Dietary Intake among Children with Acute Lymphoblastic Leukemia (ALL)

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Abstract

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Children with acute lymphoblastic leukemia (ALL) are at elevated risk for nutrition-related morbidities both during and after therapy. The degree to which dietary intake fluctuates during cancer therapy and possibly contributes to the development of nutrition-related morbidities is unknown. This study presents the results of the first prospective study describing changes in dietary intake in 667 children undergoing treatment for ALL. Dietary intake was evaluated with a food frequency questionnaire at three timepoints reflecting different intensities of cancer therapy: diagnosis (Time 1-no therapy), induction (Time 2- high-dose therapy), and continuation (Time 3- low-dose therapy). Dietary intake was compared to the Dietary Reference Intakes (DRIs) and normative data. Contrary to expectations, total caloric intake in the majority of patients exceeded the DRIs with a smaller percentage of patients below the DRI for calories. The majority of patients were within the DRI for all other macronutrients with an increase in intake of fat at Time 2. Despite adequate caloric intake, the majority of patients had low dietary intakes of calcium, vitamin D, and vitamin E while excess dietary intakes were observed for zinc and niacin. For folate, most patients were either below or above the DRI. In general, dietary intakes were reflective of normative data suggesting intakes are not significantly altered during treatment for ALL. This study was successful in identifying priority nutrients for dietary intervention and scientific inquiry. The effect of these strategies on the development of nutrition-related morbidities in children with ALL may be considered for future research initiatives.

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Dedication

This is dedicated to my father, Dr. John N. Damoulakis, whose hard work was an exemplary model for his children. To my husband, Danny Ladas, who passionately supported this work and our beloved children, Kyriaki, Alexander, and Kalliroi who patiently sat by my side throughout the doctoral process.

To all of the children and adolescents whose bravery in fighting cancer is nothing short of remarkable. It is my hope that this thesis paves the way for future studies that relieve the pain and suffering for you and your families.

Chapter 1: Introduction

This chapter provides an overview of the background, rationale, and aims of the current study.

1.0 Introduction

Although relatively rare, childhood cancer is the second leading cause of death among children and adolescents in the United States (Center for Disease Control, 2010). While the incidence of childhood cancer has increased, the establishment of research cooperative groups has aided the systematic collection of data. As a result, overall mortality in most developed areas of the world has decreased due to advances in research and a better understanding of cancer biology. Overall, five year survival rates for all childhood cancers increased from 58.1% in 1975-77 to 79.6% in 1996–2009 (National Cancer Institute, 2012). Improvements in survival have been most apparent for acute lymphoblastic leukemia (ALL). In a little over two decades, overall survival for children with ALL has increased from a mere 10%, to over 90% for patients with low risk ALL (i.e. standard risk ALL) (National Cancer Institute, 2012).

The rise in the survival rate for childhood cancer is largely, but not solely, attributed to the adoption of multi-modal therapy, which include combinations of chemotherapy, surgery, radiation, and stem cell transplantation. Research documenting the effectiveness of multi-modal therapy has been aided by the development of research consortiums, which increase investigators' access to a large number of patients and provide an assurance of quality to clinical data. Research consortiums such as The Children's Oncology Group (COG) or The Dana Farber Cancer Institute (DFCI) are two of the largest research consortiums exclusively focused on the treatment of childhood cancer. These groups conduct clinical trials that include cancer centers

from most major universities and teaching hospitals in the United States, Canada, Australia, and New Zealand. Prior to the formation of these groups, research focusing on supportive care during cancer therapy, which includes nutrition therapy, was limited due to small sample sizes and heterogeneous populations comprised of patients with varying cancer diagnoses and treatment protocols.

1.1 Background and rationale for the study

Few clinicians would dispute the importance of providing nutrition support to a child. Children who are malnourished are at increased risk for infection, reduced quality of life, and poor neurodevelopmental and growth outcomes (Picot et al., 2012). Epidemiologic data from developing countries in which children with cancer often present with overt malnutrition at diagnosis, show that poor nutrition status correlates with reduced survival (Sala et al., 2012). Recent studies have found that remediation of malnutrition, defined by anthropometric measures, has been one of many supportive care strategies leading to improved survival rates for children with cancer residing in developing countries (Antillon et al., 2012).

