. The vegetable association is consistent with previous findings that showed lower frequency of fruit and vegetable consumption was associated with higher prevalence of ADHD diagnosis.[9,10] Our study adds to this finding by linking lower vegetable intake specifically to increased severity of inattention.

Because “refined grains” is an HEI-2015 moderation component, a higher score for this component indicates less consumption of refined grains. The finding of a positive association between the refined grain component score and inattention was unexpected as it indicates that reduced consumption of refined grain is associated with higher levels of inattention. This finding is contrary to previous research where children with ADHD were reported to consume more refined grain compared to children without ADHD.[11] In addition, refined grains has been included as a component of the “Western” dietary pattern that was found to be associated with ADHD, though it was not determined if there was a specific link with ADHD and the refined grains component alone.[7]

Another significant finding is that conduct problems were negatively associated with the total fruit component score, even after adjusting for covariates. Again, these findings are consistent with research which found that improved behavior scores were associated with higher intakes of leafy green vegetables and fruit components of the healthy dietary pattern, but not with the overall healthy dietary pattern.[56] This association may be related to the micronutrient and antioxidant content of fruits which may improve neurotransmission and reduce inflammation.[56]

Of particular interest among this sample of children, family income was found to be significantly associated with all symptom severities except inattention. In general, higher family income was associated with lower symptom scores, and the association was driven primarily by the difference between scores for the lowest income group (<$30,000/year) compared to the highest income group (>$80,001/year), but also by the lowest income group compared to the 2nd highest income group ($60,001-$80,000/year). It should be noted that all significant findings reported above remained significant even after controlling for family income in the adjusted models. In the regression analysis for the adjusted model for conduct problems, the effect size of the statistically significant dietary components was several times smaller than the effect size of family income. An additional confounding factor is that lower family income level is known to be associated with poorer diet quality.[63] Our sample's higher-than-average total HEI scores may reflect that over 70% of this study sample had annual family income levels over $60,000. These findings suggest that family income must be considered in future studies when examining relationships between diet and ADHD or emotional dysregulation symptoms.

Strengths and limitations of the study

This study addresses several gaps in the existing literature on dietary quality and ADHD by being the first study to use the Healthy Eating Index to examine relationships with the severity of symptoms of ADHD and emotional dysregulation. This is also the first study to investigate the HEI dietary component scores for potential associations with these symptoms. Another strength of this study is the use of continuous variables for both diet quality and ADHD symptoms to avoid the loss of useful information caused by translating into categories.[40] Finally, the use of dietary pattern analysis compared to single nutrient analyses enables a broader picture of food and nutrient consumption, which is pertinent given the multi-factorial nature of ADHD and the potential effects of a variety of nutrients on symptoms.

A limitation of this study is the use of a FFQ to track dietary intake. While a good tool for capturing habitual dietary intake, FFQs are vulnerable to random and systematic errors,[64] making the detection of small effect size more difficult. Additionally, the relatively small sample size of this study compared to larger population studies also make detection of small effect sizes more difficult. The cross-sectional design of this study does not provide any indication of cause-and-effect relationships between diet and symptoms. Finally, the generalizability of findings from this study may be limited by the relatively high mean HEI score of this study sample; caution may be warranted in the generalization of study results to other cohorts of children with ADHD.

Implications for future research

Although ADHD affects almost 10% of the US population and the US prevalence is nearly double the global prevalence, there is a scarcity of studies examining the relationship between ADHD and US dietary patterns. The existing studies of US samples have not found relationships with ADHD and overall diet quality as measured by the Healthy Eating Index. Future research should take advantage of larger sample populations if available to enable the detection of small effect sizes. Additionally, future research should utilize dietary indices that better capture nutrients of interest which are associated with ADHD and emotional symptoms as applied to the US population. Finally, more extensive analysis of how family income may moderate the relationship between diet and emotional dysregulation symptoms should be examined.

