DIETARY INTAKE AND NUTRIENT STATUS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

by

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Abstract

Study Objective. To assess the dietary intakes of children with Attention Deficit Hyperactivity Disorder (ADHD); including macro- and micronutrient intake, the percentage of low nutrient density foods in the diet, as well as specific biochemical and anthropometric parameters. **Design.** Observational study. **Setting.** Provincial ADHD Program of BC, Children's' Hospital, Vancouver, BC. **Sample.** 44 children aged 6 - 12 years with ADHD, treatment-naïve or stable on medication for 6 months or longer. **Main Results.** ADHD Children were taller and heavier than population norms, and significantly taller than previously reported in ADHD. Of children aged 6-8 years, 28% were below the Estimate Average Requirement (EAR) for zinc and 61% of children aged 9-12 years were below the EAR for zinc. In addition, 28% of children aged 6-8 years and 39% of children aged 9-12 years were below the EAR for copper. Only 2% of children in the sample were below lab normal cutoffs for ferritin; however, 73% had serum zinc values below lab normal cut-offs and 23% had serum copper below lab normal cutoffs. Overall prevalence of serum zinc below the 2.5 percentile was 23% compared to 2% from National Health and Nutrition Examination Survey II (NHANES) data. Additionally, mean serum copper was significantly lower than NHANES II data. Mean energy intake was comparable to mean Estimated Energy Requirement (EER) based on the age, gender, height, weight and physical activity of subjects. In addition, mean dietary intake of Low Nutrient Density foods was not significantly different from NHANES II data and there was no significant difference in energy intake or the proportion of daily energy from protein, fat, and carbohydrate than what is observed from CCHS data. Medication treatment for ADHD was not associated with altered dietary intake or nutrient status. **Conclusion.** Results are suggestive of low zinc status in ADHD.

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Glossary

ADHD	Attention Deficit Hyperactivity Disorder
ADP	Adenosine-5'-triphosphate
AMDR	Acceptable Macronutrient Distribution Range
ARA	Arachidonic Acid
BMI	Body Mass Index
CCHS	Canadian Community Health Survey
Ca	Calcium
CDC	Centers for Disease Control and Prevention
DA	Dopamine
DA- -H	Dopamine -hydroxylase
DHA	Docosahexaenoic acid
DSM-IV	Diagnostic and Statistical Manual, 4th Edition
EAR	Estimated Average Requirement
EDTA	Ethylenediamine tetraacetic acid
EER	Estimated energy requirement
GLA	Glutamate
K^+	Potassium
LND	Low Nutrient Density
MRI	Magnetic Resonance Imaging
NHANES	National Health and Nutritional Examination Survey
Na	Sodium
NE	Norepinephrine
PheH	Phenylalanine hydroxylase
PLP	Pyridoxal-5'-phospate
RDA	Recommended Dietary Allowance
SER	Serotonin
TyrH	Tyrosine hydroxylase
UK	United Kingdom
5-HT	5-hydroxytryptophan
Zn	Zinc

Preface

The primary reason for conducting this study was the lack of data, especially Canadian data, describing the dietary intake and nutritional status of children with Attention-Deficit/Hyperactivity Disorder (ADHD). In interactions with numerous professionals that treat ADHD children; including psychiatrists, pediatricians and family practitioners, it was anecdotally reported that parents of ADHD children frequently express concern about the adequacy of food intake as well as what parents perceive as abnormal eating patterns in their children. Specifically, it is parents' perception that their ADHD children consume considerably more carbohydrates than their peers, and are not eating adequate Vegetables and Fruit or Milk and Milk Products (Weiss, personal correspondence).

Parents of ADHD children frequently complain that their children are what they describe as "picky eaters", defined by parents as children that either limit variety of dietary intake (consuming the same few foods), or that they have taste or texture aversions (refusing to eat whole categories of foods with disliked characteristics). Prior to the current study, no data was available for ADHD children assessing dietary intake or the adequacy of food intake as compared with the Dietary Reference Intakes (DRIs) or other national recommendations, such as Canada's Food Guide to Healthy Eating. As well, there was a lack of Canadian nutrient status data for ADHD children.

Another common complaint of parents of ADHD children to clinicians is that their children do not follow normal growth patterns; specifically, that their children are under-tall or under-weight compared with children of the same age and gender. Prior to this study, no Canadian growth data was available on children with this disorder. As stimulant medications, which are the most common type of medication used in the treatment of ADHD are potent appetite suppressors, it was wondered whether these medications might negatively affect growth or alter dietary intake via their effect on appetite.

The purpose of this descriptive study was to determine dietary intake, height, weight, and specific serum parameters of children with ADHD; both on and off different medication protocols for the disorder.

Chapter 1, the Literature Review, discusses the definition of ADHD, the potential role of nutrients in the pathogenesis of ADHD, factors that affect the bioavailability of these nutrients and the limited literature available regarding growth patterns and nutrient status of children with ADHD. Chapter 2 outlines specific research questions, the study hypotheses and the specific objectives of this study. Chapter 3 discusses the study methods used, including data handling and statistical analysis. Chapter 4 presents the results of this study, Chapter 5 discusses the significance of these findings and Chapter 6 draws some conclusions based on the data, as well as making some suggestions for future research.

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Chapter 1- Literature Review

1.1 Introduction to Attention Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurological disorder classified in the Diagnostic and Statistical Manual, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) that affects 3 – 12% of school aged children (Biederman, Faraone, & Kiely, 1996). ADHD is characterized firstly by inattention, which may or may not be accompanied by impulsivity and hyperactivity (American Psychiatric Association, 1994). While inattention, impulsivity and hyperactivity are behaviours common to some extent in all children, they are excessive in children with ADHD.

Diagnostic criteria require that individuals with ADHD exhibit six of nine characteristics (Table 1) (American Psychiatric Association, 1994). In addition, ADHD behaviours must create significant difficulty in at least two areas of life; such as home, in social settings or at school and symptoms of the disorder must be present for at least six months.

The DSM-IV diagnostic system categorizes ADHD into three subtypes:

1. ADHD predominantly inattentive type: (ADHD-IA):
2. ADHD predominantly hyperactive-impulsive type: (ADHD-HI);
3. ADHD combined type: (ADHD-CT)

Two of the ADHD subtypes, ADHD-IA and ADHD-HI have nine specific symptoms associated with each (Table 1). Symptoms of the ADHD-CT subtype include a combination of both inattentive (ADHD-IA) and hyperactive-impulsive (ADHD-HI) symptoms.

Table 1 Prevalence and Predominant Symptoms Associated With Attention Deficit Hyperactivity Disorder Subtypes, [1]

Inattentive type (ADHD-IA)	**Hyperactive-Impulsive** (ADHD-HI)	**Combined type** (ADHD-CT)
Prevalence		
• 27% in clinical studies • 50% in community studies (Weiss & Weiss, 1997)	• 2% of clinic ADHD population • may be higher preschool-early elementary (Weiss & Weiss, 1997)	• 48%-71% (Weiss & Weiss, 1997)
Symptoms		
1. Makes careless mistakes / fails to give close attention to details 2. Has difficulty sustaining attention 3. Does not appear to listen 4. Struggles to follow through on instructions 5. Has difficulty with organization 6. Avoids or dislikes tasks requiring sustained mental effort 7. Loses things 8. Is easily distracted 9. Is forgetful in daily activities	1. Fidgets with hands or feet / squirms in chair 2. Has difficulty remaining seated 3. Runs about or climbs excessively 4. Difficulty engaging in activities quietly 5. Acts as if driven by a motor 6. Talks excessively 7. Blurts out answers before questions have been completed 8. Difficulty waiting or taking turns 9. Interrupts or intrudes upon others	• must meet criteria for 6 of 9 symptoms of ADHD-IA /ADHD-HI

[1]Reference: Diagnostic and Statistical Manual IV (American Psychiatric Association, 1994)

1.2 Neurotransmitters Implicated in ADHD

Dysregulation in both dopamine (Comings, Comings, & Muhleman, 1991; Rowe, Stever, Giedinghagen et al., 1998; Smalley, Baily, Palmer et al., 1998; Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990) and norepinephrine neurotransmitter synthesis (Biederman & Spencer, 1999) is believed to underlie the pathophysiology of ADHD. Current medications such as methylphenidate (Ritalin®) or dextroamphetamine (Dexedrine®) are believed to alter the levels of dopamine in the brain by inhibiting dopamine reuptake (Seeman & Madras, 2000; Spencer, Biederman, & Wilens, 2000) and as amphetamine compounds are also believed to promote monoamine release. Atomoxetine hydrochloride (Strattera®), a non-stimulant ADHD medication, is believed to work by inhibiting norepinephrine reuptake (Mattiuz, Ponsler, Barbuch, Wood et al., 2003; Spencer et al., 2000; Spencer, Ruff, Feldman, & Michelson, 2003)

Magnetic resonance spectroscopy has revealed an increase in glutamate/glutamine activity in both the frontal cortex and striatum in a small sample of children with ADHD-HI as compared to healthy control subjects (MacMaster, Carrey, Sparkes, & Kusumakar, 2003). This finding is important, as recent studies report that there is a chelatable zinc pool in the synaptic nerve terminals that is believed to be responsible for the modulation of glutaminergic neurotransmitter receptors (Colvin, Davis, Nipper, & Carter, 2000). It is unknown whether higher glutaminergic neurotransmitter activity in ADHD may contribute to higher zinc turnover in these children.

1.3 Trace Mineral and Vitamin Cofactors in Dopamine and Norepinephrine Synthesis

Trace elements such as iron, copper and zinc are regarded as essential nutrients, although they are found in minute quantities in the body. Trace minerals were once only thought to be deficient when accompanied by an impairment of function (Gibson, 2005); however, more recently the essentiality of trace minerals is viewed more in terms of suboptimal dietary intakes that may contribute to the risk of certain disease states or sub-optimal biological functioning (Gibson, 2005). Some of the roles of trace minerals relate to functionality of metallo-enzymes (Gibson, 2005), including dopamine- -monooxygenase (Gibson, 2005; Linder & Hazegh-Azam, 1996), pyridoxal phosphate (PLP) (McCormick, Gregory, & Snell, 1961), phenylalanine hydroxylase and tyrosine hydroxylase (Oellien, 1999). These are involved in the dopamine and

norepinephrine biosynthesis (see Figure 1). In addition, vitamin B_6 is converted into pyridoxal-5'-phosphate (PLP) and is also involved in the biosynthesis of dopamine (Leklem, 1999); therefore, copper, iron and zinc as well as vitamin B_6 are all cofactors involved in dopamine and norepinphrine neurotransmitter synthesis (Figure 1).

Biosynthesis of dopamine occurs in the adrenal medulla where the conversion of phenylalanine to tyrosine is catalyzed by phenylalanine hydroxylase and the conversion of tyrosine to L-dopa (L- -(3,4-dihydroxyphenyl)- -alanine) is catalyzed by tyrosine-hydroxylase. L-dopa is then decarboxylated to dopamine (Oellien, 1999). Iron is a cofactor for both phenylalanine-hydroxylase and tyrosine-hydroxylase; two enzymes involved in dopamine synthesis (Oellien, 1999). Zinc is required for the conversion of dietary Vitamin B_6/pyridoxine to its active form pyridoxal phosphate (PLP) (McCormick et al., 1961) through the formation of zinc-adenosine-5'-triphosphate (zinc-ATP) (McCormick et al., 1961). Zinc is preferred over magnesium in the formation of an ATP-chelated co-substrate in the activation of pyridoxal kinases (McCormick & Chen, 1999; McCormick et al., 1961; McCormick DB, 1999). It is thought that low zinc status may indirectly affect the enzymatic synthesis of dopamine and norepinephrine catalyzed by PLP, a vitamin B_6/pyridoxine-dependent enzyme (Leklem, 1999; Merrill & Burnham, 1990). Copper is a cofactor for dopamine- -hydroxylase (also called dopamine- -monooxygenase) that converts dopamine to norepinephrine (Linder & Hazegh-Azam, 1996; Oellien, 1999) and which involves ascorbate (Linder & Hazegh-Azam, 1996).

PLP is involved in over 60 enzymatic reactions, including the decarboxylation reaction in the synthesis of the neurotransmitters dopamine, norepinephrine**,** serotonin, and gamma-aminobutyric acid (GABA) (Leklem, 1999; Merrill & Burnham, 1990). Vitamin B_6 is comprised of three related compounds, pyridoxine, pyridoxal and pyridoxamine and the three corresponding derivatives; namely pyridoxine 5'-phosphate (PNP), pyridoxal 5'-phosphate (PLP) and pyridoxamine 5'-phosphate (PMP). Vitamin B_6 normally refers only to pyridoxine (Thomson Healthcare, 2005). Pyridoxine, pyridoxal and pyridoxamine, once ingested, are absorbed and transported via the portal circulation to the liver. PLP and the other derivatives are synthesized from pyridoxine in the liver, with the help of enzymes that require vitamin B_2, zinc and magnesium (Leklem, 1999). PLP is subsequently transported from the liver to various tissues via

the circulation and bound to serum albumin is the major circulating form of vitamin B_6 in the blood (Leklem, 1999). The major body pool of vitamin B_6 resides in muscle.

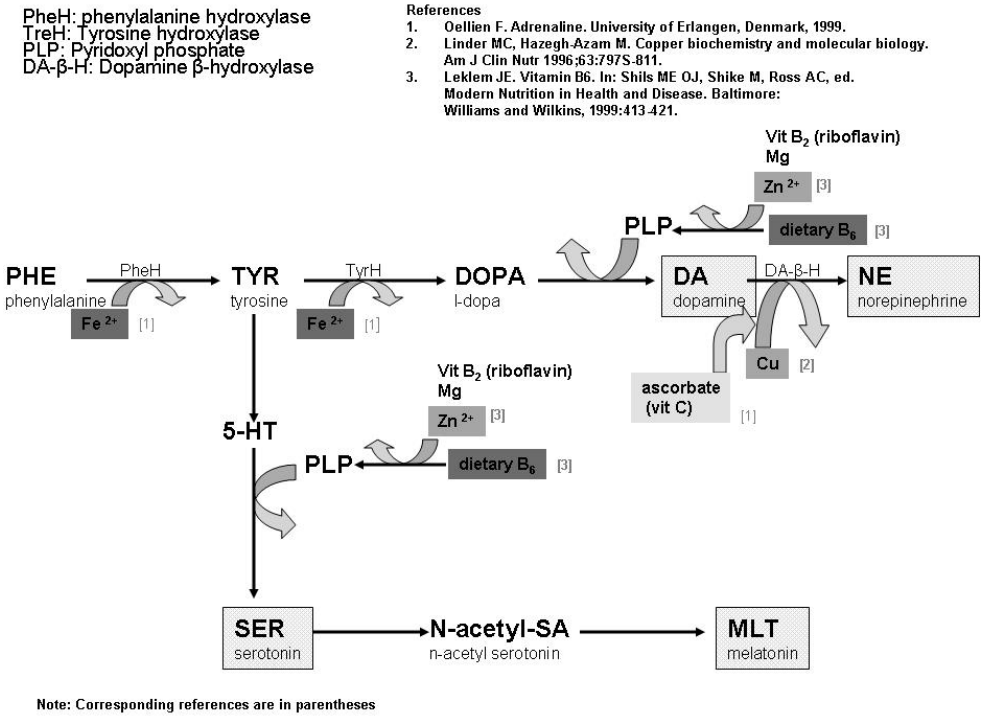

Figure 1 A Proposed Mechanism Describing the Roles of Trace Mineral and Vitamin Cofactors in Neurotransmitter Biosynthesis

1.4 Factors that Affect the Dietary Bioavailability and Biochemical Status of Copper, Iron, Zinc and Vitamin B_6

1.4.1 Trace Minerals

Trace mineral deficiencies arise for several reasons. One reason may be low dietary intake or poor bioavailability of the nutrient. Other potential factors which can produce low trace mineral status include decreased absorption due to disease states (Gibson, 2005) and a higher nutrient turnover arising from conditions that reflect a higher demand for the nutrient. Nutrient-nutrient interactions between trace minerals may also be responsible for suboptimal trace mineral status, such as zinc-copper or zinc-iron interactions (L'Abbe, 2004). Another reason for abnormal trace mineral status may be genetic defects that result in deficiency syndromes (Gibson, 2005).

1.4.1.1 Copper

Copper is an essential trace mineral component of several cupro-enzymes, including dopamine- -monooxygenase, responsible for the conversion of dopamine to norepinephrine (Gibson, 2005). Copper is widely available in foods with the richest sources being organ meats, shellfish (especially oysters), nuts and dried legumes (Gibson, 2005; Lee & Nieman, 2007; Mahan & Escott-Stump, 2000). Central nervous system disturbances that are due to copper deficiency result from abnormal catecholamine levels (Gibson, 2005). Most copper is absorbed from the small intestine, although some is absorbed in the stomach (Gibson, 2005). Once absorbed, copper is transported to the liver via the portal circulation, bound to albumin and transcuprein (Gibson, 2005). In the liver, copper is incorporated into ceruloplasmin and distributed to other tissues (Gibson, 2005). A number of factors affecting serum copper include age related changes, gender, regular strenuous activity and infection and inflammation (Gibson, 2005). Diurnal variation has been reported as being highest in the morning (Gibson, 2005). The majority of clinical features of copper deficiency are associated with changes in copper-based enzymes (Gibson, 2005).

1.4.1.2 Zinc

Zinc has a very important function in the body, being a component of a number of metallo-enzymes (Lee & Nieman, 2007). Zinc is required for the conversion of dietary Vitamin B_6 pyridoxine to its active form pyridoxal phosphate (PLP) (McCormick et al., 1961) and as a result low zinc status may indirectly affect the enzymatic synthesis of dopamine and norepinephrine catalyzed by PLP (Leklem, 1999; Merrill & Burnham, 1990). In both humans and animals, a slowing or cessation of growth in young animals or in children is an early response to zinc deficiency (Lee & Nieman, 2007). Supplementation of mildly zinc-deficient children that are growth-retarded has been reported to result in a growth response (Lee & Nieman, 2007).

Zinc has a distinctive role in a wide range of cellular processes that involve cell division and proliferation (Macdonald, Hambidge, Cousins, & Costello 2000), defense against free radicals (Bray , Kubow, & Bettger, 1986) and support of the immune system (Prasad, 1995). While zinc contributes less than 0.01% to total body weight (Hambidge, 2003), almost a quarter of cellular zinc has been reported to reside in the cell nucleus of organs such as the liver where it has an important role in gene

expression (Dreosti, Fenech, & Ferguson, 2001). Zinc is involved in deoxyribonucleic acid (DNA) transcription via zinc-containing transcription factors (Dreosti et al., 2001). These zinc-finger regions bind to DNA, and help regulate cell proliferation, differentiation and apoptosis (Dreosti et al., 2001).