Clinical studies have also demonstrated that children who are well-nourished at diagnosis often become malnourished during therapy due to the side effects of the drugs administered to treat the cancer (Brinksma et al., 2012). The incidence and severity of malnutrition is associated with the class and dose of chemotherapy and radiation (Ladas et al., 2005). For example, methotrexate is a chemotherapy agent that is used for the treatment of many childhood malignancies including ALL, solid tumors, and Non-Hodgkin's Lymphoma. At low doses, methotrexate can cause mild mouth sores (open wounds in the mouth and gastrointestinal tract) and nausea whereas high-dose

methotrexate is associated with severe mouth sores, nausea and vomiting, and loss of appetite. These nutrition-related side effects have an adverse effect on nutrition status and may lead to mild or severe malnutrition. In moderate to severe cases of malnutrition, enteral feeds or total parenteral nutrition is required to ensure minimum intake of nutrients. Unfortunately, this is not a routine part of supportive care due to the lack of evidence documenting the importance of nutrition therapy in children and adolescents undergoing treatment for cancer.

Children and adolescents with ALL may also become overweight or obese as a consequence of therapy (Withycombe et al., 2009). Prolonged exposure to steroids may contribute to the development of obesity during and after cancer therapy. Children with cancer are also at increased risk for heart disease, metabolic syndrome, and hypertriglyceridemia due to the therapy administered for the treatment of ALL (Hudson et al., 2003), risk factors that may be exacerbated by the presence of obesity. Managing both ends of the nutrition spectrum in children with ALL is an ongoing challenge for clinicians.

The rationale of the current study was to provide an understanding of dietary intake patterns in children with ALL over the course of therapy. Findings are intended to identify potential areas of high priority for nutrition intervention.

1.1.a Initial Studies Reporting on Nutrition Status in Children with Cancer

Clinical studies from the late 1970s provide the first line of evidence of the importance of nutrition support in children and adolescents with cancer. These studies examined the feasibility and safety of providing enteral feeds and total parenteral nutrition to children with cancer (Filler

et al., 1979; Filler et al., 1977; Rickard et al., 1980; Rickard et al., 1985; Van Eys, 1998; Van Eys et al., 1980). Filler *et al.* performed one of the first small pilot studies in 41 children with cancer and demonstrated that no adverse events were associated with the administration of total parenteral nutrition during cancer therapy (Filler et al., 1977). Subsequent studies provided details on the timing and severity of malnutrition, and its effect on therapy-related side effects and survival. Many of these studies were retrospective reviews performed with small sample sizes, mixed cancer diagnosis and treatment regimens, and relied on varied definitions of nutrition assessment (Brinksma et al., 2012). Despite these limitations, some clear patterns emerged. First, the provision of nutrition therapy was found to be safe among children with cancer since neither enteral or total parenteral nutrition were associated with an increase in adverse events (Filler et al., 1979; Rickard et al., 1982; Van Eys, 1982). Second, malnutrition was associated with an increase in *therapy-related side effects* such as infection and myelosupression (bone marrow suppression) (Rickard et al., 1986; Van Eys et al., 1980). Finally, well-nourished patients reported improved quality of life compared to undernourished patients (Van Eys, 1998).

1.1.b Recent Studies Reporting on Nutrition Status in Children with Cancer

The measurement of nutrition status in children and adolescents may be performed utilizing a range of indices that include: (1) assessment by history, (2) clinical assessment, (3) anthropometric assessment, and (4) laboratory assessment (American Academy of Pediatrics et al., 2004). Pre-existing risk factors, either medical or socioeconomic, medical conditions, prolonged hospital admissions, and age of the child will determine the best index. According to the American Academy of Pediatrics, a food record or diet recall combined with anthropometric

data is sufficient in denoting the nutrition status of most children and adolescents (American Academy of Pediatrics et al., 2004). For children with cancer, the current standard of care in denoting nutrition status is limited to anthropometrics with the use of diet recalls or food records only when clinically indicated (Mosby et al., 2009). In the peer-reviewed literature, classification of nutrition status is reported utilizing anthropometric measures with few authors reporting on dietary intake (Brinksma et al., 2012).