Chapter 6. Conclusions

While better vegetable and total fruit scores were associated with better symptoms in aspects of ADHD and emotional dysregulation, overall diet quality measured by the HEI was not associated with inattention, hyperactivity/impulsivity, and emotional dysregulation symptom severities among this cohort of children. Family income level was also significantly associated with severity of hyperactivity/ impulsivity, emotional problems, conduct problems, along with ODD and DMDD symptoms. Our findings could be explained by the fact that our study sample had relatively high family income and good diet quality. These findings are significant to the population of children with symptoms of ADHD and irritability because they indicate that those with more severe symptoms are more likely to not eat enough fruits and vegetables, putting them at increased risk for future diseases.

Bibliography

1. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *International Journal of Epidemiology*. 2014;43(2):434-442. https://www.ncbi.nlm.nih.gov/pubmed/24464188. doi: 10.1093/ije/dyt261.

2. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. *J Clin Child Adolesc Psychol*. 2018;47(2):199-212. doi: 10.1080/15374416.2017.1417860 [doi].

3. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, fifth edition.* 5th ed. Washington, DC: ; 2013.

4. Faraone SV, Rostain AL, Blader J, et al. Practitioner review: Emotional dysregulation in attention-deficit/hyperactivity disorder – implications for clinical recognition and intervention. *Journal of Child Psychology and Psychiatry*. 2019;60(2):133-150. https://onlinelibrary.wiley.com/doi/abs/10.1111/jcpp.12899. Accessed Mar 11, 2020. doi: 10.1111/jcpp.12899.

5. Pellow J, Solomon EM, Barnard CN. Complementary and alternative medical therapies for children with attention-deficit/hyperactivity disorder (ADHD). *Altern Med Rev*. 2011;16(4):323-337.

6. Lange KW, Hauser J, Lange KM, et al. The role of nutritional supplements in the

treatment of ADHD: What the evidence says. *Curr Psychiatry Rep*. 2017;19(2):8-1. doi: 10.1007/s11920-017-0762-1 [doi].

7. Howard AL, Robinson M, Smith GJ, Ambrosini GL, Piek JP, Oddy WH. ADHD is associated with a "western" dietary pattern in adolescents. *J Atten Disord*. 2011;15(5):403-411. doi: 10.1177/1087054710365990 [doi].

8. Abbasi K, Beigrezai S, Ghiasvand R, Pourmasoumi M, Mahaki B. Dietary patterns and attention deficit hyperactivity disorder among iranian children: A case-control study. *J Am Coll Nutr*. 2019;38(1):76-83. doi: 10.1080/07315724.2018.1473819 [doi].

9. Rios-Hernandez A, Alda JA, Farran-Codina A, Ferreira-Garcia E, Izquierdo-Pulido M. The mediterranean diet and ADHD in children and adolescents. *Pediatrics*. 2017;139(2):10.1542/peds.2016-2027. doi: e20162027 [pii].

10. Wang L, Yu Y, Fu M, et al. Dietary profiles, nutritional biochemistry status, and attention-deficit/hyperactivity disorder: Path analysis for a case-control study. *J Clin Med*. 2019;8(5). Accessed Sep 28, 2020. doi: 10.3390/jcm8050709.

11. Chou WJ, Lee MF, Hou ML, et al. Dietary and nutrient status of children with attention-deficit/ hyperactivity disorder: A case-control study. *Asia Pac J Clin Nutr*. 2018;27(6):1325-1331. doi: 10.6133/apjcn.201811_27(6).0020 [doi].

12. Wolraich ML, Hagan JF,Jr, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144(4):10.1542/peds.2019-2528. doi: e20192528 [pii].

13. Reale L, Bartoli B, Cartabia M, et al. Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. *Eur Child Adolesc Psychiatry*.

2017;26(12):1443-1457. doi: 10.1007/s00787-017-1005-z [doi].

14. Mohammadi MR, Zarafshan H, Khaleghi A, et al. Prevalence of ADHD and its comorbidities in a population-based sample. *J Atten Disord*. 2019:1087054719886372. doi: 10.1177/1087054719886372 [doi].

15. Cosgrove VE, Rhee SH, Gelhorn HL, et al. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. *J Abnorm Child Psychol*. 2011;39(1):109-123. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036783/. Accessed Mar 18, 2021. doi: 10.1007/s10802-010-9444-8.

16. Ghosh A, Ray A, Basu A. Oppositional defiant disorder: Current insight. *Psychol Res Behav Manag*. 2017;10:353-367. doi: 10.2147/PRBM.S120582 [doi].