Zinc is a component of more than 1000 proteins (Ho & Ames, 2002), including the zinc-finger DNA-binding proteins mentioned above, antioxidant enzymes such as copper-zinc superoxide dismutase (SOD), and several proteins involved in DNA-damage repair and tumor suppression, such as p53 (Walsh, Sandstead, Prasad, Newberne, & Fraker, 1992).

It is believed that zinc deficiency may compromise the integrity of DNA (Ho & Ames, 2002). In rats, zinc deficiency has been reported to result in oxidative stress and physical breakdown of the blood–brain barrier (Noseworthy & Bray 2000). Zinc deficiency is known to be associated with abnormalities in brain function, including depression (Hansen, Malecha, Mackenzie, & Kroll, 1993), delays in cognitive development (Black, 1998), and microscopic abnormalities in the brain (Sandstead, Fredrickson, & Penland, 2000).

The largest dietary source of zinc is flesh-foods and milk (Mahan & Escott-Stump, 2000). Foods that are excellent sources of zinc include meat, liver, fish and shellfish, with oysters being one of the best sources (Gibson, 2005). Generally, zinc is higher in darker red meats than in white meats. Zinc is also available in whole grain cereals, nuts and legumes; however, zinc bioavailability may be affected by the amount of phytate in these foods (Gibson, 2005). Phytates (phytic acid/inositol hexaphosphate) are phosphorus compounds found mainly in whole grain cereal products, legumes and nuts that are capable of forming a tight complex with zinc (and iron), thereby decreasing their absorption (Ho & Ames, 2002). Several methods are available to reduce the phytate content of foods including leavening of bread, fermentation and germination and milling (Lonnerdal, 2000). Fiber is often thought to negatively impact zinc absorption however recent studies indicate that most fiber-containing foods also contain phytates (Lonnerdal, 2000).

Zinc bioavailability can also be affected by the amount of protein consumed at the same time as zinc containing foods. (Gibson, 2005; Lonnerdal, 2000; Mahan & Escott-Stump, 2000). The amount of protein in a meal is positively correlated to zinc absorption (Lonnerdal, 2000) and the type of protein in a meal can also affect bioavailability. Animal proteins such as beef, eggs and cheese have been reported to counter the inhibitory effect of phytates on zinc absorption (Lonnerdal, 2000).

Unlike other trace minerals such as iron and copper, there is no large readily available mobilizable zinc store that can be released in response to variations in dietary intake (Gibson, 2005; Lee & Nieman, 2007). It is believed that there are small pools of rapidly exchangeable zinc located in bone, liver and plasma and it is thought that even small losses from these pools can lead to clinical and biochemical signs of zinc deficiency (Gibson, 2005). The body conserves or redistributes the small amount of stored zinc in order to maintain zinc homeostasis (Lee & Nieman, 2007).

Metallothionen is a zinc- and copper-binding protein found mainly in the liver, pancreas, kidney and intestinal mucosa (Lee & Nieman, 2007). Tissue metallothionen concentrations are proportional to zinc status (Hambidge, 2000; Lee & Nieman, 2007). When both serum zinc and serum metallothionen status are assessed together as biochemical assessors, a better picture of zinc status emerges. The use of both of these assessors together enables clinicians to differentiate between acute conditions such as inflammation and infection from zinc deficiency. In the case of infection or inflammation, serum zinc will decrease whereas serum metallothionen increases (Lee & Nieman, 2007). This enables clinicians to know that zinc deficiency is not present, because metallothionen is not responsive to acute stimuli such as infection or inflammation in the presence of a zinc deficiency (Lee & Nieman, 2007). In the case where both serum zinc and serum metallothionen are below expected values, it is likely that zinc deficiency may be present (King, 1990; Lee & Nieman, 2007).

A number of other factors that can affect serum zinc include age related changes and gender (Gibson, 2005; Lee & Nieman, 2007). Fasting status significantly affects serum zinc values with large fluctuations occurring as a result of food intake (Hotz, Peerson, & Brown, 2003; Mellman, Hambidge, & Westcott, 1993). Diurnal variation has also

been reported to affect serum zinc levels; with concentrations being higher in the morning regardless of the fasting status (Hotz et al., 2003).

1.4.1.3 Iron

Iron is a cofactor in two enzymes involved in the synthesis of dopamine, phenylalanine hydroxylase and tyrosine hydroxylase (Oellien, 1999). Food sources that are highest in iron are liver and kidney, mussels and red meat with lesser sources being chicken, fish and legumes (Gibson, 2005; Lee & Nieman, 2007; Mahan & Escott-Stump, 2000). Legumes, such as beans and lentils contain only non-heme iron. Bioavailable heme-iron is only found in flesh-foods. Consumption of flesh foods has an enhancing effect on non-heme iron absorption (Gibson, 2005). With respect to dietary intake, there are several substances found in the diet that can inhibit iron-absorption. Phytates can inhibit heme iron, and calcium can inhibit both heme and non-heme iron, as well. Vitamin C on the other hand, can enhance non-heme iron absorption (Gibson, 2005). The average number of days required to estimate average intake of iron for an individual is a minimum of 14 days with an average duration being 68 days (Lee & Nieman, 2007).

In healthy people, approximately 30% of iron is in a storage form; mostly as ferritin but also as hemosiderin (Lee & Nieman, 2007). As iron stores are depleted, serum ferritin concentration also decreases (Lee & Nieman, 2007). Studies frequently use serum ferritin to assess iron status, as it is a sensitive measure of first stage iron deficiency (Lee & Nieman, 2007), however once iron stores become depleted, this assessor does not reflect the severity of iron deficiency (Gibson, 2005). Serum ferritin values can be affected by a number of factors including age-related changes, gender, race, as well as illness (Gibson, 2005). Inflammation, infection and trauma can all increase serum ferritin (Lee & Nieman, 2007). Acute and chronic infections can elevate serum ferritin as well as elevated plasma glucose and high body mass index (Gibson, 2005).

1.4.2 Vitamin B_6

Vitamin B_6 is widely distributed in foods and a deficiency in this vitamin is considered rare. Good food sources of B_6 are fish, meat, poultry, some seeds and yeast. Dietary fiber is considered an inhibiting factor in B_6 absorption (Gibson, 2005). Bioavailability

of pyridoxine/vitamin B_6 in a normal mixed diet is estimated to be approximately 75% (Gibson, 2005). Dietary vitamin B_6 is converted after absorption into pyridoxal-5'-phosphate (PLP) and pyridoxamine-5'-phosphate (PMP), two active coenzymes that catalyze a number of reactions that include the conversion of 5- hydroxytryptophan (5-HT) to serotonin (5-HTT), and l-dopa to dopamine (Leklem, 1999). Factors affecting PLP levels include age-related changes, high levels of aerobic activity, infection and various disease states as well as some medications including antihistamines (Gibson, 2005). As PLP is the major transport form of vitamin B_6 in plasma, concentrations of PLP directly measure the active co-enzyme form of this vitamin (Gibson, 2005).

1.5 Zinc and Glutamate Neurotransmission

Zinc is also an important trace mineral in neural signaling, with the central nervous system containing a chelatable zinc pool in synaptic nerve terminals (Frederickson, Suh, Silva, Frederickson, & Thompson, 2000; Manzerra, Behrens, Cansoniero et al., 2002). The role of synaptic release of zinc is unknown, although it is thought to be responsible for the modulation of glutaminergic neurotransmitter receptors (Colvin et al., 2000; Frederickson et al., 2000) and voltage-sensitive cation channels sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) and Na^+/K^+-ATPase (Manzerra et al., 2002). Glutamate neurotransmission has a role in ADHD (Maayana, Yoran-Hegesh, Strousb et al., 2003; MacMaster et al., 2003). Recent studies utilizing proton magnetic resonance spectroscopy to examine metabolite levels in the frontal and prefrontal cortex of children with ADHD report an elevation in glutamatergic resonances as compared to healthy control subjects (Courvoisie, Hooper, Fine, Kwock, & Castillo, 2004; MacMaster et al., 2003). Total amount of brain zinc concentrated in the vesicles of zinc-containing neurons is believed to be quite small, with only 5% of the total zinc in the brain (Frederickson et al., 2000). Most of the zinc and glutamate is associated with peptides and proteins (Frederickson et al., 2000), with only a small amount sequestered in vesicles. Zinc containing stomata are located almost exclusively in the cerebral cortex and in the amygdala (Frederickson et al., 2000). Efferent zinc containing fibers from these regions are directed to the cerebral cortex, striatum and limbic system (Frederickson et al., 2000).

Of interest to ADHD is that zinc is needed only in the short axon (type II) small neurons of the glutamatergic pathway but not the long axon (type I) neurons (Frederickson et al., 2000). It is believed that neurons with large cell bodies and long axons (type I) are generally 'hard wired' whereas short axon (type II) small neurons generally occur later and are more plastic both in number and the number and type of connections (Frederickson et al., 2000). Vesicular zinc is believed to enable the plasticity of synaptic connections of the type II (short axon) neurons (Frederickson et al., 2000). Taking all of this information together, it is of special interest that Magnetic Resonance Image (MRI) resonances of glutamate neurons are higher in ADHD children (Courvoisie et al., 2004; MacMaster et al., 2003). It is presently unknown how low zinc status in ADHD affects glutamatergic neuron signaling.

1.6 Other Dietary Components and Their Effect on Neurotransmitters

Macro- and micronutrient dietary components such as amino acids, carbohydrates and fatty acids are known to affect neurotransmitter synthesis in the brain.

The amino acids tryptophan, tyrosine and phenylalanine serve as precursors for the synthesis of serotonin, dopamine, and norepinephrine (Fernstrom & Wurtman, 1971; Wurtman, 1987). These dietary components affect neurotransmitter synthesis in several ways; some of which involves the limited availability of precursors in the diet. Tryptophan must be provided from dietary sources (Groff, Gropper, & Hunt, 1995) and thus dietary availability is a limiting factor in the synthesis of neurotransmitters from tryptophan. A second way in which dietary components affect neurotransmitter synthesis is via competitive inhibition. Large neutral amino acids such as tryptophan and tyrosine compete with one another for carrier proteins for transport across the blood-brain barrier and this competition ultimately affects which, and what quantities of neurotransmitters are synthesized (Wurtman, 1987). The ratio of carbohydrate to protein in individual meals is another way in which dietary components directly affects neurotransmitter synthesis. Plasma and brain levels of tryptophan and the resulting synthesis of serotonin are increased following a meal composed entirely of carbohydrate but are blocked if protein is either eaten first or with carbohydrates (Fernstrom, 1995; Spring, 1984). Carbohydrate intake in the absence of protein intake in a given meal affects tryptophan levels by increasing the levels of insulin that

stimulates the uptake of competing neutral amino acids into muscle tissue (Spring, 1984). Ingestion of protein increases the levels of competing amino acids thus decreasing the likelihood that tryptophan will be transported across the blood-brain barrier (Spring, 1984).

Plasma disruptions of tryptophan have been implicated in some psychiatric disorders, including affective disorder (Carl, Hoffman, Blankenship et al., 2002), anxiety disorder and obsessive compulsive disorder (Post & Weiss, 1998), increased behavioural disinhibition and impulsivity (LeMarquand, Benkelfat, Pihl, Palmour, & Young, 1999) as well as in eating disorders such as anorexia and bulimia (Favaro, Caregaro, Burlina, & Santonastaso, 2000).

Protein metabolism has been reported to differ significantly from non-ADHD children; with greater nitrogen excretion in ADHD (Stein & Sammaritano, 1984). No dietary intake data accompanied these findings which could have shed light as to whether greater nitrogen excretion reported in ADHD is a result of fasting (Groff et al., 1995) or alternatively, high levels of dietary protein intake (Waterlow, 1986).

In an earlier study, plasma tryptophan was measured in 10 ADHD children and 12 non-ADHD children (Hoshino, Ohno, Yamamoto, Kaneko, & Kumashiro, 1985). Mean total tryptophan level was reported to be significantly higher in ADHD as compared with non-ADHD children. A positive correlation was reported between higher free plasma tryptophan and more severe hyperactivity based on scores on the Werry-Weiss-Peters Activity Scale (Hoshino et al., 1985).

A more recent study of 28 ADHD subjects reported significantly lower levels of phenylalanine, tyrosine, tryptophan, histidine, and isoleucine (Bornstein, Baker, Caroll et al., 1990) than the 20 control subjects. As mentioned above, disruptions in tryptophan and tyrosine are known factors for affecting the synthesis of norepinephrine and dopamine (Wurtman, 1987), two important neurotransmitters implicated in the pathophysiology of ADHD (Biederman & Spencer, 1999).

As described above, dietary composition affects neurotransmitter levels in a number of direct and indirect means. In addition, neurotransmitter levels may influence dietary intake. Serotonin, for example has been demonstrated to inhibit eating

behaviour in animals (Kaye & Weltzin, 1991) whereas endogenous norepinephrine has been reported to activate eating behaviour (Kaye & Weltzin, 1991).

Animal studies suggest that the fat composition of the diet may also affect brain neurotransmitter levels and neurotransmitters themselves may influence synthesis of fatty acid derived peptides. One study comparing the effect on endogenous monoamine levels in the brain of rats given diets containing- or not-containing trans alpha-linolenic acid, reported that dietary intake of trans alpha-linolenic acid was correlated with higher levels of endogenous dopamine (Acar, Chardigny, Berdeaux , Almanza, & Sebedio, 2002). An animal study from China reported that supplementation with docosahexaenoic acid (DHA) increased the levels of 5-hydroxytryptophan (5-HT), a serotonin precursor, as well as increased the levels of dopamine in hippocampus of growing rats (Li, Liu, & Zhang, 2000). Arachidonic acid (ARA) concentration is associated with dopamine release from brain neurons of goldfish (Chang, Abele, Van Goor, & Wong, 1996) and administration of docosahexaenoic acid (DHA) has been reported to increase the number of dopamine (DA2) receptors in rat brains.

An imbalance in omega 3 (n-3) fatty acids to omega 6 (n-6) fatty acids has been attributed to ADHD (Richardson & Puri, 2000, 2002). In a recent study, 21 children with ADHD were found to have lower levels of plasma docosahexaenoic acid (DHA) and arachidonic acid (ARA) compared with the 43 controls (Burgess, Stevens, Zhang, & Peck, 2000). As there was an absence of dietary intake data accompanying these findings, it is unknown whether decreased n-3 and n-6 fatty acids in these ADHD children may have resulted from decreased dietary intake of DHA, decreased caloric intake resulting in -oxidation of fatty acids for energy (DeLany, Windhauser, Champagne, & Bray, 2000; McCloy, Ryan, Pencharz, Ross, & Cunnane, 2003) or to some other factor such as higher lipid turnover rate.

1.7 Eating Behaviours, Growth Patterns and the Effect of Medication Treatment on Growth in ADHD

Numerous members of the medical profession including psychiatrists, pediatricians and family practitioners have reported that parents of ADHD children frequently express concern about the adequacy of food intake and what parents perceive as unusual eating behaviours in their children (Weiss MD, personal correspondence).

Clinician anecdotal reporting indicates that parents of ADHD children frequently complain that their children are what they describe as "picky eaters". "Picky eaters" are described by parents as children that either limit variety of dietary intake, consuming the same few foods, or that they have taste or texture aversions; and resist eating whole categories of foods with disliked characteristics.

Another common complaint of parents of ADHD children is that their children do not follow normal growth patterns; specifically, that their children are under-tall or under-weight compared with children of the same age and gender. It has been suggested that zinc status may influence growth in young children (Lee & Nieman, 2007); particularly where there is inadequate dietary intake or absorption (Brown, 2003; Lee & Nieman, 2007). Zinc deficiency is known to be associated with decreased taste sensitivity in rats (Goto, Komai, Suzuki, & Furukawa, 2001) as well as altered taste perception in humans (Komai, 2000; Watanabe, Asatsuma, Ikui et al, 2005). There have been several reports of low serum zinc status in ADHD, both from overseas (Kozielec, Starobrat-Hermelin, & Kotkowiak, 1994) and from the US (Arnold & diSylvestro, 2005; Arnold, Klaykamp, Baker et al, 1990).
While many parents of ADHD children report to clinicians that their children are shorter and lighter than other children of their age and gender, and indeed this had been the perception of many clinicians (Weiss, personal correspondence), recent North American and European data indicate that ADHD children are in fact significantly larger and taller than their peers. US height and weight data pooled from ADHD children aged 6-17 years suggests that children with the disorder are taller and heavier at earlier ages (Swanson, Feldman, Furr, & Allen, 2005) when compared with growth curves from age-matched children from the National Center for Health Statistics (Centers for Disease Control and Prevention, 2000).

The trend for ADHD children to be taller and heavier than population norms persists with stimulant medication usage, although ADHD children with prior stimulant medication treatment are significantly lighter and shorter than their stimulant-naïve counterparts (Swanson et al., 2005). Younger, pre-pubertal ADHD children have higher relative height and weight than older pubertal and late pubertal ADHD children (Table 2). Consistent with these findings is a recent study of 140 preschool children with ADHD from the US, which reports that preschool children aged 3 - 5.5

years of age with ADHD were taller and heavier than norms specified by the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention, 2000; Swanson, Greenhil, Wigal et al., 2007).

Table 2 Mean Weight, Height and Body Mass Index (BMI) of ADHD Children by Pubertal Status as Defined by Mean Percentiles and Mean z-scores [1]

Mean Weight, Height and BMI of ADHD Children										
		Stimulant-naive			Prior Stimulant			Total		
Measure	Estimated Pubertal Status	n	mean %ile	mean z-score	n	mean %ile	mean z-score	n	mean %ile	mean z-score
Weight	Pre-Pubertal	599	71.3	0.79	470	61.8	0.43	1069	67.1	0.63
	Pubertal	919	65.7	0.59	1836	56.6	0.26	2755	59.6	0.37
	Late Pubertal	130	63.1	0.44	479	60.8	0.37	609	61.3	0.38
Height	Pre-Pubertal	599	59.2	0.32	481	51.6	0.06	1080	55.8	0.22
	Pubertal	910	55.2	0.19	1818	48.3	-0.07	2728	50.6	0.20
	Late Pubertal	129	51.0	0.03	470	48.2	-0.06	599	48.8	-0.04
BMI	Pre-Pubertal	598	72.5	0.82	481	63.0	0.43	1079	68.2	0.65
	Pubertal	907	68.2	0.67	1812	60.3	0.37	2719	62.9	0.47
	Late Pubertal	129	62.5	0.44	467	59.8	0.34	596	60.4	0.36

[1] Reference (Swanson et al., 2005)

Findings that ADHD children are taller and heavier than age- and gender-matched children from the normal population was also reported in a recent European study (Coghill, 2005). In this study, researchers from the United Kingdom (UK) reported the height and weight data of 233 medication naïve subjects (mean age 9.3 years) that formed a subset of a larger pan-European study of 1478 ADHD children, both on and off stimulants. Data from this subset of treatment-naïve children were compared with age- and gender-matched children from the normal population. Results indicated that untreated ADHD children were larger and heavier than age- and gender-matched peers.