In children with cancer, studies performed within the last decade have improved the understanding of the relationship between nutrition status and therapy-related side effects and survival by performing studies in patients with a single cancer diagnosis and receiving similar cancer treatment regimens. Lange *et al.* was one of the first investigators to report on the effect of nutrition status on survival in 768 children with acute myeloid leukemia (Lange et al., 2005). This was one of the first studies conducted in a homogenous patient population with a large sample. This study found a significant difference in survival among children who were underweight (body mass index (BMI) $\leq 10^{th}$ %) or obese (BMI $\geq 95^{th}$ %) compared to normal weight children. Subsequent studies confirmed these results. Hingorani *et al.* reported that a low BMI at diagnosis was associated with increased slough (dead tissue surrounding a wound), wound infections, and arterial thrombosis in children with osteosarcoma (n=498) (Hingorani et al., 2011). A large study performed among 2,057 children with high-risk ALL found that patients who were underweight (BMI $< 5^{th}$ percentile) or obese (BMI $> 94^{th}$ percentile) experienced increased therapy-related side effects due to cancer therapy (Orgel et al., 2011). The study also found that patients who were underweight for the majority of treatment had lower survival rates when compared to healthy weight children. Finally, in 468 children with

rhabdomyosarcoma, greater than ten percent weight loss at 24 weeks was associated with more therapy-related side effects and hospital days (Burke et al., 2012). Patients who were obese (BMI > 94th percentile) at diagnosis had inferior failure free survival (the interval from diagnosis to progression or death) but not overall survival (the interval between diagnosis and death). Children and adolescents who were underweight (BMI <5th percentile) at diagnosis had borderline inferior failure free survival compared to those who were within a healthy weight range.

These were among the first studies to suggest that both patients who were underweight and overweight have increased therapy-related side effects and reduced survival compared to children who were within a healthy weight range. However, these studies could be criticized in that most have relied only on height, weight, or BMI percentile as a proxy for nutrition status. These indices are limited in denoting nutrition status since cancer or side-effects associated with cancer therapy can falsely elevate anthropometric measures such as when edema or high tumor burden falsely elevate a patients' weight (Mosby et al., 2009).

While studies utilizing more sensitive markers of nutrition status such as skinfold tests may result in more consistent findings, (Barr et al., 2011) they are still limited in that dietary intake of essential nutrients are not considered in the assessment of nutrition status. Ideally, a comprehensive assessment of nutrition status that includes both diet and anthropometric measures would provide clinicians with the most useful information in determining the nutrition status and nutrient requirements of children and adolescents with cancer.

1.1.c Studies Exploring Dietary Intake among Children with ALL

The few studies that have reported on dietary intake during cancer therapy have been performed primarily with small sample sizes or among patients treated with outdated treatment regimens. Two were performed in children with ALL and two studies were reported in children with heterogeneous cancers.

Bond *et al.* used weighed food records to describe dietary intake in 26 children (age range: 5-16 years; male=16/ female=10) with mixed cancer diagnoses compared to 26 unmatched healthy controls (Bond et al., 1992). Among children with ALL, energy intake was similar to controls groups (Patients: Mean=1822 kcal per day (SEM=140)) Controls: (Mean=1860 kcal per day (SEM=62)) and was below the recommended dietary allowance (RDA) in both groups. This finding was similar among children with solid tumors. In a small cross sectional study, food frequency questionnaires were used to describe dietary intake among 16 (male=7/female=9) children with varying types of cancer between 6-15 years of age compared to 19 age- and gender-matched controls (Galati et al., 2011). Dietary intake of calories, fat, and carbohydrate were similar between the groups. However, in comparison to controls, children with cancer had lower intakes of protein (P=0.027), zinc (P=0.01), phosphorous (P=0.038), riboflavin (P=0.013), and B12 (P=0.00) and higher intakes of potassium (P=0.017).

Among children with ALL, Delbecque-Boussard *et al.* measured dietary intake at four timepoints during therapy in 15 children (age range: 2-16 years/gender-NR) and 15 age-matched controls (Delbecque-Boussard et al., 1997). At each of the four timepoints, the caloric intake of children with ALL was below the French RDA. In controls, total calorie intake was similar to the French

RDA. Dietary intake of protein at the four timepoints was over two times the RDA among children with ALL, yet below protein intakes reported by controls. The difference in the methodology in collecting dietary intake between the two groups, a 24-hour recalls in the children with ALL and 7-day food records in the controls, limits the interpretation of these results. Finally, in another small study dietary intake and body composition was evaluated in 16 children (age range: 2-15 years; male=8/female=11) undergoing treatment for ALL (Halton et al., 1998). Dietary intake was measured with a 3-day food record. In the majority of children, total calorie intake was above the Canadian Recommended Nutrient Intake (RNI)). Protein intake was greater than 100% of the RNI in nearly all children. This was the first study to report caloric intake in excess of the recommended values among children with ALL.