17. Mayes SD, Waxmonsky JD, Calhoun SL, Bixler EO. Disruptive mood dysregulation disorder symptoms and association with oppositional defiant and other disorders in a general population child sample. *J Child Adolesc Psychopharmacol*. 2016;26(2):101-106. doi: 10.1089/cap.2015.0074 [doi].

18. van Stralen J. Emotional dysregulation in children with attention-deficit/hyperactivity disorder. *Atten Defic Hyperact Disord*. 2016;8(4):175-187. doi: 10.1007/s12402-016-0199-0 [doi].

19. Carlson GA. Presidential address: Emotion dysregulation in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2020;59(1):15-19. http://dx.doi.org/10.1016/j.jaac.2019.11.004. doi: 10.1016/j.jaac.2019.11.004.

20. Nigg JT, Karalunas SL, Gustafsson HC, et al. Evaluating chronic emotional dysregulation and irritability in relation to ADHD and depression genetic risk in children

with ADHD. *J Child Psychol Psychiatry*. 2020;61(2):205-214. doi: 10.1111/jcpp.13132 [doi].

21. Faraone SV. The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci Biobehav Rev*. 2018;87:255-270. doi: S0149-7634(17)30807-2 [pii].

22. Lepping P, Huber M. Role of zinc in the pathogenesis of attention-deficit hyperactivity disorder: Implications for research and treatment. *CNS Drugs*. 2010;24(9):721-728. doi: 10.2165/11537610-000000000-00000 [doi].

23. Konofal E, Lecendreux M, Deron J, et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. *Pediatr Neurol*. 2008;38(1):20-26. doi: S0887-8994(07)00417-1 [pii].

24. Nutraceuticals: Efficacy, safety, and toxicity. In: Gupta RC, ed. Academic Press; 2016:193-205.

25. Wendolowicz A, Stefanska E, Ostrowska L. Influence of selected dietary components on the functioning of the human nervous system. *Rocz Panstw Zakl Hig*. 2018;69(1):15-21.

26. Justo R, Cesar M, Migowski E, Cisne R. Relation between vitamins of the b complex, GABA and glutamate, and their role in neurocognitive disorders -brief review. *International Journal of Basic and Applied Sciences*. 2016;5(4):229-237. https://www.sciencepubco.com/index.php/ijbas/article/view/6707. Accessed May 8, 2020. doi: 10.14419/ijbas.v5i4.6707.

27. Black LJ, Allen KL, Jacoby P, et al. Low dietary intake of magnesium is associated with increased externalising behaviours in adolescents. *Public Health Nutr*. 2015;18(10):1824-1830. doi: 10.1017/S1368980014002432 [doi].
28. Schuchardt JP, Huss M, Stauss-Grabo M, Hahn A. Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *Eur J Pediatr*. 2010;169(2):149-164. doi: 10.1007/s00431-009-1035-8 [doi].
29. Mousain-Bosc M, Roche M, Polge A, Pradal-Prat D, Rapin J, Bali JP. Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. I. attention deficit hyperactivity disorders. *Magnes Res*. 2006;19(1):46-52.
30. Hemamy M, Heidari-Beni M, Askari G, Karahmadi M, Maracy M. Effect of vitamin D and magnesium supplementation on behavior problems in children with attention-deficit hyperactivity disorder. *Int J Prev Med*. 2020;11:4. doi: 10.4103/ijpvm.IJPVM_546_17 [doi].
31. Huss M, Volp A, Stauss-Grabo M. Supplementation of polyunsaturated fatty acids, magnesium and zinc in children seeking medical advice for attention-deficit/hyperactivity problems - an observational cohort study. *Lipids Health Dis*. 2010;9:105-105. doi: 10.1186/1476-511X-9-105 [doi].
32. Bilici M, Yildirim F, Kandil S, et al. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(1):181-190. doi: S0278-5846(03)00247-1 [pii].
33. Sorgi PJ, Hallowell EM, Hutchins HL, Sears B. Effects of an open-label pilot study

with high-dose EPA/DHA concentrates on plasma phospholipids and behavior in children with attention deficit hyperactivity disorder. *Nutr J*. 2007;6:16-16. doi: 1475-2891-6-16 [pii].