There was also a trend for untreated ADHD European children to be taller and heavier then untreated ADHD North American children. Mean height percentile in the European subset (Coghill, 2005) was 60.2% compared to 51.6% in the North American study (Swanson et al., 2005). Mean weight percentile in the European subset was also

higher, 66% (Coghill, 2005) compared with 61.7% from from the North American study (Swanson et al., 2005).

Stimulant medications, which are potent appetite suppressors, are frequently used in the treatment of ADHD children. These medications have been reported to be associated with weight loss in children with ADHD (Spencer , Ruff, Feldman et al, 2003) and a slowing of growth rates (Swanson, 2004). For example, as compared with medication-naïve children, use of stimulant medication in ADHD children has been reported to be associated with a 1.44 cm/year suppression of height and a 2.48 kg/year suppression of weight (The MTA Cooperative Group, 2004) in children aged 7-9 years over a 14-month study period. Similarly, a recent study of 95 preschool ADHD children aged 3-5.5 years treated with stimulant medication reported annual growth rates that were 1.38 cm/year less than expected based on pre-treatment heights and annual weight gain rates that were 1.32 kg/year less than expected based on pre-treatment weights (Swanson et al., 2007).

Atomoxetine hydrochloride, a non-stimulant medication, has been reported to be associated with a much more modest slowing of growth velocity of only .3 cm/year over the initial 18 months of treatment (Spencer, Kratochvil, Sangal et al., 2006; Spencer et al., 2003). After 2 years of atomoxetine medication treatment, observed heights and weights were close to those predicted by baseline weight and height (Spencer et al., 2003) with a resumption of pre-treatment height-, weight- and Body Mass Index (BMI)-percentiles occurring by 3 years (Spencer et al., 2006).

1.8 Energy and Macronutrient Intake in the General Population and in ADHD

1.8.1 Macronutrient Intake in the General Population

Macronutrient intake in the general population was recently assessed by the Canadian Community Health Survey (CCHS) (Statistics Canada, 2004), a cross-sectional survey that collected data related to health determinants in the Canadian population. The CCHS operates on a two-year collection cycle, with the first year of the cycle being a large sample involving the general population and the second year of cycle being a smaller survey providing results on specific health topics. The most recent second cycle information was collected between January 2004 and January 2005 in ten provinces from persons of all ages, living in private occupied dwellings. Excluded

from the sample were individuals living in any of the three Territories, on First Nation (Indian) Reserves, in institutions or full-time members of the Canadian Forces (Statistics Canada, 2004). Limited data are now available for the Canadian population from the CCHS study (Statistics Canada, 2004) released in July 2006. Canadian data for children aged 4 to 8 years (n=3358) is combined for boys and girls and is only separated by gender for children aged 9-13 years and older (n=2149 males, n=2145 females) (Statistics Canada, 2004). Energy and macronutrient data for children from British Columbia is available as a subset of the CCHS data (Statistics Canada, 2004) and is given in Table 3. Sample sizes of the subset of the CCHS data are n=339 for ages 4-8 years (both genders) and n=236 for males age 9-13 years and n=235 for females age 9-13 years (D. Garriguet, personal correspondence).

Table 3 Mean Energy and Macronutrient Intake, Canadian Community Health Survey (CCHS) for British Columbia Boys and Girls Aged 4-13 Years[1, 2]

MACRONUTRIENT	Boys and Girls aged 4-8 years	Boys age 9-13 years	Girls age 9-13 years
ENERGY, **kcal**	1,895 ± 35	2,446 ± 71	2,035 ± 45
PROTEIN (% kcal)	14.5 ± .6	14.2 ± .7	14.1 ± 1.1
CARBOHYDRATES (% kcal)	55.6 ± 1.5	54.0 ± 2.6	55.9 ± 2.5
TOTAL FAT (% kcal)	29.9 ± 1.2	31.8 ±1.7	30.0 ± 1.2

[1]CCHS data collected from British Columbia (Statistics Canada, 2004).
[2]Values represent mean percentages of energy as macronutrients except for energy which is expressed as kilocalories

1.8.2 Macronutrient Intake in ADHD

To date, there are only three studies that have assessed the dietary intake status of children with ADHD. Of these studies, one used an adapted adult food frequency questionnaire to generate data (Arnold, Bozollo, Hallway et al, 2005) whereas the other two studies employed food records. The first of two studies (Kaplan, McNicol, Conte, & Moghadam, 1989) utilizing food record data was conducted during the late 1980's and involved only preschool ADHD boys. The fact that study subjects were restricted to preschool boys limits the application of the data to ADHD children of other age groups or to children of both genders. A second study employing a three day food record was conducted in South East Asia (Chen, Hsu, Hsu, Hwang, & Yang, 2004) and was very specific to that population's culture. It difficult to extrapolate this data to North American ADHD children.

Kaplan conducted a study of preschool hyperactive boys and controls, aged 3 ½ - 6 years (Kaplan et al., 1989), where 24 were treatment-naïve ADHD subjects and 27 were non-ADHD controls. In addition to a primary diagnosis of ADHD, inclusion criteria for children to participate in the study was the presence of sleep disorders or other kinds of somatic complaints such as gastrointestinal, respiratory, or dermal anomalies. The goal of this study was to assess normal eating patterns with blood collections taken to evaluate serum calcium, magnesium, trace minerals (including zinc and copper), B_{12}, and folate. Parents and day-care workers of the children were instructed to keep food records for 21 days and nutrient analyses were conducted on the food diaries for the last 14 days for each child. No differences were observed in the percentage of energy consumed as protein or fat between the ADHD and non-ADHD children however ADHD children consumed more energy and a higher percentage of energy as carbohydrates than non-ADHD children (Kaplan et al., 1989).

There are relatively few studies published that have examined the potential relationship between macro- and micro-nutrient intake and the incidence of ADHD. A Taiwanese study, using a three day food record compared the dietary intake of 58 children aged between 4-12 years with ADHD, with 52 control subjects (Chen et al., 2004). Results indicated that energy intake was not statistically different in the ADHD children compared to controls and that there was no significant difference in the percentage of energy from protein, fat and carbohydrate between the two groups. Mean energy intake was 1742 ± 556 kilocalories for the ADHD children and 1685 ± 524 kilocalories for the controls. The percentage of energy derived from protein was 13.4 ± 5.5 in ADHD and 13.5 ± 4.4 in controls, the percentage of energy derived from fat was 33.3 ± 9.9 in ADHD and 35.1 ± 11.3 in controls and the percentage of energy derived from carbohydrate was 51.7 ± 11.9 in ADHD and 51.0 ± 13.0 in controls. Since dietary intake patterns in these children likely reflect local Taiwanese culture (Chen et al., 2004), there are limitations to applying these results to a North American ADHD population.

A second study conducted in the United States with ADHD children aged 5-10 years of age assessed dietary intakes using an adult food frequency questionnaire (FFQ) adapted for use in children with ADHD. No information was given as to how the food frequency questionnaire was adapted for use in ADHD children, or how, or if it

was previously validated (Arnold et al., 2005). The mean energy intake was estimated to be 2027 ± 634 kilocalories, and mean intake of protein, fat and carbohydrate was estimated as 78.7 ± 29.0 grams, 78.7 ± 29.0 grams, and 259.8 ± 90.5 grams. These estimates were reported to be equivalent to 107% of the Estimated Energy Requirement (EER), 328% of the Recommended Dietary Allowances (RDAs) for protein and 200% of the RDAs for carbohydrate for this age group of ADHD children. The authors concluded that the FFQ may have overestimated the actual daily food intake, a shortcoming of the tool (Gibson, 2005). The authors compared mean macronutrient intake of this group of ADHD children to the RDAs; however, RDAs are used to assess the nutrient intake of individuals, not groups.

1.9 Micronutrient Intake and Micronutrient Status in the General Population and in ADHD

1.9.1 Micronutrient Intake in the General Population

Dietary micronutrient intake in the general population was recently assessed by the 2004 CCHS (Statistics Canada, 2004) study, although data are not yet available. Twenty four hour recall data from NHANES III for 2383 boys and 2469 girls between the ages of 8 to 18 years were analyzed for specific nutrients including iron, zinc and vitamin B_6 (National Center Health Statistics, 1996a). Mean dietary intake of iron, zinc and copper in children aged 6 - 11 years was assessed by NHANES III as 12.8 ± 5.5 mg/day, 6.40 ± 3.3 mg/day, and 0.72 ± 0.45 mg/day, respectively (National Center Health Statistics, 1996a). Mean dietary intake of vitamin B_6 in children in this same age group was assessed as 1.01 ± .52 mg/day (National Center Health Statistics, 1996a).

1.9.2 Micronutrient Intake in ADHD

Only two studies have assessed the micronutrient intake of children with ADHD, and only one of these studies was performed in North America. As mentioned earlier, a Taiwanese study used a three day food record to compare the dietary intake of 58 children aged 4-12 years with ADHD and 52 control subjects (Chen et al., 2004). This study reported a mean daily intake of iron to be 10.6 ± 9.3 mg/day compared to 7.5 ± 2.9 mg/day in controls. The difference between the two groups was significantly different with the ADHD group having higher iron intake than controls. While mean daily intake of iron was significantly above the mean dietary intake of the control group, mean dietary intake of iron for both the ADHD group and controls is below

the US mean dietary intake of 12.8 ± 5.5 mg/day iron of children aged 6 - 11 years as assessed by NHANES III (National Center Health Statistics, 1996c). As dietary intake patterns in the Taiwanese children reflect local cultural norms, extrapolation of this data to a North American ADHD population is difficult.

Mean dietary iron intake as assessed in a US study of ADHD children aged 5-10 years of age was reported to be 14.4 ± 5.1 mg/day (Arnold et al., 2005). This was said to be 160% the RDA for iron (see note, below). Mean dietary iron intake level was above the US mean dietary intake of 12.8 ± 5.5 mg/day iron of children aged 6 - 11 years as assessed by NHANES III (National Center Health Statistics, 1996c). Mean zinc intake was 11.4 ± 4.3 (Arnold et al., 2005), which was reported to be 190 % of the RDA for zinc (see note, below). Mean dietary intake of the group was well above the mean dietary intake of zinc as assessed by NHANES III (National Center Health Statistics, 1996c) in children aged 6 - 11 years, 6.40 ± 3.3 mg/day (National Center Health Statistics, 1996b).

Note: It is incorrect to compare mean micronutrient intake of groups to the RDAs (National Academy Press, 2000). The proportion of individuals in a group with micronutrient intake below their requirements can be estimated by using the so-called 'cut-point method' of the Estimated Average Requirements (EARs) (National Academy Press, 2000). If mean group intake of a nutrient is less than the EAR, approximately half of the group is expected to have intake less than requirement (National Academy Press, 2000). Furthermore, the RDA is the intake level that exceeds the requirements of a more than 97 percent of all individuals in the group, therefore incorrectly estimating the prevalence of nutrient inadequacy using the RDAs will always lead to an overestimation of the true prevalence of inadequacy (National Academy Press, 2000).

1.9.3 Micronutrient Status in the General Population

Biochemical micronutrient status for iron, copper and zinc in the general population are available from NHANES III (National Center Health Statistics, 1996a). Mean serum ferritin, zinc and copper status of children aged 9-11 years is 37.5 ± 20.8 µg/mL (37.5 ± 20.8 µmol/L), 83.05 ± 13.72 mcg/dL (12.7 ± 2.1 µmol/L) and 127.5 ± 22.38 mcg/dL (19.5± 3.4 µmol/L), respectively (National Centre Health Statistics, 1996).

1.9.4 Micronutrient Status in ADHD

There is some evidence of low iron status is children with ADHD; however, since one study is from France (Konofal, Lecendreux, Arnulf, & Mouren, 2004) and the other from Taiwan (Chen et al., 2004), information on iron status in the disorder is limited to overseas populations. Application of this data to North American ADHD children is problematic, as it is difficult to make extrapolation on how iron status from children of different cultures, with different patterns of food intake, relate to US and Canadian ADHD children.

In France, mean serum ferritin of 53 ADHD children and 27 controls aged 4-14 years was reported as 23 ± 13 ng/mL in ADHD children and 44 ± 22 ng/mL in the control group (Konofal et al., 2004). Low serum ferritin levels were correlated with more severe ADHD symptoms, as measured with a Conner's rating scale (Pearson correlation coefficient, $r=0.38$; $P<.02$).

The Taiwanese study (Chen et al., 2004) reported iron status to be 19.7 ± 6.4 in the ADHD children and 16.1 ± 6.8 µmol/L for the controls however, the study did not specify whether serum ferritin or serum iron was assessed.

There are several reports of low serum and urinary zinc levels among ADHD children although most data are from the Middle East where the prevalence of zinc deficiency is widespread (Arnold et al., 2005; Arnold LE, 1990; Bekaroglu, Aslan, Gedik et al., 1996; Kozielec, Starobat-Hermelin & Kotkowiak, 1994; Starobat-Hermelin, 1998; Toren, Elder, Sela, Wolmer et al, 1996). A recent US study of children aged 5-10 years referred to previously (Arnold et al., 2005) reported that low zinc status in ADHD children was associated with greater parent-teacher ratings of inattention even though all children in the study fell within the normal lab reference range of 66-110 mcg/dL (10.10 -16.83 µmol/L). It is important to note that all ADHD children had serum zinc levels within lab normal reference values of 66-110 mcg/dL (10.10 -16.83 µmol/L), however 27% of ADHD children had serum zinc levels below the population normal mean of 83 ± 14 mcg/dL (12.7 ± 2.1 µmol/L) reported for children aged 9-11 years (National Centre Health Statistics, 1996).

1.10 Low Nutrient Density Food Intake and Food Group Intake

It is a prevalent opinion that high consumption of low nutrient density foods is associated with displacement of important nutrients in the general population. More specifically, studies have associated higher consumption of low nutrient density (LND) foods with lower intakes of zinc, iron and vitamin B_6 (Kant, 2003). It is important to note that studies from France (Konofal et al., 2004) and Taiwan (Chen et al., 2004) indicate lower iron status in ADHD children than in controls and almost a third of US ADHD children were reported to have serum zinc status below population means (Arnold et al., 2005). At present, there is no information on the intake of low nutrient density foods (LND) in ADHD children.

The LND group of predominantly sweet substances contributes nearly 25% of caloric intake in US children and adolescents of this age groups (Kant, 2003). Another 5% of daily energy intake comes from visible fat such as butter, margarine, dressing, and gravy, salty snacks such as potato, corn and tortilla chips or coffee, tea or condiments (Kant, 2003). It is important to note that foods such as fried chicken and commercially produced hamburgers belong to the Meat and Beans food group and are not categorized as a LND food. Similarly, French fries are classified under the Vegetable food group.

A significant percentage of daily energy intake in the general population of US children aged 8 - 18 years of age comes from LND foods (Kant, 2003). Up to 30% of daily energy intake in US children aged 8 - 18 years of age comes from low nutrient density (LND) foods (Kant, 2003). Table 4 presents the percentage of LND food intake from all sources as reported by gender for children aged 8-12 years of age.

Table 4 Percentage of Daily Energy From All Low Nutrient Density Foods (LND) Reported by Age Group and Gender [1]

Gender	Age, years	Sample Size	% Low Nutrient Density Foods
Boys	8-12	1286	28.6 ± 0.8
Girls	8-12	1258	29.4 ± 0.8

[1] NHANES III 1988-1994 data as reported in Kant 2003

The 2004 CCHS data indicates that Canadian children and adolescents age 4 - 18 years consume an average of 22.3% of calories from "other foods" (Garriguet, 2004). Data on the consumption of "other foods" from the CCHS study are not yet available. "Other foods" are foods or beverages not falling under grain products, vegetables and fruit, meat and alternatives or milk and milk products (Garriguet, 2004). Taken as a whole, "other foods" under the Canadian definition are similar in type to those foods categorized as low nutrient density foods in the US study of children aged 8-12 years (Kant, 2003).

Recent food group intake of children is available from the British Columbia component of the CCHS study (Garriguet, 2004). It is important to note that while there is a currently a new food guide entitled Eating Well with Canada's Food Guide (2007), the current research project was done prior to its release and refers to Canada's Food Guide to Healthy Eating (1992) (Health Canada, 1992).

This food guide recommended that children 4-9 years of age consume 2-3 servings of milk and milk products per day. Children aged 10-14 years were recommended to consume 3-4 servings of milk and milk products per day (Health Canada, 1992). Twenty four hour recall data from the CCHS study have indicated that only 63% of Canadian children aged 4-9 years consumed the recommended minimum number of servings of milk products (Garriguet, 2004; Statistics Canada, 2004), with 37% of children in this age group being below the recommended number of servings (Garriguet, 2004). Only 39% of Canadian boys and 17% of Canadian girls aged 10-16 consumed the recommended minimum number of servings of milk products on the recall day (Garriguet, 2004; Statistics Canada, 2004).

Canada's Food Guide to Healthy Eating (Health Canada, 1992) recommended that children consume 5-10 servings of vegetables and fruit per day (Health Canada, 1992) however, twenty-four hour recall data from the CCHS study report that only 29% of Canadian children aged 4 to 8 years met the recommended number of servings of vegetables and fruit (Garriguet, 2004; Statistics Canada, 2004). Vegetable and fruit consumption increased somewhat for children aged 9-13 years. 38% of boys and 32% of girls in this age group met the recommended number of servings of vegetables and fruit (Garriguet, 2004; Statistics Canada, 2004).

Canada's Food Guide to Healthy Eating (Health Canada, 1992) recommended that all children consume 5 - 12 servings of grain products per day (Health Canada, 1992). Twenty-four hour recall data have indicated that 73% of Canadian children aged 4-8 met the recommended number of servings of grain products. This increased slightly to 74% for girls aged 9-13. No data are available for boys in this age group as the data were considered too unreliable to be published (Garriguet, 2004; Statistics Canada, 2004).