Overall, these studies suggest that the dietary intake of children with cancer may be under or over the recommended values for calories with no definitive trends identified. Based upon two small studies in children with ALL, protein intake appears to exceed recommendations. The studies must be interpreted with caution considering their small size, multiple confounding variables such as diagnosis, phase of therapy, or type of treatment were not considered in these studies. These limitations underscore the need for prospective studies exploring dietary intake in patients with a single cancer diagnosis at consistent timepoints to explore the effects of cancer therapy on dietary intake and how they compare to normative and recommended values.

1.1.d Dietary Intake and Therapy-Related Side Effects and Survival in Children with Cancer

To date, there have not been any studies that have comprehensively evaluated overall diet on therapy-related side effects. However, there have been several studies that have explored dietary intake or serum assessment of *select nutrients* and the frequency and severity of side effects. Micronutrients of interest have been bone-metabolizing nutrients due to bone morbidities associated with treatment for ALL; antioxidants due to the theoretical effect that antioxidant properties may minimize therapy-related side effects, and B vitamins due to the administration of anti-folate medications for the treatment of ALL. Comprehensive reviews of these nutrients have been previously published (Ladas et al., 2004; Robien, 2005; Tylavsky et al., 2010). Select studies are highlighted below.

One study explored the effect of dietary intake of antioxidants on therapy-related side effects and survival in children with cancer. This was a prospective study in 103 children with ALL (age range: 2.1-15.1 years; male=60/female=43) and collected dietary intake with both a 24-hour recall and FFQ at three timepoints during therapy (Kennedy et al., 2004). The authors found children with higher, compared to children with lower, dietary intake of beta-carotene and vitamin C experienced reduced hematologic or non-hematologic side effects (P=0.04), lower risk of hematologic or non-hematologic side effects (P=0.01), fewer delays in the administration of scheduled chemotherapy (P=0.04), and fewer days spent in the hospital (P=0.04). Children with higher dietary intakes of vitamin A were more likely to have a slow response to treatment (P=0.05), whereas those with higher vitamin E intakes were more likely to have a rapid response to treatment (P=0.05). The authors concluded poor dietary intake of select nutrients was associated with increased therapy-related side effects. This was one of the first studies to

highlight the need for dietary counseling during cancer therapy so as to potentially minimize the risk of side effects due to poor dietary intake of select nutrients.

To date, no studies have explored dietary intake of bone-metabolizing nutrients during cancer therapy. One cross-sectional study explored bone-metabolizing nutrients in survivors of ALL. Investigators found that the majority of patients were below the RDA for calcium, vitamin D, potassium, and magnesium (Tylavsky et al., 2010). Whether reduced intakes accelerate the development of bone morbidities associated with cancer therapy or if children with cancer are more susceptible to bone morbidities irrespective of dietary intake is unknown. A better understanding of dietary intake of bone-metabolizing nutrients during all phases of treatment is sorely needed to better understand which patients may be at risk for bone morbidities and warrant intervention.

To date, no studies have explored dietary intake of B vitamins during cancer therapy in children with ALL. Folate, in particular, is a nutrient of high interest due to the inclusion of methotrexate (an anti-folate drug) for the treatment of ALL. While patterns of dietary folate alone may not be relevant, dietary intake of folate within the context of serum folate and polymorphisms in folate metabolizing enzymes are of clinical interest (Robien, 2005). Some studies have suggested a role of B vitamins in the development of neuropathy, a side effect of therapy for ALL (Abbas et al., 1997; Ang et al., 2008). These studies have focused on serum levels of B nutrients and supplementation rather than dietary intake.

Taken together, studies to date suggest that nutrition status, either measured by BMI or dietary intake, may influence the development of therapy-related side effects. Children and adolescents at weight extremes appear to have reduced survival when compared to children within a healthy weight range. The few studies that have reported on dietary intake have done so in a limited fashion focusing on select nutrients of interest rather than a comprehensive evaluation of diet.

1.1.e Current Dietary Guidelines for Children and Adolescents with Cancer

Current clinical nutrition practice in children and adolescents with cancer is primarily based upon the expert opinion of the physician, dietitian, and nurse with efforts focused on the treatment of malnutrition or obesity rather than the prevention. Little consideration is given to the broader scope of nutrition therapy that includes dietary counseling on healthy dietary patterns, especially during cancer therapy. Optimizing cancer care includes placing emphasis on all aspects of supportive care interventions that include nutrition therapy (Ladas, 2009). This is especially important for the child with cancer as clinicians have the additional challenge of supporting growth and development while delivering the recommended doses of anticancer therapy. Clinicians should be compelled to include this into the scope of cancer care however the paucity of data has prevented nutrition therapy from being systematically incorporated into the care of every child and adolescent with cancer.