34. Mozaffarian Dariush, Rosenberg Irwin, Uauy Ricardo. History of modern nutrition science—implications for current research, dietary guidelines, and food policy. *BMJ*. 2018;361.

35. Hu FB. Dietary pattern analysis: A new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002;13(1):3-9. doi: 10.1097/00041433-200202000-00002 [doi].

36. Neuhouser ML. The importance of healthy dietary patterns in chronic disease prevention. *Nutr Res*. 2019;70:3-6. doi: S0271-5317(18)30222-7 [pii].

37. Donini LM, Serra-Majem L, Bulló M, Gil Á, Salas-Salvadó J. The mediterranean diet: Culture, health and science. *Br J Nutr*. 2015;113 Suppl 2:1. Accessed Mar 13, 2020. doi: 10.1017/S0007114515001087.

38. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH collaborative research group. *N Engl J Med*. 1997;336(16):1117-1124. Accessed Mar 13, 2020. doi: 10.1056/NEJM199704173361601.

39. Grotto D, Zied E. The standard american diet and its relationship to the health status of americans. *Nutrition in Clinical Practice*. 2010;25(6):603-612. https://onlinelibrary.wiley.com/doi/abs/10.1177/0884533610386234. Accessed Sep 16, 2020. doi: 10.1177/0884533610386234.

40. Krebs-Smith SM, Pannucci TE, Subar AF, et al. Update of the healthy eating index:

HEI-2015. *J Acad Nutr Diet*. 2018;118(9):1591-1602. doi: S2212-2672(18)30838-4 [pii].

41. Imamura F, Micha R, Khatibzadeh S, et al. Dietary quality among men and women in 187 countries in 1990 and 2010: A systematic assessment. *Lancet Glob Health*. 2015;3(3):132. doi: 10.1016/S2214-109X(14)70381-X [doi].

42. Mikkila V, Vepsalainen H, Saloheimo T, et al. An international comparison of dietary patterns in 9-11-year-old children. *Int J Obes Suppl*. 2015;5(Suppl 2):17. doi: 10.1038/ijosup.2015.14 [doi].

43. Banfield EC, Liu Y, Davis JS, Chang S, Frazier-Wood AC. Poor adherence to US dietary guidelines for children and adolescents in the national health and nutrition examination survey population. *J Acad Nutr Diet*. 2016;116(1):21-27. Accessed Sep 28, 2020. doi: 10.1016/j.jand.2015.08.010.

44. Thomson JL, Tussing-Humphreys LM, Goodman MH, Landry AS. Diet quality in a nationally representative sample of american children by sociodemographic characteristics. *The American Journal of Clinical Nutrition*. 2019;109(1):127-138. https://doi.org/10.1093/ajcn/nqy284. Accessed Mar 18, 2021. doi: 10.1093/ajcn/nqy284.

45. Azadbakht L, Esmaillzadeh A. Dietary patterns and attention deficit hyperactivity disorder among iranian children. *Nutrition*. 2012;28(3):242-249. doi: 10.1016/j.nut.2011.05.018 [doi].

46. Woo HD, Kim DW, Hong YS, et al. Dietary patterns in children with attention deficit/hyperactivity disorder (ADHD). *Nutrients*. 2014;6(4):1539-1553. doi: 10.3390/nu6041539 [doi].

47. Mian A, Jansen PW, Nguyen AN, Bowling A, Renders CM, Voortman T. Children's

attention-deficit/hyperactivity disorder symptoms predict lower diet quality but not vice versa: Results from bidirectional analyses in a population-based cohort. *J Nutr*. 2019;149(4):642-648. doi: 10.1093/jn/nxy273 [doi].

48. van Egmond-Frohlich AW, Weghuber D, de Zwaan M. Association of symptoms of attention-deficit/hyperactivity disorder with physical activity, media time, and food intake in children and adolescents. *PLoS One*. 2012;7(11):e49781. doi: 10.1371/journal.pone.0049781 [doi].

49. Holton KF, Johnstone JM, Brandley ET, Nigg JT. Evaluation of dietary intake in children and college students with and without attention-deficit/hyperactivity disorder. *Nutr Neurosci*. 2019;22(9):664-677. doi: 10.1080/1028415X.2018.1427661 [doi].