According to the CCHS study, children aged 4-8 years eat on average 118 grams of meat or alternates per day. Canada's Food Guide to Healthy Eating (Health Canada, 1992) recommended that all children consume 2 - 3 servings of Meat and Alternates per day (Health Canada, 1992); where one serving of meat, fish or poultry is 60-90g (Health Canada, 1992) and alternates for one serving of meat include 60ml of peanut butter to 250 ml cooked dried peas, beans or lentils, 125 ml of nuts or seeds or 60g of cheddar cheese. Children in this age group consuming 118 grams of meat or alternates may meet or be below recommended levels of this food group, depending on what percentage of intake originates from meat, fish or poultry, and what percentage of intake comes from alternates. Calculating the number of servings of meat equivalents from the number of grams of meat and alternates group consumed is estimated by dividing the number of grams of meat and alternates by 50 gm (personal correspondence, Garriguet, Statistics Canada, Sept 2007). Based on this estimator, children aged 6-8 years in this study consumed an average 2.4 servings of meat and alternates per day.

Boys aged 9-13 years consume 176 grams per day of meat and alternates and girls age 9-13 years consume 130 grams per day of meat and alternates per day (Statistics Canada, 2004). Based on the conversion of grams per day of meat and alternates to meat equivalents, boys age 9-13 years consume 3.5 servings of meat equivalents per day and girls age 9-13 years consume 2.6 servings of meat equivalents per day.

Chapter 2: Current Research Questions, Study Hypothesis and Specific Objectives

2.1 Current Research Questions

At the present time very little is known about the dietary intake of children with ADHD. As discussed previously, widespread perceptions by both parents and practitioners that ADHD children have abnormal dietary intake has not yet been studied. As well, perceptions by both parents and clinicians that ADHD children are shorter and lighter than non-ADHD children does not seem to be supported by recent studies, however no Canadian data have been collected. To date, no study has assessed growth, dietary intake or nutrient status in light of different medication protocols used in treating ADHD. This information would be important to support or dispel myths regarding the dietary intake and growth patterns of ADHD children and to understand the impact medications prescribed to treat the disorder may have on dietary intake, nutrient status and growth.

There is some evidence of low nutrient status of iron and zinc in ADHD although prior to this study, no Canadian data were available. Low serum ferritin and low serum zinc have been reported from France (Konofal et al., 2004) and the United States (Arnold et al., 2005). There is; however, a lack of corresponding dietary intake data (Konofal et al., 2004) or dietary intake data are thought to be too unreliable due to overestimation of daily intake (Arnold et al., 2005). While some studies have reported that children with ADHD have a higher intake of iron containing foods (Chen et al., 2004) or a higher energy intake or a greater percent of energy from carbohydrate than non-ADHD children (Kaplan et al., 1989) there are no recent North American data on macro- and micro-nutrient intake in the disorder.

Only one study attempted to assess the adequacy of dietary intake of a group of ADHD children; however, comparison was made with the Recommended Dietary Allowances (RDAs) (Arnold et al., 2005) rather than the Estimated Average Requirements (EARs) for group micronutrient intake, and the Acceptable Macronutrient Distribution Range (AMDRs) for group macronutrient intake. The RDAs provide an assessment of adequacy of individual dietary intake, and not an

assessment of adequacy of a group (National Academy Press, 2000). An additional shortcoming of this study was that dietary intake was thought to have been overestimated due to the use of a food frequency questionnaire as the assessment tool (Arnold et al., 2005).

It is thought that use of a three day food record as the primary assessment tool in the present study will enable more reliable collection of intake information (Gibson, 2005); especially if parents and children receive instructions and training regarding portion sizes (Lee & Nieman, 2007) and subjects are provided with visible portion estimators (Cypel, Guenther, & Petot, 1997). Comparison of group macronutrient intake with the Acceptable Macronutrient Distribution Range (AMDR) and group micronutrient intake with the EARs will give some insight into dietary adequacy of ADHD children. In addition, comparing dietary intake with Canada's Food Guide to Healthy Eating should clarify what ADHD children eat as compared with what is recommended for their life-stage and whether their diets are indeed abnormal, as their parents believe. Collecting 24-hour recall data from ADHD children and employing established and published methodology to analyze the percentage of low nutrient density foods in the diet (Kant, 2003) will make clear whether ADHD children consume high levels of so-called "junk-foods". This will help elucidate whether low nutrient density foods might be displacing nutrient-rich foods from the diet, possibly contributing to low-trace mineral status in ADHD. Finally, conducting blood analysis for specific markers of nutrient status will enable comparison between dietary intake and serum assessors of those nutrients.

This is a descriptive study with the overall purpose of assessing the dietary intake and nutrient status of children with ADHD; comparing the resulting data with the Dietary Reference Intakes, the recommendations of Canada's Food Guide to Healthy Eating, population normal data as well as lab normal data originating from healthy, normal subjects from the same local population.

2.2 Study Hypotheses

1. There are no differences in dietary intake and nutrient status between the three medication treatment groups (stimulant-medicated, atomoxetine-medicated and medication-naïve) of ADHD children.
2. There are no differences in assessors of zinc and iron status in ADHD as compared with lab normal and population normal data.
3. There are no differences between height-for-age and weight-for-age in the ADHD population than in the general population.

2.3 Specific Objectives:

1. To compare dietary intakes of ADHD children with the established standards of the Dietary Reference Intakes (DRIs),
2. To compare the dietary intakes of children with ADHD to the dietary recommendations of Canada's Food Guide to Healthy Eating,
3. To compare the dietary intakes of children with ADHD to age- and gender-matched normative population,
4. To determine whether dietary intake is altered by drug treatment,
5. To measure biochemical parameters of iron, zinc, copper and pyridoxine that may have an impact on ADHD,
6. To measure heights and weights of ADHD children.

Chapter 3 - Methods

3.1 Methods

3.1.1 Study Population

Eighteen (18) stimulant-treated, 9 atomoxetine-treated and 17 treatment-naïve children aged 6-12 years inclusively were recruited for this study from the Provincial ADHD Program of BC Children's Hospital in Vancouver, British Columbia.

3.1.2 Subject Selection Criteria

Inclusion criteria for selecting subjects for this study consisted of a primary diagnosis of ADHD; with subjects being either treatment-naïve or stable on either stimulant- or atomoxetine-treatment. Stable on medication for both the stimulant treatment group and atomoxetine treatment group was defined as subjects on medication for a minimum of 6 months, 7 days per week. The types of stimulant received by subjects, as well as drug duration (7 or 12 hour) was recorded. Treatment-naïve subjects had no previous exposure to any ADHD medication. Exclusion criteria was the use of Risperdone, or any other medication known to alter food intake. Female subjects were premenarchal.

Dr. Margaret Weiss (Clinical Associate Professor at University of British Columbia and Director of Mental Health Research Unit and the Provincial ADHD Program of BC) or other clinicians at the Provincial ADHD Program located at Children's Hospital presented the study to each consecutive eligible patient prospectively.

3.1.3 Ethics

The University of British Columbia Clinical Research Ethics Board and the British Columbia Children's and Women's Hospital Research Committee approved the study protocol (see Appendix 1a & 1b). Infomed consent was obtained by either Dr. Margaret Weiss or by Joy Y. Kiddie. At the time of recruiting, subjects were given a study-specific identification number which was used to identify all dietary collection forms and laboratory results.

3.1.4 Assessment Methods:

3.1.4.1 Participant Interview

Face-to-face interviews were scheduled with each study participant and their parent/legal guardian at the Provincial ADHD Program of BC, located at Children's Hospital. Parents/legal guardians were asked to read and sign an informed consent form (Appendix 2) and study participants were asked to read and sign an assent form (Appendix 3). Any questions regarding the study were answered prior to the participants and their parents/legal guardian signing the consent and assent forms. Consent forms were signed and dated. Dr. Margaret Weiss or one of the other clinicians/staff in the Provincial ADHD Clinic then witnessed consent forms. After signing the informed consent/assent forms, subjects were weighed and their heights were measured according to standard clinical practice (Lee & Nieman, 2007). Weight in kilograms and height in centimeters were recorded for each subject. Subjects' parents/legal guardians were then asked questions from the socio-demographic questionnaire (Appendix 4). A 24-hour food recall (Appendix 5) was administered according to a multi-pass time interview format, where children and their parents/legal guardians were asked to recall all food and beverages consumed in the previous 24-hour period (from midnight to midnight) including any vitamin and/or mineral supplements or nutraceuticals consumed. Information obtained from the socio-economic questionnaire and the 24-hour food recall was recorded on the data collection form (Appendix 6). Children and their parents/legal guardians were then instructed on the completion of the three-day food record (Appendix 7) which was to be completed at home over two non-sequential weekdays, and one day on a weekend, with the days being assigned according to a computer generated randomized table. Parents of subjects were provided with a three-day food record journal (Appendix 7) for recording dietary intake and a stamped self-addressed envelope for returning the three-day food record. Detailed operation instructions appeared on the covering page of the three-day food record, such as to record all food or beverages at the time they are consumed, to record intake of gum, candy and water, etc., as well as other instructions (see Appendix 7). At the end of the interview, subjects and their parents were escorted to the Outpatient Laboratory of British Columbia Children's Hospital to have venous blood samples collected according to the Study Requisition (Appendix 8). Subjects were offered a syringe-shaped ballpoint pen as a token gift to thank them for participating in the study.

3.1.4.2 Blood Collection

Blood collection kits containing 1 x 7 ml non-Additive tube, 2 x 4 ml lavender top ethylenediamine tetraacetic acid (EDTA) tubes and a 6" x 4" piece of foil were assembled by the graduate student researcher and accompanied each subject brought to the Outpatient Laboratory. A registered phlebotomist drew three tubes; the 7 ml tube was drawn for Complex Chemistry; to process and analyze the sample for trace minerals including iron, copper and zinc. The first 4 ml tube was drawn for Routine Hematology; to process and analyze the Complete Blood Count (CBC) as per established operational procedures. The second 4 ml tube was drawn and wrapped in the foil contained in the collection kit and frozen at -80° C in the Outpatient Laboratory freezer, to be sent at a later date in batches to Hospitals in Common (HIC) for B_6 analysis. Shipping dates to HIC was coordinated with the Lab Study Coordinator.

3.2 Data Handling

3.2.1 Analysis of the 24 hour food recall

Dietary intakes provided by the 24-hour food recall and used in the determination of the percentage of Low Nutrient Density (LND) foods in the diet, were entered into a computer nutrient database (Food Processor SQL 2005-06, ESHA Research, Salem, Oregon) modified to include the Canadian Nutrient File. If a specific brand consumed by a participant was not in the nutrient database, the closest brand of food or beverage was chosen based on label information or product information obtained via the manufacturer's website. Food codes corresponding to those used by the Food Processor program, as well as amount codes corresponding to the amount of food as reported by subjects were recorded on the 24-hour food recall and the items were then entered into the nutrient database. Twenty-four hour recalls were analyzed based on all standard macro- and micro-nutrient parameters performed by Food Processor SQL and printout reports were made for each subject. Reported data from the printouts were then entered into the SPSS database. Assessment of LND foods was performed according to the methodology published in a study on the proportion of LND foods in the diets of US children aged 8 - 18 years; obtained from NHANES II (Kant, 2003) and supplied by Dr. Ashima Kant (personal correspondence). The number of mentions of LND foods, the total number of grams of LND foods

consumed as well as the proportion of daily energy from LND foods was determined and recorded on the Assessment of Intake of Low Nutrient Density (LND) foods (Appendix 9).

3.2.2 Analysis of the Three Day Food record

Dietary intakes provided in the three day food records were then entered into the computer nutrient database (Food Processor® SQL 2005-06, ESHA Research, Salem, Oregon) that was modified to include the Canadian Nutrient File. The procedures used to retrieve appropriate dietary information for the three day food records were exactly as described for the 24-hour recall (see 2.4.1).

The percent of subjects below, within, and above the Acceptable Macronutrient Distribution Ranges (AMDR) for protein, fat and carbohydrate was then determined (National Academy Press, 2005).

Energy intake for each subject was assessed using Estimated Energy Requirement (EER) prediction equations developed by the DRI Committee based on age, gender, body weight in kilograms, height in meters and a physical activity (PA) coefficient (Lee & Nieman, 2007; National Academy Press, 2005). In order to determine the PA coefficient, the physical activity level of subjects was assessed during the face-to-face interview. Subjects were asked what activities they normally did during the course of a week, including the amount of time each day that they watched TV, played video games, read, played sports, as well as the specific details as to the type of sports they played, if applicable and how many times a week and for how long they played / practiced. Subjective assessment was then used to assess activity level as sedentary, low active, active or very active.

It is important to note that unmedicated children with the hyperactive form of ADHD (ADHD-HI) may spend considerable time fidgeting, tapping feet/fingers, squirming and frequently getting out of their chairs when they are expected to remain seated. This excessive activity is part of the diagnostic criteria for ADHD-HI (American Psychiatric Association, 1994) but may or may not be present in individual subjects. The amount of this activity that unmedicated hyperactive subjects were engaged in

was not assessed; and therefore, was not included in assessing the physical activity coefficient.

Micronutrient intake was assessed using the 'cut-point method' of the Estimated Average Requirements (EARs) (Lee & Nieman, 2007). As there is significant within-person variability in dietary intake, the preferred method would have been to determine the 'usual intake distribution' to correct for this variation. As the software was not available to determine usual intake distribution, the three day food record data served as an approximation of usual intake for determining the proportion of the group below the EARs for specific micronutrients.

The percentage of Low Nutrient Density (LND) foods in the diet of subjects was determined by the same method used in the published study "Reported Consumption of Low-Nutrient-Density Foods by American Children and Adolescents: Nutritional and Health Correlates, NHANES III, 1988 to 1994" (Kant, 2003). The author (Kant, A., personal correspondence) supplied specific methodology.

Dietary intake was categorized by food group based on Canada's Food Guide to Healthy Eating (1992) (Health Canada, 1992). The percentage of children below, at or above these recommendations for each food group was then determined.

3.2.3 Summary of Nutritional Assessment

Following dietary analysis of the three-day food record and receipt of laboratory results, a Summary of Nutritional Assessment (Appendix 10) was compiled for each subject. This report form included a summary of all measured data (anthropometric and biochemical data) and calculated data (dietary intake of specific nutrients, food group servings, Body Mass Index (BMI), weight-for-age, etc.) Recommendations for dietary follow-up were noted. All Summaries of Nutritional Assessment were reviewed by a Registered Dietitian prior to nutrition information being taught to subjects and/or parents/legal guardians by the graduate student. Nutrition education sessions primarily focussed on the role of zinc or copper in the growth and development of children, as well as foods that are an excellent, very good, or good source of these nutrients. Other educational sessions focussed on the division of responsibility for

eating between parent and child, as well as what parents can do if their child is a "picky eater".

3.2.4 Demographic Data Analyses

Categorical variables from the socio-demographic questionnaire were assigned values and entered into the SPSS spreadsheet. These variables included the primary language spoken at home, the total number of people in the household, the number of children under 19 years of age in the household, the child's family living situation (such as whether they lived with one or both birth parents), the child's birth order within the family, the highest level of education obtained by the child's parent(s), parents' main activity during the preceding 12 months, as well as their occupation category and total household income.

3.2.5 Anthropometric Data Analyses

Height and weight of children collected during the face-to-face interview and recorded on the data collection form were then entered into the SPSS spreadsheet. Weight-for-age percentiles, height-for-age percentiles and BMI for age were determined from Center for Disease Control (CDC) growth charts, recorded on the data collection form and then entered into the SPSS spreadsheet.

3.2.6 Blood Parameter Analyses

Laboratory data from the Complex Chemistry trace mineral analysis and the Complete Blood Count (CBC) from Routine Hematology received back from the Outpatient Laboratory and Children's Hospital and the Hospitals in Common (HIC) analysis were entered into the SPSS spreadsheet. Data received from the hospital laboratory provided the comparative normal ranges by age and gender.

3.2.7 Miscellaneous Data Handling

Subject identification (ID) code, date of birth, subject activity level as assessed through a series of interview questions, collection date, day of the week that data was collected, use of vitamin and/or mineral supplements as well as type of medication treatment for ADHD was recorded.

3.3 Statistical Analysis

Dietary intake data collected during the 24-hour recall and three day food records were analyzed using Food Processor® SQL with the Canadian Nutrient File® (2006) (SPSS® version 14 for Windows, Chicago, Illinois). All statistical comparisons were performed using two-tailed tests set at the .05 level of significance, except where otherwise indicated. Chi-square tests were used to determine differences in categorical data between sample and populations. Independent sample t-tests were used to evaluate differences between groups of continuous, normally distributed variables. Comparisons of data obtained from the present study and previous population studies were conducted by first transforming the standard error given by population studies (such as NHANES) to a standard deviation statistic, based on population size. Independent sample t-tests were then used to compare the results.

Chapter 4 Results

4.1 Participant Characteristics

Forty-four children between the ages of 6 and 12 years were recruited for this study. Of these, 17 were medication- naïve, 18 were stimulant medicated and 9 subjects were atomoxetine medicated. All the subjects / parents completed the socio-economic questionnaire and all the children completed the 24-hour recall. Ten subjects (22.7%) did not return the three day food record, despite numerous follow up phone calls.

Table 5 shows the different ages of children who participated in this study. There were slightly more than 5 times as many boys as girls in the study, with 37 males (84%) and 7 females (16%) in all participating. The mean age of the children was 8.5 years. More than half of the children (52.3%) in the study were between the ages of 6 and 8 years (n=23). Eighty percent of the children in the study were under the age of 9 years (n=35). Only a fifth (20.4%) of children were between the ages of 10 and 12 years (n=9).

Table 5 Age of Children in the Study, in Years

Age, years	n	%	cumulative %	
6	9	20.5	52.3	79.6
7	7	15.9		
8	7	15.9		
9	12	27.3	27.3	
10	2	4.5	20.4	20.4
11	2	4.5		
12	5	11.4		

4.2 Socio-Economic Demographics of ADHD Children and Their Family

A variety of socio-economic data was collected on the families of the ADHD children in the study; including education level, marital status of the parents, total household income and total number of people in the household. The ADHD child's place in family birth order was also recorded and data are presented in Table 9.