Presently, dietary guidelines for children during and after cancer therapy are generally centered on the prevention of cancer and are reflective of those guidelines set forth for healthy children (www.choosemyplate.gov) without a history of cancer or for survivors of adult malignancies (www.aicr.org or www.cancer.gov) (American Institute for Cancer Research, 2012; Chlebowski,

2003). These guidelines include the importance of weight management, fruits and vegetables, whole grains, and lean protein however do not address potential nutrient deficiencies that may develop as a result of cancer therapy. Moreover, the guidelines are not modified to reflect the increased risk of nutrition-related conditions such as heart disease, metabolic disease, or obesity that are widely prevalent among survivors of childhood cancer. Often, nutrition recommendations mirror those for healthy children, are extrapolated from other pediatric conditions, or are adapted from the adult literature. It is reasonable to hypothesize that nutrition therapy guidelines may require modification for children with cancer especially given the extensive duration of cytotoxic therapy and myriad of nutrition-related side effects that are frequently encountered by children with cancer. However, before epidemiologic studies investigating the benefit of nutrition intervention for children receiving cancer therapy can be undertaken, an understanding of the unique nutritional needs of this vulnerable population is warranted.

1.2 Purpose of Study

The present study builds upon the existing science by exploring dietary intake among children with ALL representing a large population of children with a single cancer diagnosis on a standard treatment protocol. This study will evaluate changes in the dietary intakes of macronutrients and micronutrients at three different timepoints in therapy: Time 1 (no therapy), Time 2 (high dose therapy), and Time 3 (low dose therapy). This study is the first study to explore the magnitude of variation in dietary intake in a relatively large, homogenous pediatric patient population. This study will be the first to describe how variations in dietary intake differ from normative values as reported in the National Health and Nutrition Examination Survey and

the Dietary Recommended Intakes (DRI) set forth by the National Academy of Science. The information obtained from this study will be used to make recommendations for the optimal timing and priority areas in which subsequent nutrition interventions may be designed and tested for children and adolescents with ALL.

1.3 Statement of research questions or hypothesis

This study aims to evaluate the following research objectives:

Study Objective 1: To describe macronutrient and micronutrient dietary intakes at three different time points: Time 1 (diagnosis (no therapy); Time 2 (end of induction (high dose therapy)); Time 3 (continuation (low dose therapy)) in children undergoing treatment for acute lymphoblastic leukemia.

Hypothesis: Dietary intake will fluctuate over the course of ALL cancer therapy due to different intensities in therapy (high dose compared to low dose). Lower intakes will be observed during high dose therapy (induction); higher intakes during the low dose phase of therapy (continuation).

Study Objective 2: To compare mean dietary intake of macronutrients and micronutrients at three different time points: Time 1 (diagnosis (no therapy); Time 2 (end of induction (high dose therapy)); Time 3 (continuation (low dose therapy)), in children undergoing treatment for acute lymphoblastic leukemia to dietary intakes of children reported in National Health and Nutrition Examination Survey (NHANES).

Hypothesis: Children undergoing treatment with ALL will have dietary intakes that are significantly different from that of normative values provided by NHANES due to the diagnosis of cancer even during a period of low dose chemotherapy.

Study Objective 3: To describe the percentage of children undergoing treatment for acute lymphoblastic leukemia that are below, meet, or exceed the dietary recommended intakes for macronutrients and micronutrients at three different timepoints in therapy: Time 1 (diagnosis (no therapy)); Time 2 (end of induction (high dose therapy)); Time 3 (continuation (low dose therapy)).

Hypothesis: A larger proportion of patients with ALL will be under or exceed Dietary Reference Intakes compared to patients meeting the Dietary Reference Intakes. Differences will be observed between phase of therapy and age with most deficiencies being observed during the initial phases of therapy (Time 1 and Time 2) and excesses observed during later phases due to lower dose therapy (Time 3) .

1.4 Significance of Study

A better understanding of variations in dietary intake during cancer therapy and the degree to which children deviate from the DRIs is a necessary first step in developing standardized guidelines for clinical intervention that are evidence-based rather than derived from clinical experience. Understanding the degree to which intakes are below or exceed the DRIs will aid in the identification of priority areas for potential nutrition interventions at various phases of cancer

treatment. This study is the first to explore how diet intake in pediatric patients with ALL compared to two routinely referenced dietary data sets: 1) National Health and Nutrition Examination Survey which provides normative values reflecting intakes of children residing in the United States, and 2) The Dietary Reference Intakes which are reference values used to assess and plan for individual and group dietary goals. The results of this study will provide a description of dietary intake at various timepoints in therapy. An understanding of dietary intake that is above or below the recommended values may be beneficial in ultimately designing future nutrition interventions that may minimize therapy related side effects and maximize cancer survival.