50. Arvidsson L, Eiben G, Hunsberger M, et al. Bidirectional associations between psychosocial well-being and adherence to healthy dietary guidelines in european children: Prospective findings from the IDEFICS study. *BMC Public Health*. 2017;17(1):926-5. doi: 10.1186/s12889-017-4920-5 [doi].

51. Wiles NJ, Northstone K, Emmett P, Lewis G. 'Junk food' diet and childhood behavioural problems: Results from the ALSPAC cohort. *Eur J Clin Nutr*. 2009;63(4):491-498. doi: 1602967 [pii].

52. Peacock PJ, Lewis G, Northstone K, Wiles NJ. Childhood diet and behavioural problems: Results from the ALSPAC cohort. *Eur J Clin Nutr*. 2011;65(6):720-726. doi: 10.1038/ejcn.2011.27 [doi].

53. Trapp GS, Allen KL, Black LJ, et al. A prospective investigation of dietary patterns and internalizing and externalizing mental health problems in adolescents. *Food Sci Nutr*.

2016;4(6):888-896. doi: 10.1002/fsn3.355 [doi].

54. Kohlboeck G, Sausenthaler S, Standl M, et al. Food intake, diet quality and behavioral problems in children: Results from the GINI-plus/LISA-plus studies. *Ann Nutr Metab*. 2012;60(4):247-256. doi: 10.1159/000337552 [doi].

55. Abbasalizad Farhangi M, Dehghan P, Jahangiry L. Mental health problems in relation to eating behavior patterns, nutrient intakes and health related quality of life among Iranian female adolescents. *PLoS One*. 2018;13(4):e0195669. doi: 10.1371/journal.pone.0195669 [doi].

56. Oddy WH, Robinson M, Ambrosini GL, et al. The association between dietary patterns and mental health in early adolescence. *Preventive medicine*. 2009;49(1):39-44. https://www.clinicalkey.es/playcontent/1-s2.0-S0091743509002643. doi: 10.1016/j.ypmed.2009.05.009.

57. Johnstone JM, Leung B, Gracious B, et al. Rationale and design of an international randomized placebo-controlled trial of a 36-ingredient micronutrient supplement for children with ADHD and irritable mood: The micronutrients for ADHD in youth (MADDY) study. *Contemp Clin Trials Commun*. 2019;16:100478. Accessed Aug 19, 2020. doi: 10.1016/j.conctc.2019.100478.

58. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2700030/. Accessed Sep 14, 2020. doi: 10.1016/j.jbi.2008.08.010.

59. Alan R Kristal, Ann S Kolar, James L Fisher, Jesse J Plascak, Phyllis J Stumbo, Rick Weiss, Electra D Paskett, Kristal AR, Kolar AS, et al. Evaluation of web-based, self-administered, graphical food frequency questionnaire. *Journal of the Academy of Nutrition and Dietetics*. 2014;114(4):613-621.

60. Gadow KS. Checkmate Plus. Child and adolescent symptoms inventory-5. 2015; Child and Adolescent Symptoms Inventory-5.

61. Hall CL, Guo B, Valentine AZ, et al. The validity of the strengths and difficulties questionnaire (SDQ) for children with ADHD symptoms. *PLoS ONE*. 2019;14(6).

62. YouthinMind. Scoring the strengths & difficulties questionnaire for age 4-17. https://www.sdqinfo.org Web site. https://www.sdqinfo.org/py/sdqinfo/b3.py?language=Englishqz(USA). Updated 2015. Accessed March 18, 2021.

63. French S, Tangney C, Crane M, Wang Y, Appelhans B. Nutrition quality of food purchases varies by household income: The SHoPPER study. *BMC Public Health*. 2019;19(231). https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-6546-2.

64. McClung HL, Ptomey LT, Shook RP, et al. Dietary intake and physical activity assessment: Current tools, techniques, and technologies for use in adult populations. *American journal of preventive medicine*. 2018;55(4):e93-e104. http://dx.doi.org/10.1016/j.amepre.2018.06.011. doi: 10.1016/j.amepre.2018.06.011.