Table 6 Education Level of Parents of ADHD Children

Education Completed	Accompanying Parent			Other (Non-Accompanying) Parent		
	n	%	cumulative %	n	%	cumulative %
some high school	5	10.9	10.9	3	6.8	6.8
graduated high school	8	17.4	17.4	10	22.7	22.7
trade / vocational certificate	3	6.5	36.9	6	13.6	31.8
college / non-university	14	30.4		8	18.2	
some university	8	17.4	17.4	3	6.8	6.8
bachelors degree	5	10.9	13.1	6	13.6	22.7
above bachelors degree	1	2.2		4	9.1	
don't know *	0	0	0	1	2.3	2.3
n/a (single parent)	0	0	0	3	6.8	6.8

* education level of non-accompanying parent was not known by accompanying parent

Overall education level of parents was high, with half of parents who accompanied the child to the appointment (50%) having obtained a trade or vocational certificate, a college certificate, or a university degree (Table 6). The majority of "other parents" (54.5%) i.e. those not accompanying the child to the appointment, had also obtained a vocational or college certificate or university degree. In one case, the accompanying parent did not know the education level of the non-accompanying parent. In three cases, the child was from a single-parent family therefore questions pertaining to the non-accompanying parent were not applicable.

Total household income was high in families of children in the study (Table 7). Over half of the children (61.4%) were from families where the gross income was over $60,000 per year (n=27). More than a quarter of children (27.3%) originated from families that had gross incomes greater than $100,000 (n=12). Only two children came from families where the gross family income was less than $15,000.

Table 7 Total Household Income of Families of Children With ADHD

Gross Annual Income, in	**Family**	
	n	**%**
< 15	2	4.5
15-30	6	13.6
30-45	3	6.8
45-60	6	13.6
60-80	11	25.0
80-100	4	9.1
100+	12	27.3

Table 8 shows the total family size of families from which ADHD children in this study originate.

Table 8 Number of Persons in the Household of the ADHD Child

Number of People in the Household	Family	
	n	%
2	4	9.1
3	9	20.5
4	15	34.1
5	11	25.0
6	2	4.5
7	2	4.5
8	0	0
9+	1	2.3

The majority of children in the study (59.1%) were first-born (Table 9).

Table 9 ADHD Child's Place in the Birth Order of Children in the Family

Child's Place in birth Order	Family	
	n	%
Oldest	26	59.1
Youngest	10	22.7
Middle	7	15.9
Other	1	2.3

As presented in Table 10, most parents of the ADHD children in the study were married (70.5%) and a little over a fifth (20.5%) were either separated or divorced.

Table 10 Marital Status of Parents of Children Aged 6-12 years

Marital Status	Family	
	n	%
married	31	70.5
common-law	2	4.5
separated	5	11.4
divorced	4	9.1
never married	2	4.5

4.3 Height -for-Age and Weight-for-Age Data

More than 60% of children in the study had height-for-age just above or just below the 50th percentile. Twenty percent of children were above the 97th percentile for height-for-age (Table 11). Almost 60% of children in the study had weight-for-age that was a little above or below the 50th percentile. Twenty percent of children were above the 90th percentile for weight-for-age. Mean height-for-age was 77th percentile and mean weight-for-age was 75th percentile.

Table 11 Height-for-Age and Weight-for-Age of ADHD Children Aged 6-12 Years of Age

Percentile	Height-for-Age		Weight-for-Age	
	n	%	n	%
3-<10	0	0	1	2.3
10-<25	4	9.1	2	4.5
25-<50	11	25.0	16	36.4
50-<75	17	38.6	10	22.7
75-<90	3	6.8	6	13.6
90-<97	0	0	2	4.5
97-100	9	20.5	7	15.9

4.4 Use of Vitamin and Vitamin-Mineral Supplements

Table 12 shows that of the 24 children that took supplements, 14 took vitamin-mineral combinations that contained iron, zinc and copper. Only three children took vitamin supplements that contained only iron and seven took multi-vitamins that did not contain any minerals.

Table 12 Supplement Usage in ADHD Children Aged 6-12 Years of Age

Supplement	n	%	cumulative
Vitamins alone	7	15.9	54.5
Vitamins with iron	3	6.8	
Vitamin-mineral - with iron, zinc and copper	14	31.8	
no supplements	20	45.5	45.5

4.5 Macronutrient Intake

4.5.1 Energy Intake

Estimated Energy Requirements (EERs) based on the age of the subjects, their PA coefficient based on activity level (as assessed in the face-to-face interview) as well as measured weight and height were compared to mean energy intakes as assessed by the three-day food record (Table 13). The percent difference in EER was 107% when considering all subjects (n=34), however as one subject's mean intake could be attributed to errors in portion estimation (i.e. 263%), the mean percent difference was also determined excluding the dietary intake of this individual. The mean difference between mean energy intake and the mean EERs excluding this subject was 102% (Table 13).

Table 13 Mean Energy Intake Compared With the Estimated Energy Requirement (EER) Based on Gender, Age, Physical Activity Coefficient (PA), Height and Weight

Gender	Age	Physical Activity Coefficient (PA)	Weight	Height	Mean Intake, kcal	EER	% of EER
male	9	1.26	45.5	1.36	2399	2634	91
male	12	1.42	39.2	1.56	2923	2857	102
male	6	1.26	20.0	1.18	1606	1753	92
male	12	1.26	45.5	1.37	1804	2460	73
male	6	1.42	19.3	1.13	1278	1918	67
male	9	1.13	30.6	1.37	1985	1878	106
male	7	1.13	18.8	1.13	1956	1398	140
male	7	1.42	35.7	1.52	1505	2978	51
male	7	1.26	74.3	1.65	2335	4052	58
male	8	1.13	23.5	1.22	1371	1567	87
male	7	1.13	28.6	1.38	1528	1946	79
male	9	1.13	28.4	1.36	2683	1801	149
male	6	1.13	60.0	1.52	2146	3098	69
male	9	1.42	26.3	1.33	5933[1]	2259	263[1]
male	9	1.26	37.3	1.49	2073	2507	83
male	8	1.42	25.6	1.34	2706	2302	118
male	6	1.13	35.7	1.48	2020	2324	87
male	8	1.42	25.8	1.28	1739	2233	78
male	9	1.26	25.7	1.34	2339	1946	120
male	12	1.13	32.0	1.45	1685	1816	93
male	12	1.42	36.6	1.52	2589	2707	96
male	12	1.13	35.0	1.45	1976	1906	104
male	9	1.26	45.5	1.47	1711	2760	62
male	6	1.42	20.0	1.15	1866	1970	95
male	10	1.13	37.4	1.47	3280	2123	154
male	7	1.26	26.5	1.18	2415	1909	127
male	10	1.13	37.4	1.47	2308	2123	109
male	9	1.26	34.9	1.46	1656	2392	69
male	8	1.13	30.8	1.24	2076	1808	115
male	9	1.26	51.2	1.51	3149	2997	105
male	6	1.26	20.9	1.15	1824	1749	104
male	6	1.26	21.9	1.18	1735	1816	95
female	8	1.16	21.8	1.26	1643	1527	108
female	8	1.31	31.3	1.42	1780	2061	86
female	6	1.31	21.4	1.20	2112	1719	123
female	11	1.56	43.0	1.55	2310	2751	84
						average % of EER (n=34)	107

[1] Dietary intake of this individual can be considered a statistical outlier

4.5.2 Protein Intake

The Acceptable Macronutrient Distribution Ranges (AMDR) for protein intake for children aged 4-8 years and 9-13 years is 10-30% of energy intake (National Academy Press, 2002/2005). Most of the children in this study (94.4%) had protein intakes within 10-30% of energy. A little over 5% (n=2) had protein intakes below 10% of energy; whereas, no subjects had protein intakes greater than 30% of energy.

4.5.3 Carbohydrate Intake

The Acceptable Macronutrient Distribution Range (AMDR) for carbohydrate intake for children aged 4-8 years and 9-13 years is 45-65% of energy intake (National Academy Press, 2002/2005). Two-thirds of children (n=24) in the study had carbohydrate intakes that were within the AMDR. Of the remaining children, 16% (n=6) had intakes that were less than the AMDR and 16% (n=6) had intakes that exceeded the AMDR for carbohydrate.

4.5.4 Fat Intake

The DRI for Macronutrients establishes the AMDR for fat intake for children aged 4-8 years and 9-13 years at 25-35% of energy intake (National Academy Press, 2002/2005). Over half of children (55.6%) aged 6-8 years (n=20) were within the AMDR for fat, only 5.6% were below the AMDR for fat (n=2) whereas, 38.9% consumed more than 35% of energy as fat (n=14).

4.5.5 Macronutrient Intake Compared with General Population Data

Tables 14 and 15 present an analysis of comparisons for macronutrient intake obtained from the present study with that of the CCHS study (Garriguet, 2004). Macronutrient intake for the ADHD group did not differ significantly from the CCHS data, as can be seen in Table 14 for children up to and including 8 years of age and in Table 15 for ages 9-12 years.

Table 14 Energy and Proportion of Macronutrients as Energy; Comparison Between ADHD Children and CCHS Data for British Columbia Children Aged 4-8 Years

Macronutrient	n	Mean, ADHD	Std Dev	n, CCHS	Mean, CCHS	Sign (2 tailed)	95% CI of the Difference	
							Lower	Upper
Protein (%)	18	14.1	2.9	339	14.4	.596	-1.8204	1.0786
Carbohydrate (%)	18	56.8	9.2	339	55.6	.599	-3.4380	5.7625
Fat (%)	18	32.6	8.1	339	22.9	.177	-1.328	6.7342
Energy (kcal)	18	1881	377	339	2041	.090	-347.64	28.02

CCHS Data from (Garriguet, 2004)

Table 15 Energy and Proportion of Macronutrients as Energy; Comparison Between ADHD Boys Aged 9-12 Years and CCHS Data for British Columbia Boys Aged 9-13 Years

Macronutrient	n	Mean, ADHD	Std Dev	n, CCHS	Mean, CCHS	Sign (2 tailed)	95% CI of the Difference	
							Lower	Upper
Protein (%)	1	13.5	2.5	236	14.2	.248	-2.0734	.5664
Carbohydrate	1	53.5	9.1	236	54.0	.827	-5.3626	4.351
Fat (%)	1	34.9	6.6	236	31.7	.080	-.4222	6.707
Energy (kcal)	1	2477	1042	236	2041	.081	59.45	931.0

CCHS Data from (Garriguet, 2004)

4.6 Adequacy of Micronutrient Intake

Vitamin B_6 intake for children aged 6-8 years averaged 0.9 mg/day (Table 16). This value is considerably higher than the 0.5 mg/d of the Estimated Average Requirement (EAR) for children aged 4-6 years. While 11% of children aged 6-8 years of age did not meet the EAR for vitamin B_6, the majority of children in this age group (89%) met the EAR for this vitamin. Vitamin B_6 intake for boys aged 9-12 years averaged 1.18 mg/day (Table 16); which is higher than the 0.8 mg/d of the Estimated Average Requirement (EAR). Almost three quarters of children (78%) aged 9-12 years met the EAR for vitamin B_6 with 22% not meeting the EAR for this vitamin.

An average intake of iron in children aged 6-8 years was 12.6 mg/day (Table 16). This value is higher than EAR for iron; which is 4.1 mg/d for children aged 4-8 years of age. All children (100%) aged 6-8 years of age met the EAR for iron. Iron intake for boys and girls aged 9-12 years was on average 14.06 mg/day (Table 16). This is

substantially higher than the 5.9 mg/d for boys and the 5.7 mg/d for girls of the EAR. All of the children (100%) age 9-12 years met the EAR for iron.

Mean group zinc intake for children aged 6-8 years (n=18) averaged 6.44 mg/day (Table 16). While this value is higher than the 4 mg/d of the EAR for zinc, more than a quarter of children (28%) aged 6-8 years did not meet the EAR. Zinc intake for boys and girls aged 9-12 years averaged 6.79 mg/day (Table 16), which is less than the 7 mg/d of the Estimated Average Requirement (EARs) for zinc. As expected when mean intake is less than the EAR, more than half of children (61%) were below the EAR for zinc.

Copper intake for children aged 6-8 years (n=18) averaged .68 mg/day; which greatly exceeds the .340 mg/d of the EAR for copper (Table 16). That being said, more than a quarter of children (28%) aged 6-8 years did not meet the EAR for copper. Copper intake for boys and girls aged 9-12 years (n=18) averaged .75 mg/day. While average group intake exceeds the .54 mg/d of the EAR for copper; more than a third of children (39%) aged 9-12 years did not meet the EAR and less than two-thirds (61%) met the EAR for this mineral.

Table 16 Dietary Intakes of Micronutrients in mg/day of ADHD Children Compared with the Estimated Average Requirement (EAR)

Micronutrient	**ADHD Children Aged 6-8 years**				**ADHD Children Aged 9-12 years**			
	n	**Mean Dietary Intake, mg/day**	**EAR[1] mg/day**	**% meeting EAR**	**n**	**Mean Dietary Intake, mg/day**	**EAR[1] mg/day**	**% meeting EAR**
Vitamin B6	18	0.9 ± .5	0.5	89	18	1.18 ± .7	0.8	78
Iron	18	12.6 ± 6.3	4.1	100	18	14.06 ±	5.9[2]/5.7[3]	100
Zinc	18	6.44 ± 3.6	4.0	72	18	6.79 ± 2.8	7.	39
Copper	18	0.7 ± .4	.34	72	18	0.8 ± .5	.5	61

[1] EAR taken from the Dietary Reference Intakes (National Academy Press, 2002/2005)
[2] EAR for males aged 9-13 years
[3] EAR for females aged 9-13 years

Canadian data for micronutrient intake are not yet available from the CCHS study. The most recent population data on micronutrient intake is NHANES III from the United States (National Center Health Statistics, 1996a). Micronutrient intake data from the current study compared with population data from the US are presented in Table 17. It is important to note that dietary intake of vitamin B_6, zinc and copper in the ADHD children in the present study were are all significantly ($p<0.01$) below NHANES III population norms (Table 17).

Table 17 Comparison Between ADHD Children Aged 6-12 Years and Population Data[1], Micronutrient Intake in mg/day

Micronutrient	n	Mean, ADHD, mg/day	Std Dev	n, NHANES	Mean, NHANES III, mg/day	Std Dev	Sign (2 tailed)	95% CI of the Difference	
								Lower	Upper
Vitamin B_6	36	1.1	0.5	1581	1.7	1.7	.0000*	-.8194	-.4829
Iron	36	17.2	23.4	1581	14.1	12.9	.431	-4.8052	11.013
Zinc	36	6.6	3.2	1581	10.0	9.5	0000*	-4.4683	-2.3001
Copper	36	0.7	0.4	1581	1.1	1.1	0000*	-.5317	-2.447

[1]US Population Data from NHANES III (National Center Health Statistics, 1996b)

4.7 Dietary Intake of Low Nutrient Dense Foods (LND)

There was no significant difference in the percentage of Low Nutrient Density foods consumed by ADHD boys (n=17) aged 8-12 years in the current study (28.3%), compared with the boys aged 8-12 years from a US population study (28.6%) using NHANES II data (Kant, 2003). There were insufficient girls in the present study to enable comparison with population normal data. The Kant study only analyzed data for 8-12 year olds; therefore, no comparison data were available for children aged 6 and 7 years of age.

4.8 Serum Assessors Compared with Lab Normal & Population Normal Data and Other ADHD Studies

4.8.1 Serum Assessors Compared with Lab Normal Values

None of the children in the study had pyridoxine values below lab normal. Almost two-thirds (66%) of children (29/44 children) had serum zinc values below the lower limits of lab normal cut-offs (Table 18).

Table 18 ADHD Children Below Lab Normal Cutoffs for Zinc by Age and Gender

Age	Gender	zinc,	Age	Gender	zinc, µmol/L
6	male	13.1	**9**	male	7.3*
	male	12.7		male	11.2*
	male	10.3*		male	11.5*
	male	11.1*		female	12.5
	female	11.8		male	11.5*
	male	9.7*		male	10.9*
	male	9.1*		male	11.1*
	male	10.2*		male	11.6*
	male	9.2*		male	10.0*
7	male	12.0		male	10.6*
	male	9.5*		female	13.5
	male	11.8		male	11.3*
	male	12.0	**10**	male	9.6**
	male	11.7*		male	11.7
	male	14.0	**11**	male	11.9
	male	11.6*		female	13.2
8	female	11.5*	**12**	male	12.6
	male	9.0*		male	10.8**
	male	8.8*		male	10.5**
	female	10.6*		male	9.4**
	male	15.5		male	11.8
	male	10.4*			
	female	11.1*			

* Below the lower limit of lab normal values, ages 6-9 years (<11.8 µmol/L)
** Below the lower limit of lab normal values, boys ages 10-12 years (<11.6 µmol/L)
Note: lower limit of lab normal values for girls aged 10-12 years < 12.1 µmol/L

A comparison of results of the serum assessors with lab normal values is given in Table 19 and 20. Serum zinc was significantly lower ($p<0.05$) for the younger ADHD children aged 6-9 years (Table 19), but was not reproduced in older (10-12 year old) boys (Table 20). It should be noted that the sample size of the older boys tested in this study was likely too limited to show significance. There were insufficient ADHD girls aged 10-12 years to allow comparison with lab normal values.

Table 19 Trace Mineral Serum Assessors Compared With Lab Normal Values for Younger ADHD Children

Serum Assessor	**n**	**Mean**	**Std Dev**	**Lab Normal Range**	**z-score**
serum zinc, age 6-9	35	11.1 µmol/L	1.6	11.8-16.4	.44
serum ferritin, age 6-9 years	35	36.9 µg/L	19.7	10-55 µg/L	-6.067
serum copper, age 6-9 years	35	15.4 µmol/L	2.9	13.2-21.4 µmol/L	-1.29

Table 20 Trace Mineral Serum Assessors Compared With Lab Normal Values for ADHD Boys Aged 10-12 Years

Serum Assessor	**n**	**Mean, umol/L**	**Std Dev**	**Lab Normal Range**	**z-score**
serum zinc	8	11.3 µmol/L	1.30	11.6-15.4 µmol/L	.26
serum ferritin	8	38.6 µg/L	21.5	23-70 µg/L	-3.36
serum copper	8	15.3 µmol/L	2.1	12.6-19.0 µmol/L	-1.86

In addition to findings of low serum zinc, almost a quarter (22.7%) of children in the study (10/44 children) had serum copper below the lower limit of the lab normal values. Nine of the children with serum copper below the lower limit of lab normal values were between the ages of 6-8 years of age.

4.8.2 Serum Assessors Compared with Population Normal Data

Serum zinc and serum copper were significantly lower than population normal data (National Center Health Statistics, 1996a) for ADHD children aged 6-8 years of age and 9-11 years of age (Table 21 and Table 22).