1.5 Scope and Delimitations

This study focuses only on children and adolescents with cancer that received treatment at a center that is part of the Dana Farber Cancer Consortium. The results of this study are limited to the demographics of the participating centers and to children and adolescents with ALL.

1.6 List of Abbreviations

ADMR- Acceptable macronutrient distribution range

ALL- Acute lymphoblastic leukemia

AML- Acute myeloid leukemia

ANOVA- Analysis of Variance

BIA- Bioelectrical impedance assay

BMI- Body mass index

COG- Children's Oncology Group

DFCI- Dana Farber Cancer Institute

DRI- Dietary Reference Intakes

HSFFQ- Harvard food service food frequency questionnaire

FFQ- Food frequency questionnaire

MUAC- Mid upper arm circumference

NHANES- National Health and Nutrition Examination Survey

NFCS- Nationwide Food Consumption Survey

NR- Not reported

RBW- Relative body weight percentage

RDA- Recommended Dietary Allowance

REE- Resting energy expenditure

RNI- Recommended Nutrient Intake

TPN- Total parenteral nutrition

TSF- Triceps skinfold test

WFH- Weight for height

YAFFQ- Harvard Youth & Adolescent food frequency questionnaire

Chapter 2: Literature Review

The following chapter will provide a comprehensive review of the published literature describing nutrition metabolism, nutrition status, and dietary intake in children and adolescents with cancer. A focus on the effect of nutrition status on therapy-related side effects and survival will be presented as well as the current clinical guidelines supporting nutrition practice in children with cancer.

2.0 Acute Lymphoblastic Leukemia

Childhood cancer is the second leading cause of death in the United States in children between the ages of five to fourteen, following accidental deaths (Center for Disease Control, 2010). Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and accounts for 23% of children diagnosed with cancer under the age of 15 (National Cancer Institute, 2002). Since 1975, significant increases in the five-year survival rate for ALL have been observed. Reasons for improved survival are targeted central nervous system therapy, alterations in length of therapy, combination of drugs, advances in supportive care, identification of novel prognostic factors, and risk stratified therapy. Overall survival for low risk ALL is 90% whereas survival for high risk ALL is 70% (National Cancer Institute, 2012).

Although no risk factor is identified in most cases of ALL, prenatal exposure to x-rays, postnatal exposure to high doses of radiation, Down syndrome and other genetic conditions, and inherited genetic polymorphisms are known risk factors for the development of the disease (Wiemels, 2012). The incidence of ALL is higher in children who are Caucasian compared to children who

are black and is most common among Hispanic children (Goggins et al., 2012). Slightly more males than females are diagnosed with ALL with improved survival among females. A full review of the risk factors and their effects on treatment outcomes has been reviewed elsewhere (Stanulla et al., 2009).

Children with ALL are categorized into two main risk groups, low risk (also referred to as standard risk) and high risk. According to some protocols, children may be classified as very high risk. Classification of risk category is contingent upon features at diagnosis such as age, white blood cell count, and if the cancer has spread to the central nervous system. Diagnostic features associated with standard risk ALL are: children between the ages of 1-9 years old at diagnosis, a white blood cell count less than 50,000/μL, and precursor B-cell immunophenotype. Failure to respond to therapy within the first phase of therapy (referred to as the induction phase) may result in reclassification into very high risk.

2.0.a Treatment for ALL

Treatment for childhood leukemia typically consists of chemotherapy and may include administration of radiation for a sub set of patients including those with leukemia in the central nervous system. As per the Dana Farber Cancer Institute (DFCI) treatment protocol (the protocol relevant to the current investigation), treatment for ALL is divided into six phases of therapy each of which delivers high- or low-dose chemotherapy over a two year period. The overall treatment schema is summarized in Table 1.