Table 21 Serum Assessors Compared With Population Normal Data* for ADHD Children Aged 6-8 Years From NHANES III

Serum Assessor	n	Mean	Std Dev	n, NHANES	Mean, NHANES	Std Dev	Sign (2 tailed)	95% CI of the Difference	
								Lowe	Upper
serum zinc, age 6-8 years	23	11.1 µmol/L	1.6	557	12.9 µmol/L	2.1	.0000*	-2.463	-1.015
serum ferritin, age 6-8 years	23	36.9 µg/L	19.7	704	34.3 µg/L	24.8	.582	-7.2207	12.5294
serum copper, age 6-8 years	23	15.4 µmol/L	2.9	560	21.07 µmol/L	3.7	0000*	-6.846	-4.278

Population Data from NHANES III (National Center for Health Statistics, 1996a)

Table 22 Serum Assessors Compared with Population Normal Data for ADHD Children Aged 9-11 Years From NHANES III

Serum Assessor	n	Mean	Std Dev	n, NHANES	Mean, NHANES	Std Dev	Sign (2 tailed)	95% CI of the Difference	
								Lowe	Upper
serum zinc, age 9-11 years	16	11.2 µmol/L	1.5	663	13.6 µmol/L	2.2	.0000*	-3.163	-1.612
serum ferritin, age 9-11 years	16	39.7 µg/L	17.2	762	38.5 µg/L	19.4	.786	-7.9672	10.3422
serum copper, age 9-11 years	16	15.4 µmol/L	2.9	668	19.73 µmol/L	3.5	0000*	-5.562	-2.834

Population Data from NHANES III (National Center for Health Statistics, 1996a)

Almost a quarter of children (22.7%) in the study (10/44) were below the 2.5th percentile of the NHANES II cutoffs for zinc, which is set at • 10.1 µmol/L (66 µg/dL) for non-fasted individuals (Hotz et al., 2003) (see Table 23). All subjects in this study had non-fasted morning blood draws.

Six of the 23 children between the ages of 6-8 years were below the NHANES II cutoffs for zinc (i.e. below the 2.5th percentile). In this age group, NHANES II cutoffs are 10.1 µmol/L (66 µg/dL) for non-fasted individuals of either gender. Prevalence of zinc below the NHANES II cutoffs for 6-8 year olds in this study was 26% (6/23 children), see Table 23. Normally, the prevalence of zinc below the NHANES II cutoffs for children aged 3-8 years in the general population is 3.3% for males and 3% for females (Hotz et al., 2003). In the current study, there is 9 times the prevalence of zinc below these cutoffs as is normally found in the general population.

Four of the 21 children between the ages of 9 and 12 years were below the 2.5th percentile cutoffs for zinc (Table 23). In this age group, NHANES II cutoffs are 10.1 µmol/L (66 µg/dL) for non-fasted individuals of either gender. The prevalence of zinc below the NHANES II cutoffs for children aged 9-19 years in the general population is normally 1% in females and slightly less than 1% in males (Hotz et al., 2003). In the

current study there is 19 times the prevalence of zinc below the 2.5th percentile than is normally found in the general population.

Table 23 ADHD Children Below the NHANES II Cutoffs for Zinc Deficiency by Age and Gender

Age	Gender	zinc,	Age	Gender	zinc, µmol/L
6	male	13.1	**9**	male	7.3*
	male	12.7		male	11.2
	male	10.3		male	11.5
	male	11.1		female	12.5
	female	11.8		male	11.5
	male	9.7*		male	10.9*
	male	9.1*		male	11.1
	male	10.2		male	11.6
	male	9.2*		male	10.0*
7	male	12.0		male	10.6
	male	9.5*		female	13.5
	male	11.8		male	11.3
	male	12.0	**10**	male	9.6
	male	11.7		male	11.7
	male	14.0	**11**	male	11.9
	male	11.6		female	13.2
8	female	11.5	**12**	male	12.6
	male	9.0*		male	10.8
	male	8.8*		male	10.5
	female	10.6		male	9.4*
	male	15.5		male	11.8
	male	10.4			
	female	11.1			

* below the 2.5th percentile NHANES II cutoffs of 10.1 µmol/L (66 µg/dL) for non-fasted individuals

The suggested revised NHANES II cutoffs proposed by Hotz (Hotz et al., 2003) reanalyzes the NHANES II data factoring in gender, time of day of blood draw, as well as the fasting status of subjects, as these all affect serum zinc. Revised cutoffs are •10.7 µmol/L for boys with a morning, non-fasted blood draw and •10.1 µmol/L for girls with a morning, non-fasted blood draw. As shown in Table 24, almost a third of children (29.5%) in this study were below the revised NHANES II cutoffs.

Table 24 Non-fasted Morning Serum Zinc of ADHD Children Below the Revised NHANES II Cutoffs for Zinc Deficiency by Age and Gender

Age	Gender	zinc, µmol/L	Age	Gender	zinc, µmol/L
6	male	13.1	**9**	male	7.3*
	male	12.7		male	11.2
	male	10.3*		male	11.5
	male	11.1		female	12.5
	female	11.8		male	11.5
	male	9.7*		male	10.9
	male	9.1*		male	11.1
	male	10.2*		male	11.6
	male	9.2*		male	10.0*
7	male	12.0		male	10.6*
	male	9.5*		female	13.5
	male	11.8		male	11.3
	male	12.0	**10**	male	9.6*
	male	11.7		male	11.7
	male	14.0	**11**	male	11.9
	male	11.6		female	13.2
8	female	11.5	**12**	male	12.6
	male	9.0*		male	10.8
	male	8.8*		male	10.5
	female	10.6**		male	9.4*
	male	15.5		male	11.8
	male	10.4*			
	female	11.1			

* •10.7 µmol/L for boys with a morning, non-fasted blood draw

** •10.1 µmol/L for girls with a morning, non-fasted blood draw

4.8.3 Serum Assessors Compared with Other ADHD Studies

Almost two thirds (62.2%) of children between the ages of 5 - 10 years in the current study had mean serum zinc levels below the lab normal cutoffs of 11.6 µmol/L). This is twice the prevalence of low serum zinc status (27.1%) previously reported in ADHD children aged 5-10 years (Arnold et al., 2005).

4.9 Food Group Consumption as Compared to Recommendations of Canada's Food Guide for Healthy Eating

Half of the ADHD children were found to be below the recommendations of Canada's Food Guide to Healthy Eating for the Meat and Alternates group and more than half of children were below the recommendations for the Vegetables and Fruit group (Health Canada, 1992). Table 25 presents data on food group consumption of subjects studied compared with the recommendations of Canada's Food Guide for Healthy Eating (1992) (Health Canada, 1992).

Table 25 Food Group Consumption as Compared to Canada's Food Guide to Healthy Eating

Food Group	n	%	Valid %*
Meat & Alternates			
below recommendations	18	41	50.0
at recommendations	15	34	41.7
above recommendations	3	7	8.3
missing	8	18	
Vegetables & Fruit			
below recommendations	19	43	52.8
at recommendations	15	34	41.7
above recommendations	2	5	5.6
missing	8	18	
Milk & Milk Products			
below recommendations	16	36	44.4
at recommendations	18	41	50.0
above recommendations	2	5	5.6
missing	8	18	
Grain Products			
below recommendations	4	9	11.1
at recommendations	27	62	75.0
above recommendations	5	11	13.9
missing	8	18	

* valid % is the percentage of children in the study corrected for subjects that did not return 3 day food records

A recent report based on the Canadian Community Health Survey Data (CCHS) (Garriguet, 2004) compared the dietary intake of 6-9 year olds of both genders to the recommendations of Canada's Food Guide for Healthy Eating. Comparing food-group consumption data from 6-9 year olds in the current study to food group consumption data for 6-9 year olds from the CCHS study, children with ADHD do not eat significantly differently than children in the general population of the same age. It is

important to note that eighty percent of children (35/44) in the current study were between the ages of 6-9 years of age.

4.9.1 Milk & Milk Product Intake

Of the 35 children between the ages of 6-9 years that returned three day food records, 57.1% were at the recommended levels for Milk and Milk Product consumption (Table 26). This is not significantly different (^{2}= 0.7255) than recent Canadian data which reported that 63% of children in this age group met the recommended levels for Milk and Milk Product intake (Garriguet, 2004).

Table 26 Consumption of Milk and Milk Products for ADHD Children Aged 6-9 Years of Age

Compared to Canada's Food Guide	**n**	**%**	**Valid %***
below recommended	10	28.6	35.7
at recommended levels	16	45.7	57.1
above recommended	2	5.7	7.1
missing	7		

** valid % is the percentage of children in the study corrected for subjects that did not return 3 day food records

4.9.2 Vegetable and Fruit Intake

Almost half (46.4%) of ADHD children between the ages of 6-9 years of age (n=35) met the recommendations for the Vegetable and Fruit group (Table 27) compared with only 29% of children in the same age group as reported in the CCHS study (Garriguet, 2004). Significantly more ADHD children (^{2}=6.4452, p • 0.0225) met the recommendations for the Vegetable and Fruit Group.

Table 27 Consumption of Fruit and Vegetables for ADHD Children Aged 6-9 Years of Age

Compared to Canada's Food Guide	**n**	**%**	**Valid %***
below recommended	13	37.1	46.4
at recommended levels	13	37.1	46.4
above recommended	2	5.7	7.1
missing	7		

* valid % is the percentage of children in the study corrected for subjects that did not return 3 day food records

4.9.3 Grain Products

There was no significant difference in the percentage of ADHD children that consumed the recommended servings of Grain Products (85.7%) compared with the normal population (73%) (Garriguet, 2004), (^{2}=4.92, p • 0.05) (Table 28).

Table 28 Consumption of Grain Products for ADHD Children Aged 6-9 Years of Age

Compared to Canada's Food Guide	n	%	Valid %*
below recommended	3	8.6	10.7
at recommended levels	21	60.0	85.7
above recommended	4	11.4	14.3
missing	7		

* valid % is the percentage of children in the study corrected for subjects that did not return 3 day food records

4.9.4 Meat and Alternates

Table 29 shows that 36% of children aged 6-9 years met the recommendations of 2-3 servings per day of Meat and Alternates based on Canada's Food Guide for Healthy Eating (Health Canada, 1992). Population data on the percentage of children meeting the recommendations of Canada's Food Guide for the Meat and Alternates group has not yet been released from the CCHS study (Garriguet, 2004); therefore, it is not possible to determine whether consumption differs significantly in ADHD from the normal population.

Table 29 Consumption of Meat and Alternates for ADHD Children Aged 6-9 Years of Age

Compared to Canada's Food Guide	n	%	Valid %*
below recommended	17	48.6	60.7
at recommended levels	10	28.6	35.7
above recommended	1	2.9	3.6
missing	7		

* valid % is the percentage of children in the study corrected for subjects that did not return 3 day food records

4.10 Differences in Trace Mineral Status in Those that Met and Did Not Meet the Recommendations for the Meat and Alternates Group

As the main source of zinc and copper in the diet is obtained from the Meat and Alternates group, independent sample t-tests were conducted to determine if there was a difference between serum zinc and serum copper status in those that met or did not meet the recommendations of Canada's Food Guide for Healthy Eating, Meat and Alternates group. Mean serum zinc was actually higher in children that did not meet the recommendations of Canada's Food Guide for Healthy Eating, Meat and Alternates group compared with those that did meet recommendations (11.5 µmol/L ± 1.7 versus 10.2 µmol/L ± 1.2). Mean serum copper was higher (16.3 µmol/L ± 2.6) in children that did not meet the recommendations for Meat and Alternates than those that did meet the recommendations for Meat and Alternates (15.2 µmol/L ± 2.8). Independent sample t-tests did not find a difference between serum zinc status (t=1.138, p=.177) and serum copper status (t=1.204, p=.238) in subjects that met or did not meet the recommendations of Canada's Food Guide for Healthy Eating for the Meat and Alternates group.

4.11 Relationship Between Trace Mineral Status and Dietary Intake

Pearson correlations did not show a relationship between dietary intake of zinc and serum zinc status (r=-.134, p=.218) but did show a relationship between dietary intake of copper and serum copper status (r=.420, p=.004).

4.12 Relationship Between Trace Mineral Status and Vitamin-Mineral Intake

In subjects that took vitamin-mineral supplements, mean serum zinc and mean serum copper (n=20) was 10.9 µmol/L and 15.5 µmol/L respectively; whereas in subjects that did not take vitamin-mineral supplements, mean serum zinc was 11.4 µmol/L and mean serum copper was 15.4 µmol/L respectively. Independent sample t-tests did not show a difference between the use of vitamin mineral supplements and below lab normal serum zinc (t=1.544, p=.130) or below lab normal serum copper (t=1.404, p=.168) values.

4.13 Whether Serum Status is Moderated by Drug Treatment

Recruitment of atomoxetine-only treated children was limited because most children taking atomoxetine also took either stimulant medication and/or Risperdone, a medication on the exclusion criteria due to its effect on appetite. As there was insufficient atomoxetine-only treated children (n=9), the stimulant-medicated group (n=18) and the atomoxetine treated group (n=9) were collapsed into a single drug treatment group (n=27). Mean serum zinc of the drug treated subjects and drug-naïve subjects were both 10.9 µmol/L. Mean serum copper of drug treated subjects was 15.1 µmol/L compared with 15.9 µmol/L for drug naïve subjects. Independent sample t-tests found no significant difference in serum copper status between drug treated and drug naïve subjects (p=.376).

4.14 Whether Dietary Intake is Moderated by Drug Treatment

The percentage of energy from protein that drug-treated subjects consumed (n=23) was 17.1% compared with 13.7% for drug naïve subjects (n=13). The percentage of energy consumed from carbohydrate and fat was 55.4% and 33.1% respectively for drug treated subjects (n=23) compared with 55.0 % and 35.4% for drug naïve subjects (n=13). Mean energy intake for drug-naïve subjects was 2156 kilocalories compared with 2219 kilocalories for drug-treated subjects. Independent sample t-tests determined that there was no significant difference in dietary intake between drug-naïve and drug- treated participants based on protein (p=.580), carbohydrate (p=.233) and fat (p=.740). In addition, independent sample t-tests determined that there was no significant difference in the number of calories consumed by drug-naïve subjects as compared with drug-treated subjects (p=.740).

4.15 Whether Height-for-age or Weight-for-age is Moderated by Drug Treatment

Mean height-for-age of drug-treated subjects (n=27) was 72.5% percentile whereas mean height-for-age of drug-naïve subjects (n=17) was 75.1 percentile. Mean weight-for age of drug-treated subjects (n=27) was 75.1% percentile whereas mean weight-for-age of drug-naïve subjects (n=17) was 78.1% percentile. Independent sample t-tests determined that there was no significant difference of height-for-age and medication status (p=.910) or weight-for-age (p=.627) and medication status.

4.16 Whether Height-for-age is Moderated by Low Serum Zinc Status

Poor zinc status has been suggested to influence growth in young children (Lee & Nieman, 2007), particularly where there is inadequate intake or absorption (Brown, 2003; Lee & Nieman, 2007). Independent sample t-tests determined that there was no significant difference in height-for-age in those that had below lab normal values for serum zinc (t=.916, p=.365) or serum zinc values below the NHANES II cutoffs for zinc (<2.5 %ile) (t=.790, p=434).

Chapter 5: Discussion

Subject interest in participating in the current study was high. One notable difficulty was finding children that took only atomoxetine, the non-stimulant medication. Most children taking this medication also took stimulant medication in conjunction with atomoxetine, or took Risperdal, a medication listed on the exclusion criteria due to its effect on appetite. The inability to recruit sufficient atomoxetine-only children prevented three-way comparison between medication-naïve, stimulant-medicated and atomoxetine-medicated ADHD children. Due to the lack of atomoxetine-only subjects, the two medication treatment groups (i.e. stimulant-medicated and atomoxetine-medicated) were collapsed into one group, resulting in only two comparison groups; treatment-naïve ADHD children and medicated-treated ADHD children. Despite these limitations, the two-group comparison on ADHD children enabled dietary and nutrient status analysis that had not been previously conducted.

There were 5 times as many boys as girls in the study, which was not unexpected as many more boys than girls are referred to ADHD clinics for treatment (Weiss & Weiss, 1997). There were almost an equal number of children recruited for this study between the ages of 6 and 8 years and between 9 and 12 years. This division with subject ages in the present study enabled a ready comparison with Canadian and US population data, such as the CCHS (Garriguet, 2004) and NHANES data (National Center Health Statistics, 1996a, 1996b, 1996c) which are grouped similarly. Unfortunately, there were insufficient older girls recruited in the study, which limited comparisons between older girls and normal population data.

Three-quarters of children enrolled in this study came from two-parent families (married or common-law). For more than half of families, annual gross income was over $60,000 and more than a quarter of families in this study had a combined annual income of more than $100,000. Approximately 50% of the parents of ADHD children had obtained either a vocational or a college certificate or university degree. Eighty percent of the families had between three and five members, and most ADHD children were first born with only one sibling. Approximately a quarter of children came from families whose parents were married or had common-law spouses. Low dietary intake of zinc has been associated with low socio-economic populations

(Hotz, Lowe, Araya, & Brown, 2003) which is not consistent with the findings of the current study.

ADHD children in this study were significantly taller and heavier than their non-ADHD peers; which is consistent with findings from previous US studies (Swanson et al., 2005; Swanson et al., 2007). As previously reported, weight-for-age and height-for age of medication-naïve and previously medicated pre-pubertal ADHD children have been reported to be 67th percentile and 56th percentile, respectively (Swanson 2005). Mean weight-for-age and height-for-age in the current study was in the order of 75th percentile and 77th percentile, respectively.

Zinc status is reported to influence growth in young children (Lee & Nieman, 2007) particularly where there is inadequate intake or absorption (Brown, 2003; Lee & Nieman, 2007). While cessation of growth in children is an early response to zinc deficiency (Lee & Nieman, 2007), it is important to note that low serum zinc status in ADHD children did not adversely affect height-for-age. In fact, ADHD children in this study were not only taller and heavier than non-ADHD children of the same age and gender (Centers for Disease Control and Prevention, 2000) but significantly taller, but not heavier than previously reported in other ADHD studies (Swanson 2005).

Despite the fact that parents reported that children's dietary intake was abnormal, mean dietary intake of energy and macronutrients was unremarkable. Mean energy intake in this group of children was close to the recommendations of the EERs based on the subjects' height, weight, age and activity level (Lee & Nieman, 2007). In addition, there was no significant difference in the amount of energy consumed as compared with children of the same age and gender in the normal population (Garriguet, 2004). The percentage of calories derived from protein, carbohydrate, fat consumed by ADHD children aged 6-8 years in the current study was similar to the corresponding macronutrient data from children aged 4-8 years in the CCHS study (Garriguet, 2004). Similarly, ADHD boys aged 9-12 years in the current study had comparable intakes of macronutrients to those reported in boys age 9-13 years from across Canada (Garriguet, 2004). There were insufficient girls aged 9-12 years to enable comparison.