Table 1. Overview of Treatment Schema for ALL (Dana Farber ALL Cancer Consortium)						
Phase	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
Duration	3 Days	4 Weeks	3 Weeks	3 Weeks	27 Weeks	~ 70 Weeks
Name of Phase	Prophase	Induction	Consolidation	CNS Therapy	Consolidation II	Continuation
Type/Intensity of Therapy	Steroids	High-Dose Therapy	High-Dose Therapy	Central Nervous System Therapy	High-Dose Therapy	Low-Dose Therapy

Upon diagnosis with ALL, patients immediately begin on a 3-day course of steroids. The second phase of therapy, referred to as the induction phase, delivers high dose chemotherapy and its purpose is to kill the leukemia cells and put the patient in remission. The third phase of therapy is the consolidation phase of therapy and continues to deliver high dose chemotherapy to kill any remaining leukemia cells. The final phase of therapy is the continuation phase of therapy in which cancer therapy is administered in lower doses than those used in earlier phases of therapy. The phase of therapy varies in length and can be a minimum of 32 days (induction phase) to 15 months (continuation phase). After the continuation phase of therapy, children and adolescents have completed treatment for ALL.

2.0.b Therapy-Related Side Effects of Treatment for ALL

Phases of therapy that deliver higher doses of chemotherapy (Phase 2, 3, 4, and 5) are associated with increased frequency and severity of therapy-related side effects that may elevate the risk of developing malnutrition. Therapy-related side effects of cancer therapy are graded by a standardized five-point Likert grading scale developed by the National Cancer Institute that range from mild to death (National Cancer institute, 2010). Grading of a therapy-related side effect is based upon a standard set of clinical criteria that is a component of the clinical assessment of the patient. The type and severity of side effect will depend on the class of drug, the dose, and duration. Common *therapy-related side effects* encountered by children with ALL

are neuropathy (pain in the nervous system), fatigue, alopecia (loss of hair), and myelosupression (bone marrow suppression). Of the drugs used to treat ALL, many of them may cause therapy-related side effects that can reduce the patient's ability to maintain dietary intake either through affecting an individual's desire to eat or making eating difficult, these types of side effects are often denoted as *nutrition-related side effects*. Some of the most common nutrition-related side effects that affect dietary intake throughout cancer treatment are constipation, loss of appetite, weight loss, weight gain, mouth sores (open sores in the mouth), and nausea and vomiting. Drugs administered during the treatment of ALL that are associated with nutrition-related side effects include cytarabine (nausea, vomiting, mouth sores, diarrhea), dexamethasone (appetite stimulant, hyperglycemia), dexrazoxane (constipation), doxorubicin (mucositis), etoposide (nausea, vomiting, diarrhea, mucositis, anorexia), 6-mercaptopurine (nausea, vomiting, mucositis), methotrexate (mucositis, nausea, vomiting), and vincristine (neuropathy (loss of deep tendon reflexes and muscle weakness), pain). Combined, these may lead to either excess or reduced dietary intake. A summary of drugs, doses, and associated nutrition-related side effects used for the treatment of ALL are described in Table 2.

Table 2.
Treatment of Standard Risk ALL: Name of Cancer Agent, Dose, and Side-Effects

Drug	Dose Ranges	Nutrition-Related Side Effects
MethylPrednisone, Prednisone, or Dexamethasone	6-40mg/m2	Increase appetite, hyperglycemia
Vincristine	1.5-2 grams/m2	Constipation, Nausea, Vomiting
Methotrexate	5-40mg/m2	Mouth Sores, Nausea, Vomiting, Loss of Appetite, Pain
Doxorubicin	30mg/m^2	Mouth Sores, Nausea, Vomiting, Loss of Appetite
Asparaginase	2500 units/m^2	Taste Changes
6-Mercapturine	50mg/m^2	Mouth Sores, Nausea, Vomiting
Cytarabine	9-15 mg	Nausea, Vomiting, Mouth Sores, Diarrhea
Etoposide	100mg/m^2	Nausea, Vomiting, Mouth Sores, Diarrhea, Anorexia

While there are a number of nutrition-related side effects encountered by children undergoing treatment for ALL, their cumulative effects on aspects of nutrition status such as energy metabolism, height, weight, or dietary intake are largely unknown. Moreover, the degree and direction (increased or decreased) at which either cancer therapy or the associated side effects impact dietary intake in children with ALL is also unknown. It is unclear whether children and adolescents with ALL are meeting nutrition guidelines or whether they are experiencing profound deficiencies or excesses in dietary intake throughout therapy.