In the current study, dietary intake of macronutrients of ADHD children did not differ from what was previously reported in ADHD (Arnold et al., 2005), although it needs to be noted that dietary assessment tools in the previous study differed substantially and involved the use of an adapted adult food frequency questionnaire. There was no significant difference in energy intake in children aged 5-10 years in the current study (2127 ± 839) compared with children of the same age from the Arnold study (2027 ± 634). Similarly, there was no significant difference in dietary consumption in terms of the grams of protein, fat or carbohydrate in the current study compared with the Arnold study (Arnold et al., 2005); 71 ± 24 vs. 78 ± 29, 79 ± 33 vs. 78 ± 29, 300 ± 136 vs. 259 ± 90, respectively.

It is interesting that more than half of subjects in this study regularly consumed some kind of vitamin or vitamin-mineral supplement to compensate for what caregivers perceived as deficient or abnormal dietary intake in the ADHD children. Data from the current study did not support parental anecdotal reports that ADHD children consume considerably more energy from carbohydrates or that ADHD children eat less Vegetable and Fruit and/or Milk and Milk Products than their peers. In fact, macronutrient intake was similar to data from age- and gender-matched children from the normal population (Garriguet, 2004) as well as with findings of a previous ADHD study (Arnold et al., 2005).

Micronutrient intake; however, was found to be below recommendations (National Academy Press, 2002/2005) with more than a quarter of children aged 6-8 years not meeting the EAR for zinc or copper, three-fifths of children aged 9-12 years not meeting the EAR for zinc and two-fifths of children aged 9-12 years not meeting the EAR for copper. Both zinc and copper intakes were below population normal data (National Center Health Statistics, 1996b; National Center Health Statistics, 1996b).

There was no significant difference in mean iron intake of ADHD children aged 5-10 years in the current study (12.9 mg/day ± 5.6) compared with children in the same age range from the Arnold study (14.4 mg/day ± 5.1) (Arnold et al., 2005). However, comparing dietary intakes of zinc of children aged 5-10 years in the two studies (6.5 mg/day ± 3.3 versus 11.4 mg/day ± 4.3) yielded a statistically significant difference (p=.0000). It is important to note that dietary assessment methodology between the

two studies differed significantly. That being said, dietary intake of zinc in the current study was almost half of that previously reported in the disorder (Arnold et al., 2005).

An important finding of this study is that while the dietary intake of macronutrients did not differ significantly from age- and gender- matched children in the normal population (Garriguet, 2004), dietary intake of copper and zinc was significantly below population normal data (National Center for Health Statistics, 1996b). In addition, almost two-thirds of children in this study had serum zinc values below lab normal cutoffs and a quarter of children had serum copper below lab normal values. Both serum zinc and serum copper analysis for ADHD children and laboratory normal data were conducted at the same laboratory at BC Children's Hospital and all blood samples were drawn in the morning while all subjects were in a non-fasted state. The difference noted in ADHD; therefore, cannot be attributed to differences in methodology. For the purposes of nutrient status comparison, lab normal values represent a control group; as data were obtained from healthy children of the same age and gender recruited from the same hospital population.

Significantly, both serum zinc and serum copper were significantly below population normal data for children of comparable ages and gender (National Centre Health Statistics, 1996). Given the significant numbers of children that had low serum zinc and low serum copper, it would logically follow that low serum status of both zinc and copper might have resulted from low dietary intake of those trace minerals. Low serum zinc was not associated with low dietary intake of zinc however; low serum copper was associated with low dietary intake of copper. Almost a third of children took supplements containing zinc and copper, as well as iron. It is wondered whether a relationship between dietary zinc intake and serum zinc status might have been observed had the sample size been larger.

A number of possible explanations (other than dietary intake) for low serum zinc and copper were explored. As two-thirds of children in the study had serum zinc below lab normal values and almost a quarter of children in the study had serum copper below lab normal values, it was postulated that nutrient-nutrient interaction in the supplements might offer some explanation to low trace mineral status. Supplemental iron of 38 - 65 mg/day of elemental iron is reported to decrease zinc absorption and

supplemental zinc of 50 mg/day or more can interfere with copper bioavailability (Hotz et al., 2003). While nutrient-nutrient interaction between iron and zinc and zinc and copper is known (Hotz et al., 2003; L'Abbe, 2004), it is unlikely to have occurred in the relatively small amounts of zinc, copper and iron found in children's multivitamin-mineral formulations.

It was also wondered whether food group consumption, particularly of the Meat and Alternates group might offer some explanation to low trace mineral status. Of the 35 children in this study between 6 and 9 years of age (i.e. 80% of the sample), 60% had dietary intakes below the Canada's Food Guide for Healthy Eating recommendations for the Meat and Alternates group. On first glance, this would seem to be an important finding, as the Meat and Alternates group is a significant source of zinc and copper in the diet (Gibson, 2005) however, independent sample t-tests did not find a difference between serum zinc and serum copper status in those meeting or not meeting the recommendations of the Meat and Alternates group.

It was also thought that the amount of low nutrient density foods in the diet of the ADHD children in this study may have contributed to findings of low zinc status. There was however, no significant difference in the percentage of Low Nutrient Density foods consumed by ADHD boys aged 8-12 years in the current study compared with the boys aged 8-12 years from a US population study (Kant, 2003). As the amount of low nutrient dense foods in the diet in ADHD children in this study did not differ from population normal data, displacement of nutrient-rich foods by low nutrient dense foods did not explain findings of low zinc status in ADHD.

Almost a quarter of children were below the 2.5th percentile of the original NHANES II cutoffs for zinc deficiency (Hotz et al., 2003). Prevalence of serum zinc below the 2.5th percentile in children aged 6 to 8 years of age was 26% in the current study, compared to a reported 3% in the general population (Hotz et al., 2003). Prevalence of serum zinc below the 2.5th percentile in children aged 9-12 years in the current study was 19% compared with a reported 1% in the general population (Hotz et al., 2003). In addition, almost a third of children in the current study were below the suggested revised NHANES II cutoffs, based on gender, time of day of blood sampling and fasting status (Hotz et al., 2003).

Higher glutaminergic resonances observed in ADHD (MacMaster et al., 2003) combined with the fact that there is a chelatable zinc pool in the synapses of these neurons (Colvin et al., 2000) may suggest that there is higher zinc turnover in the disorder and possibly a higher zinc requirement in ADHD. It is also possible that poor trace mineral absorption and/or transport, or some other factors such as genetic differences in the number of receptors and/or transporters in ADHD may also contribute to low trace-mineral status in the disorder.

Zinc deficiency has been reported to result in both oxidative stress and physical breakdown of the blood–brain barrier in rats (Noseworthy & Bray 2000) as well as to be associated with abnormalities in brain function (Hansen et al., 1993) (Black, 1998; Sandstead et al., 2000). While height-for-age was not adversely affected by low zinc status, it is unknown whether low serum zinc status observed in these children contributes to alterations in the permeability of the blood-brain barrier or to other abnormalities; such as higher Magnetic Resonance Image (MRI) resonances of glutamate neurons observed in ADHD children (Courvoisie et al., 2004; MacMaster et al., 2003).

Chapter 6: Conclusion

The results of this study do not support the anecdotal reports of abnormal macronutrient intake in ADHD children. In particular, previous findings that have reported preschool ADHD boys consumed more overall calories and a higher percentage of calories from carbohydrate (Kaplan et al., 1989) were not replicated in the current ADHD population. Rather, the dietary intake of macronutrients by ADHD children was found to be comparable to data from age- and gender-matched children from the normal population (Garriguet, 2004) as well as previous ADHD studies (Arnold et al., 2005).

A considerable percentage of children were below the EARs for age and gender for both zinc and copper (National Academy Press, 2000). Mean dietary intake of copper and zinc of ADHD children in this study was significantly below age- and gender-matched population normal data (National Center Health Statistics, 1996b) and dietary intake of zinc in children aged 5-10 years was significantly lower than children in the same age range from a previous ADHD study (Arnold et al., 2005).

Two-thirds of ADHD children had serum zinc values that were below that of normal, healthy children of comparable age and gender drawn from the same hospital population (i.e. below lab normal cutoffs from Children's Hospital lab). In addition, serum copper levels were also significantly below lab normal data and population normal data for children of comparable age and gender (National Center Health Statistics, 1996c). While height-for-age was not adversely affected by low zinc status, it is unknown whether low serum zinc status observed in these children contributes to alterations in the permeability of the blood-brain barrier or to other abnormalities such as higher Magnetic Resonance Image (MRI) resonances of glutamate neurons observed in ADHD children (Courvoisie et al., 2004; MacMaster et al., 2003).

Striking was that almost a quarter of children in the present study had serum zinc values below the 2.5th percentile of the original NHANES II cutoffs (Hotz et al., 2003). For children aged 6 to 8 years, prevalence of serum zinc below the NHANES II cutoffs was almost 9 fold greater than that reported in the general population (Hotz et al., 2003). Furthermore, prevalence of serum zinc below the NHANES II cutoffs for

children aged 9-12 years was 19 times more than reported in the general population (Hotz et al., 2003).

It is intriguing that more than a quarter of the younger children aged 6-8 years and considerably more than half of older children aged 9-12 years were below the EAR for zinc, yet lower zinc intakes were not associated with low serum zinc. It is thought that perhaps sample size was too small to notice an effect.

Several conclusions can be drawn as to what is not the underlying cause for low zinc status in ADHD.

1. Nutrient-nutrient interaction from supplementation is an unlikely contributor to low zinc status observed in ADHD children since relatively small amounts of trace minerals were present in the children's multivitamin-mineral formulations.

2. There was no relationship between serum zinc status and whether children met, or did not meet the recommendations of Canada's Food Guide to Healthy Eating for the Meat and Alternates group. Assuming that the dietary intakes observed were reflective of subjects' usual intake, it may be concluded that intake of the Meat and Alternates group did not contribute to low serum zinc status observed in ADHD children.

3. The amount of low nutrient density foods in the diet in ADHD children did not explain the finding of a low zinc status in ADHD children.

While lower than normal dietary intake of zinc (as evidenced by the percentage of children below the EAR for this nutrient) may be a contributing factor to low serum zinc status, it is unlikely that it is the only factor as a third of subjects were taking vitamin-mineral supplements containing zinc. Higher zinc turnover, poor trace mineral absorption and/or transport, or other genetic-physiological deficiencies or limitations (e.g. fewer receptors and/or trace mineral chaperones in ADHD) may be other worthwhile areas for examining the link between low trace mineral status and ADHD instances in children.

There are two limitations to this study. Firstly, there was no specific control group. It could be argued that the lab normal values, obtained from healthy children of the same age and gender from the same hospital population do, in fact represent a control group for nutrient status results. Secondly, only serum zinc status was used to assess zinc status and it is not sensitive to small changes in chronic zinc status (Gibson, 2005) and may only reflect prolonged or severe zinc deficiency. In addition, serum zinc is affected by inflammation and other physiological stress (Gibson, 2005). The use of both serum zinc and serum metallothionen to assess zinc status would have made for data that are more conclusive. Metallothionen is the predominant storage form of zinc and concentrations of metallothionen reflect changes in hepatic metallothionen levels (King, 1990). Additionally, metallothionen is sensitive to changes in dietary zinc intake (King, 1990). Further research is needed to determine whether ADHD is characterized by difference in trace mineral levels, and how differences in zinc and copper levels affect ADHD pathology.

Following this study, the next logical step to this research would be to initiate a two-phased study with phase one designed to replicate the current study with the addition of a normal control group for dietary intake. Phase two would be a double-blind placebo controlled trial with zinc supplementation to determine what impact zinc supplementation has on serum zinc and metallothionen levels, and whether or not any effect of zinc supplementation is observed to influence ADHD outcome measures / symptoms.

Chapter 7 - BIBLIOGRAPHY

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Chapter 8 - Appendices

Appendix 1a - UBC Certificate of Full Board Approval (Ethics)

The University of British Columbia
Office of Research Services,
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

Certificate of Full Board Approval

Clinical Research Ethics Board Official Notification

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER
Weiss, M.	Psychiatry	**C05-0464**

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Children's & Women's Health Centre, Other

CO-INVESTIGATORS:

Kiddie, Joy, Land & Food Systems

SPONSORING AGENCIES

Eli Lilly Canada Inc.

TITLE:

Dietary Intake and Nutrient Status in Children with ADHD

APPROVAL DATE	TERM (YEARS)	DOCUMENTS INCLUDED IN THIS APPROVAL:
11 October 2005	1	Protocol version 1 dated June 2005; Subject Consent Form version 3 dated October 2005; Assent Form version 2 dated October 2005; Summary of Nutritional Assessment Results version 1 dated May 2005; Three Day Food Record Diary version 1 dated May 2005; Advertisement; Brochure; Twenty-Four Hour Recall Questionnaire version 3 dated October 2005; Parental/Guardian Demographic Questionnaire version 1 dated October 2005

CERTIFICATION:

In respect of clinical trials:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.

2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.

3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.

The CREB approval for this study expires one year from the approval date.

(signature on file)

Approval of the Clinical Research Ethics Board by one of:
Dr. Gail Bellward, Chair
Dr. James McCormack, Associate Chair

Appendix 1b - Children and Women's Hospital Certificate of Approval (Ethics)

Room 202, 950 West 28th Avenue
Vancouver, BC V5Z 4H4
Phone: 604-875-3103/3194
Fax: 604-875-2496

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

Research Review Committee

November 4, 2005

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER
Weiss, Margaret	Medicine	W05-0185

CO-INVESTIGATORS:

Kiddie, Joy Yaffa

C&W DEPARTMENTS, PATIENT BASED PROGRAMS AND ADMINISTRATIVE JURISDICTIONS IMPACTED BY THIS STUDY:

Pathology;

SPONSORING AGENCIES:

Eli Lilly Pharmaceutical Co.

TITLE

Dietary Intake and Nutrient Status in Children with ADHD

APPROVAL DATE	TERM OF APPROVAL
November 4, 2005	November 4, 2005 - October 10, 2006

CERTIFICATION:

The protocol for the above-named project has been reviewed by the Research Review Committee and has been found to be appropriate with respect to ethics, methodology, patient impact and availability of C&W resources

(signature on file)

Approval of the C&W Research Review Committee
Dr. M. Levine, Chair
Dr. M. Bond, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the research protocol

Appendix 2 - Informed Consent Form

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

Department of Child & Adolescent Psychiatry

THE UNIVERSITY OF BRITISH COLUMBIA

Department of Psychiatry, Division of Child Psychiatry

MENTAL HEALTH RESEARCH UNIT

Tel: 604-875-XXXX
Fax: 604-875-XXXX

Address:
Children's & Women's Health Centre of BC
Room B430 – 4500 Oak Street
Vancouver, BC V6H 3N1

Parent Consent Form and Attachment 1:

Some Qualifications to Take Part in this Study

STUDY TITLE: Dietary Intake and Nutrient Status in Children with Attention Deficit Hyperactivity Disorder (ADHD)

PRINCIPAL INVESTIGATOR

Margaret Weiss, M.D., Ph.D. Tel: (604) XXX-XXXX

ADDITIONAL INVESTIGATOR

Joy Y. Kiddie M.Sc. (Human Nutrition) Candidate

24-Hour Emergency Contact Number: (604) XXX-XXXX

Introduction: You are invited to take part voluntarily in a research study about the food habits of children with Attention Deficit Hyperactivity Disorder (AD/HD).

Background; ADHD affects 3-12% of children. ADHD children are easily distracted, unable to sit still, have problems listening, paying attention, and finishing tasks, and often interrupt others and act on impulse. Despite the fact that children with ADHD have been thought to eat differently, there is no published information on what children with ADHD actually eat, whether children with ADHD have any essential nutrient deficiencies or whether some of the medicine children take for ADHD changes what they eat. Our objective is to find out what children with ADHD eat and whether this is affected by the type of medication they take. We also want to know if children with ADHD have any nutrient deficiencies and whether children on some types of ADHD medication have better nutrient status than children on other types of medication. Our goal is to improve the nutrition knowledge of children with ADHD and their families.

Purpose of the Study; The purpose of this study is to determine what children with ADHD eat and whether various medication treatments impact on diet. Your child is being invited to participate in this study because they have been diagnosed with ADHD and are attending the Provincial ADHD Program Clinic at Children's and Women's Hospital.

Qualifications to Participate; The doctor involved with this study has discussed with you the requirements for your child's participation in this study. Your child should not participate in this study if he or she does not meet all qualifications. To be in this study, both the child must be between 6 and 12 years of age, and if they are a girl they must not yet get their period (menstruate). You and your child must speak and write English well. Your children must be healthy and not have any major medical or psychiatric conditions requiring treatment. To participate in this study your child must be between 6 and 12 years fold and not yet menstruating. They must have a diagnosis of ADHD.

Study Procedures; If you agree to have your child participate we will meet with you and your child only once. At that time, we will measure your child's height and weight and ask you and your child to tell us everything they ate the previous day. We want them to be able to be totally honest about what they eat, so we ask that even if they eat something you did not want them to, that they are able to tell us. We will accompany you and your child to the Outpatient's Department in Children's Hospital so that a small quantity of blood (about 2 tsp) can be taken for analysis by someone trained to do this with children. This blood sample will be used to determine the levels of essential nutrients in your child's blood and tell us whether your child is low on certain vitamins or minerals. The results will also be compared with information you will provide on what your child eats for two weekdays and one weekend day, over a two week period.

Risks; There are no known risks to participating in this study. A certified lab technician, nurse or other trained and qualified person will draw the small amount of

blood. Minor discomfort and some temporary discoloration may occur at the site of the blood draw.

Possible Benefits; This study may identify low levels of important nutrients in your child's blood tests which can be corrected by providing a multi-vitamin and mineral supplement. The information we collect will help us give you and your child nutrition education information to better help your child. The results of the nutrition assessment will be given to your doctor so that they can provide you with feedback if your child is or is not eating well. The information that you help us to collect in this study will contribute to our understanding of the importance of diet in children with ADHD.

Confidentiality; Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

Reporting Concerns; If you have any concerns about the rights of your child as a research subject, you may contact the Research Subject Information Line at the University of British Columbia at 604-XXX-XXXX.

Consent; The objectives and procedures of the study have been explained to my satisfaction and I understand that my child may withdraw from the study at any time. I have the right to refuse my child's participation or voluntarily withdraw from the study without consequence to continuing medical care or treatment at the Provincial ADHD Program Clinic. I understand that I will receive a copy of this consent form, and that by signing this consent form, I authorize the recording of information obtained from questionnaires, interviews, study staff measurement, and lab tests. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else.

Parent Information and Consent Form
Signature Page

For your child to become a part of this study, a parent or legal guardian must sign this page. By signing this page, you are confirming the following:

- You have read all of the information in this Study Information and Consent Form, and you have had time to think about it.
- All of your questions have been answered to your satisfaction.
- You voluntarily agree for your children to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or investigators, as requested.
- You or either or both of your child may freely choose to stop being a part of this study at any time, and will still be able to choose a gift certificate and come to the hospital and AD/HD clinic as before.
- You have received a copy of this Study Information and Consent Form to keep for yourself.

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

SIGNATURE AREA for consent by Parent

Subject Name (Print or Type)

_____
Parent (Print or Type)

_____ _____
Signature of Parent | Date (ddMMyy)

_____
Witness Name (Print or Type)

_____ _____
Signature of Witness | Date (ddMMyy)

_____
Name of Individual Conducting Informed Consent Discussion (Print or Type)

_____ _____
Signature of Individual Conducting Informed Consent Discussion | Date (ddMMyy)

Appendix 3 - Subject Assent Form

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA
Department of Child & Adolescent Psychiatry

THE UNIVERSITY OF BRITISH COLUMBIA
Department of Psychiatry, Division of Child Psychiatry

MENTAL HEALTH RESEARCH UNIT
Tel: 604-875-XXXX
Fax: 604-875-XXXX
Address:
Children's & Women's Health Centre of BC
Room B430 – 4500 Oak Street
Vancouver, BC V6H 3N1

Subject Assent Form and Attachment 1: Some Qualifications to Take Part in this Study

STUDY TITLE: Dietary Intake and Nutrient Status in Children with Attention Deficit Hyperactivity Disorder (ADHD)

PRINCIPAL INVESTIGATOR

Margaret Weiss, M.D., Ph.D. Tel: (604) XXX-XXXX

ADDITIONAL INVESTIGATOR

Joy Y. Kiddie M.Sc. (Human Nutrition) Candidate

24-Hour Emergency Contact Number: (604) XXX-XXXX

Subject Assent Form and

Assent Signature Page (Attachment 3)

Purpose of the Study; The purpose of this study is to find out what children with ADHD eat and whether the medicine they take for ADHD effects what they eat. You are being asked to participate in this study because you have been diagnosed with ADHD and are attending the ADHD Clinic at Children's and Women's Hospital.

Study Procedures; If you agree to participate, you will be asked to fill out a questionnaire with the help of your parents. We will ask you to tell us what you ate the previous day. We will measure your height and weight. We will teach you and your parents how to fill out a food diary, and ask you to do it at home for three days out of a two week period of time. One of those days will be on a weekend and the other two days will be on weekdays. Before you go home, we will take you and your parent(s) to the Outpatient's Department in the hospital so that a small quantity of blood (about 2 tsp) can be taken for analysis. This blood will help us find out how about the vitamins and minerals in your blood. This information will help us find out if your blood is low in any of these important nutrients. It will also help us compare what you eat with what we see on the blood tests. The whole visit will take about less than two hours and will not interfere with you regular visit to the ADHD Clinic.

Confidentiality; Your privacy will be respected. No information about who you are will be released or published without your permission. Records used in this research and your medical records that do have your name on them may be looked at by the researchers doing this study or the people at the University of British Columbia that make sure this research is done properly. No papers that identify you by name or by your initials will be allowed to leave the office of those doing this research.

Permission / Assent; This study has been explained to me in a way that I can understand. I can stop being part of this study at any time if I want and that won't change anything. I will still be able to keep coming to appointments at the ADHD Clinic. I will get a copy of this permission form to keep. By signing this permission form, I agree to let the researchers write down information that they get from the questionnaires I answer, from discussions and interviews, from the measurements that are done of my height and weight and lab tests. My signing this permission form does not change my legal rights against the sponsor, researchers /investigators, or anyone else.

Assent Signature Page (Attachment 3)

SUBJECT'S ASSENT TO PARTICIPATE IN RESEARCH

- This study has been explained to me in a way that I can understand.
- I can stop being part of this study at any time if I want and that won't change my ability to come to the hospital or to clinics.
- Even if I stop being part of this study, I will still be able to keep coming to my scheduled appointments at the ADHD Clinic and will still get to choose a gift certificate.
- I will get a copy of this permission form (also called and assent form) to keep.
- By signing this assent form, I agree to let the researchers write down information that they get from the questionnaires I answer, from discussions and interviews, from the measurements that are done of my height and weight and skin fold thickness and lab tests.
- My signing this permission form does not change my legal rights.
- I agree to participate in this study.

Signature of Subject Date (ddMMyy)

Appendix 4 - Socio-Demographic Questionnaire Form

Parental / Guardian Demographic Questionnaire

The first few questions are about you and the people currently live in your household.

1. **Is your first language** English □ French □ Other □
2. **Including yourself, how many people live in your household?** _____
3. **How many of them are less than 19 years old?** _____
4. **What is your marital status?**

1	married	□
2	common-law/live with partner	□
3	separated	□
4	divorced	□
5	widowed	□
6	single/never married	□
8	refused	□

5. **Enter respondent's gender**

1	□	male
2	□	female

6. **Which of the following bests describes this child's family situation?**

1	lives with both parents (either natural or adoptive)	□
2	lives with one natural or adoptive parent and this parent's spouse or partner	□
3	lives with one parent (natural or adoptive parent) parent's spouse or partner	□
4	lives in a shared custody arrangement	□
5	other arrangement, specify _____ _____ _____	□
6	refused	□

Of the children now living in your household, is this child…

1	the oldest child?	□
2	the youngest child?	□
3	the middle child?	□
4	other, specify	□
	_____	
	_____	

What is the highest grade level of education you have ever attained?

1	grade 8 or lower	□
2	some high school	□
3	graduated high school	□
4	trade/vocational certificate	□
5	college (non-university) certificate e.g. nursing	□
6	some university	□
7	bachelor's degree	□
8	above bachelor's degree	□
9	don't know	□
10	refused	□

What is the highest grade level of education ever attained by the other parent/guardian in the household? (one-parent family, n/a)

1	grade 8 or lower	□
2	some high school	□
3	graduated high school	□
4	trade/vocational certificate	□
5	college (non-university) certificate e.g. nursing	□
6	some university	□
7	bachelor's degree	□
8	above bachelor's degree	□
9	don't know	□
10	refused	□

Which of the following bests describes your MAIN activity during the last 12 months? Were you…

1	working at a job or business?	□
2	looking for work?	□
3	raising a family?	□
4	retired?	□
5	going to school?	□
6	other	□

Which of the following bests describes the MAIN activity of the other parent/guardian in the household during the last 12 months? (one-parent family, n/a)

1	working at a job or business?	□
2	looking for work?	□
3	raising a family?	□
4	retired?	□
5	going to school?	□
6	other	□

Which of the following bests describes your occupation?

1	management	□
2	professional	□
3	technologist, technician or technical occupation	□
4	administrative, financial or clerical	□
5	sales or service	□
6	trades, transport, equipment operator	□
7	fishing, farming, mining	□
8	processing, manufacturing utilities	□

Which of the following bests describes the occupation of the other parent/guardian in the household?

1	management	□
2	professional	□
3	technologist, technician or technical occupation	□
4	administrative, financial or clerical	□
5	sales or service	□
6	trades, transport, equipment operator	□
7	fishing, farming, mining	□
8	processing, manufacturing utilities	□

I would like to ask you about your financial income. What is your best estimate of the *total household income* for the last 12 months before taxes and deductions?

1	less than $15,000	□
2	$15,000 - under $30,000	□
3	$30,000 - under $45,000	□
4	$45,000 - under $60,000	□
5	$60,000 - under $80,000	□
6	$80,000 - under $100,000	□
7	$100,000 or more	□
8	don't know	□
9	refused	□

Thank you for completing this survey. This will help us in the statistical analysis for this study.

Appendix 5 - Twenty-four Hour Recall Form

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

Twenty-four Hour Recall Questionnaire for Ages 6 to 12

Subject's ID Code:_____
weight _____kg height _____ cm
Date of birth: (yyyy/mm) _____
Gender: Male □ Female □
Age: 6 □ 7 □ 8 □ 9□ 10 □ 11 □ 12□
Today's Date: _____
Day of the week: _____

Place Eaten	Time	Description of food or drink (Give brand name if applicable)	Quantity	LAB USE ONLY		
				Day code	Food Code	Amount code

Additional Questions:

Was what you ate unusual or different in any way? ☐ Yes ☐
If yes, how? _____

_____

Do you take vitamin or mineral supplements? ☐ Yes ☐
If yes, please describe type and how often you take it _____

Appendix 6 - Data Collection Form

Case Report Form:

subject ID Code: _____ **weight, kg** (closest 100 gm)_____ **height, cm** (closest 0.1 cm) _____ height, m (m/100cm) _____ **DOB** yyyy/mm _____ **activity level:** **1** **s**edentary, **2** **l**ightly **a**ctive **3** **a**ctive **4** **v**ery **a**ctive **Gender**: 1 m 2 f **age, years**: 1 6 2 7 3 8 4 9 5 10 6 11 7 12	**Collection date:** yyyy/mm/dd _____ **Day of the week**: 1 monday 2 tuesday 3 wednesday 4 thursday 5 friday **24hr: unusual intake:** 1 yes 2 no **24hr:vit/min supplements:** 1 yes 2 no **Rx medication**: 1 stimulant 2 atomoxetine **3** none
weight for age percentile, growth chart 1 < 3rd % 2 3 - < 10 % 3 10 - < 25 % 4 25 - < 50 % 5 50 - < 75 % 6 75 - < 90 % 7 90 - < 97 % 8 > 97th **height for age percentile, growth chart** 1 < 3rd % 2 3 - < 10 % 3 10 - < 25 % 4 25 - < 50 % 5 50 - < 75 % 6 75 - < 90 % 7 90 - < 97 % 8 > 97th **BMI (kg / m^2) _____**	**BMI-for-age, growth chart** 1 < 3rd % 2 3 - < 10 % 3 10 - < 25 % 4 25 - < 50 % 5 50 - < 75 % 6 75 - < 90 % 7 90 - < 97 % 8 > 97th **Demographics** **1. mother tongue**: 1 E 2 F 3 other **2. no. in household:** 1 2 2 3 3 4 4 5 5 6 **6** 7

3. no less than 19 yrs:

1 1
2 2
3 3
4 4

4. marital status, respondent

1 married
2 common law
3 separated
4 divorced
5 widowed
6 single / never married
7 refused

5. respondent's gender

1 male
2 female

6. child's family situation

1 lives with both parents
2 lives with one natural or adoptive parent and this parent's partner
3 lives with one parent / single parent family
4 shared custody
5 other
6 refused

7. of the children in household, **is this child**

1 oldest
2 youngest
3 middle
4 other

8. highest grade level, respondent _____

9. highest grade level, other parent / guardian (n/a if single parent) _____

1 > or = Gr. 8
2 some HS
3 grad. HS
4 trade/voc cert.
5 college / non-univ cert.
6 some univ
7 bachelor's deg.
8 above bachelors deg.
9 don't know
10 refused
11 n/a

10. main activity (respondent) last 12 months? _____

11. main activity of other parent/guardian last 12 months? (n/a if single parent) _____

12 working at job / business
13 looking for work
14 raising a family
15 retired
16 going to school
17 other
18 n/a

12. respondent's occupation _____

13. other parent / guardian's occupation (n/a if single parent) _____

19 management
20 professional
21 technologist / technician
22 admin./ financial / clerical
23 sales / service
24 trades/transport/equip. operator
25 fishing/farming/mining
26 processing/manufacturing/utilities
27 n/a

14. total household income

28 > $15,000
29 $15,000 - > $30,000
30 $30,000 - > $45,000
31 $45,000 - > $60,000
32 $60,000 - > $80,000
33 $80,000 - > $100,000
34 $100,000 or
35 don't know
36 refused

Place Eaten	Time	Description of food or drink (Give brand name if applica	Quantity	LAB USE ONLY		
				Day code	Food Code	Amount code

Appendix 7 - Three-Day Food Record Form

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

Three Day Food Record Diary

Instructions
The information you record in your food diary will help us know more about what you usually eat.

1. You will need to complete this diary for **THREE DAYS in a TWO WEEK PERIOD**
2. **TWO of the days you complete must fall on a WEEKDAY** (i.e. Monday-Friday)
3. **You must choose two weekdays that do not come one after the other** eg. if you choose Monday as the first day, then the next day you choose cannot be the next day, Tuesday .
4. **The THIRD day must fall on a weekend**, either a Saturday or a Sunday.

How much:
In this space provided, indicate ***how much*** of the particular food item you ate or drank.
To help you estimate portion sizes, you can refer to **t**he following visual measures:

1 tsp /5ml	1 tbsp /15ml	1oz /28g	1 ½ oz / 43g	3 oz /85g	1/3 cup /78ml	¼ cup /60ml	½ cup /125ml	1 cup /250ml

What kind:
In the space provided, write down the **TYPE of food** you ate or drank.
Be as specific as you can. For example if you ate a sandwich, break the description down into the number of slices of bread (eg. 2) and the type of bread (white sandwich bread, whole wheat bread), the amount and type of filling and anything else that was in the sandwich such as mayonnaise, mustard, lettuce, etc. If you drank milk, please list if was it homogenized, 2%, Homo or some other kind, like goat milk or soya milk..
Remember to include any sauces, gravies and dressings you use, and the amounts you ate
Write down everything, even if you don't think of it as "food", like gum, candy, vitamins, etc. Even include water.

Time:
Write the time of day you ate the food or candy or drank the drink

Remember:
There are no "right" answers!
Don't change what you would normally eat just because you are writing it down.
Keep the form with you, and write down everything you eat, even if it doesn't seem like a meal or snack.
Write it down when you eat it. Don't try to remember it all at the end of the day.
Be specific: If you ate potato chips, write potato chips, not potatoes.

Subject's ID Code:_____
Day of the Week: _____

HOW MUCH	WHAT KIND of food or drink (Give brand name if applicable)	Time	LAB USE ONLY		
			Day code	Food Code	Amount code

Subject's ID Code:_____
Day of the Week: _____

HOW MUCH	WHAT KIND of food or drink (Give brand name if applicable)	Time	LAB USE ONLY		
			Day code	Food Code	Amount code

Subject's ID Code:_____
Day of the Week _____

HOW MUCH	WHAT KIND of food or drink (Give brand name if applicable)	Time	LAB USE ONLY		
			Day code	Food Code	Amount code

Appendix 8 - Study Requisition

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

STUDY REQUISITION

PATHOLOGY & LABORATORY MEDICINE

HOSPITAL #	SEX	BIRTHDATE DAY MO YR
LAST NAME	FIRST NAME	INITIAL
ADDRESS ADDRESSOGRAPH		
PHN #		TELEPHONE
STUDY SUBJECT ID:		

STUDY NAME: ADHD2	**STUDY #: R262**

LOG IN: U–R-G_S

At *"bill to"* enter: R262

Standing Order Code: ADHD2

Panel Codes: ABP, FER, MNS, SSE, COP, ZNP AND RS

COLLECTION: ***ONLY COLLECT WHAT IS ASKED FOR ON THIS REQUISITION****

DISREGARD ULTRA LABEL CODES

TWO 4ml EDTA tubes
#1 minimum volume=1ml for Hematology
#2 minimum volume= 2ml ***WRAP IN FOIL TO PROTECT FROM LIGHT*** for lab coordinator

ONE 7ml NAVY BLUE top tube KEEP UPRIGHT (no additive) minimum volume=2ml

DISPATCH:

#1 EDTA – Hematology, Program 1
#2 EDTA – **IN FOIL –** to Lab Research Coordinator local 7989
NAVY BLUE TOP – UPRIGHT – to Complex Chemistry

SPECIAL INSTRUCTIONS:

HEMATOLOGY PROGRAM 1: - ABP - process as usual standard operating procedures

COMPLEX CHEMISTRY : - process as per usual standard operating procedures
FERRITIN (aliquot from navy tube first)
MNS, SSE, COP, ZNP

LAB STUDY COORD: Spin foil wrapped EDTA tube at 3700rpm's for 8minutes. Aliquot a minimum volume of 500ul plasma into a cryovial and store in -80 freezer to be shipped to Hospitals in Common at a later date.

COLLECTION DATE: _____. TIME: _____. INITIALS: _____.

C&W CONSISTS OF BC CHILDREN'S HOSPITAL & SUNNY HILL HEALTH CENTRE FOR CHILDREN
AND BC WOMEN'S HOSPITAL & HEALTH CENTRE

AND IS AN ACADEMIC HEALTH CENTRE AFFILIATED WITH THE UNIVERSITY OF BRITISH COLUMBIA
AND THE B.C. RESEARCH INSTITUTE FOR CHILDREN'S & WOMEN'S HEALTH

Appendix 9 - Low Nutrient Density Foods

Assessment of Intake of Low Nutrient Dense (LND) Foods

Subject Number: R262____

LND Food Variable	**Number =** Number of Mentions LND	**Amount** = grams, LND	**Proportion daily Energy** = % kcal LND
Visible Fat (VF)			
Sweeteners (SW)			
Baked and Dairy Desserts (BD)			
Salted Snacks (SS)			
Misc (MC)			
TOTALS	(**NoMent**:)	(**LNDgrams)**	(**%kcalLND)**

Visible Fat (VF); butter, oil, dressings, gravy, etc
Sweeteners (SW); sugar, syrup, candy, carbonated and non-carbonated sweetened drinks, etc
Baked and Dairy Desserts: (BD); cookies, cakes, pies, pastries, ice cream, puddings, cheesecake, etc
Salted Snack (SS): potato, corn and tortilla chips, etc
Miscellaneous (MS): coffee, tea, condiments, etc

NoMent: Number of mentions of LND foods & beverages
LNDgrams: amount in grams of LND foods and beverages
%kcalLND: percentage of total energy from LND foods and beverages

Appendix 10 - Summary of Nutritional Assessment

Summary of Nutritional Assessment Results

SUBJECT					
Subject ID Code					
DoB (yyyy/mm)					
Age (years)					
Gender					
COLLECTION INFO					
Date (yyyy /mm/dd)					
Day of Week (#1-5)					
Rx					
medication:1= yes / 2= no					
stimulant:1= yes / 2= no					
atomoxetine:1= yes / 2= no					
MEASURES					
Weight, g (100 g)					
Height, cm (0.1cm)					
CALCULATED					
Weight for age percentile					
Height for age percentile					
BMI					
INTAKE					
CFG Group		**Ref.**	**Intake:CFG**		
			L	**N**	**H**
GRAIN		5-12			
F & V		5-10			
MEAT / ALT		2-3			
MILK	age 4-9	2-3			
	age 10-16	3-4			