2.1 Overview of Cancer on Nutrition Metabolism

Understanding alterations in nutrition metabolism that may be caused by a diagnosis of cancer is necessary for the development of dietary guidelines. Both preclinical and clinical studies suggest that cancer cells induce changes in energy and nutrient metabolism in the patient with cancer in order to foster cancer cell growth (Torosian et al., 1986). Identification of aberrations in nutrient metabolism have led to the use of chemotherapy agents targeting micronutrient metabolism or specialized diets as a component of anticancer treatment. For example, the understanding that cancer cells require folate to support cell division led to the use of antifolates. This class of chemotherapy agents interferes with the uptake of folate in rapidly dividing cells thereby causing cell death in cancer cells. Methotrexate is an antifolate agent and the most widely used anticancer medication. Methotrexate inhibits cancer cell growth by inhibiting the enzyme, dihydrofolate reductase, which prevents the conversion of folic acid to tetrahydrofolic acid, a cofactor in the metabolism of many amino acids and nucleic acids. Alterations in carbohydrate, fat, and protein utilization have also been observed among individuals with malignancies (Torosian et al., 1986). An understanding of protein utilization in cancer cells led

to the discovery of l-asparaginase, a drug that inhibits the breakdown of the amino acid asparagine preventing uptake from the tumor cell. Finally, the observation that tumor cells preferentially uptake glucose for functioning led to the use of low carbohydrate diets for the treatment of certain types of cancer (Klement et al., 2011; Nebeling et al., 1995).

2.1.a Overview of the Effect of Cancer on Carbohydrate Metabolism

The role of carbohydrate in cancer growth is embedded in the early work of Otto Warburg, who discovered that cancer cells preferentially underwent glycolysis for energy production, even in the presence of oxygen (Klement et al., 2011). Now termed the Warburg effect, this observation has become one of the most consistent hallmarks of cancer (Hanahan et al., 2011). Most of the investigations observing the effect of tumor cells on carbohydrate metabolism have been completed in animal models and have not been replicated in clinical studies. Animal models suggest that glucose intolerance is multifactorial and is associated with the use of insulin, increased gluconeogenesis, and increased use of the Cori cycle resulting in elevated levels of lactate in the body (Berchard et al., 2002; Van Eys, 1985). Increased lactate levels may also be the result of the tumor cell itself producing lactate (Van Eys, 1985). The aberrations in carbohydrate metabolism has been linked to an increase in the release of cytokines such as interleukin 6, which has been shown to stimulate gluconeogenesis and lactate acid formation (Argiles et al., 1999).

The clinical implications of carbohydrate metabolism on cancer cell growth and survival of cancer in adults and children with cancer is less understood. In women with breast cancer, increased glucose levels have been linked to reduced survival (Niraula et al., 2012; Villarreal-

Garza et al., 2012). The role of elevated glucose levels in children with cancer is not known. Increased levels of glucose have been associated with increased infections in children with ALL (Sonabend et al., 2008). Insulin resistance may be a factor contributing to obesity among survivors of ALL, (Chow et al., 2012) however elevated levels of glucose does not appear to be related to obesity (Bang et al., 2012). Case series have reported on the effect of low carbohydrate diets for the treatment of brain tumors in children (Nebeling et al., 1995). However, randomized clinical trials have not been reported most likely due to the difficulty in administering a low carbohydrate diet to children and adolescents. Additional research is clearly needed in this area so as to better define if carbohydrates may be a potential therapeutic target in the treatment or management of cancer.

2.1.b Overview of the Effect of Cancer on Fat Metabolism

Body fat depletion, increased lipolysis, and decreased lipogenesis has been the hallmark of fatty acid metabolic aberrations in patients with cancer (Shils et al., 1999). This generally correlates with increased plasma triglycerides and loss of body fat in the tumor- bearing host. Investigators have observed increased lipoprotein lipase activity, hormone-sensitive lipase, and liver lipogenesis (Shils et al., 1999). This is often result in aberrant lipid profiles that may include decreased high-density lipoproteins and increased very low-density lipoproteins. As with carbohydrate metabolism, these anomalies may be precipitated by production of certain cytokines, specifically tumor necrosis factor, interleukin 1, interleukin 6, and interferon α (Argiles et al., 1999). No clinical trials have been conducted targeting aberrations in fat metabolism as a target for the treatment of childhood cancer.

2.1.c Overview of the Effect of Cancer on Protein Metabolism

Protein metabolism has been the most thoroughly researched of the macronutrients and findings from these investigations have led to the development of effective anticancer agents for the treatment of certain malignancies including ALL. The development and use of the anticancer agent L-asparaginase stemmed from that finding that T-cell ALL cells heavily depend on asparagine for cellular reproduction. The use of L-asparinganse reduces the availability of aspargine to T-cell ALL cells inducing cell death. Asparaginase is now a backbone drug for the treatment of ALL and T-cell lymphoma.

Protein metabolism is affected by tumor burden and the diagnosis of the patient. The primary source of proteins in the human body is skeletal muscle thus decreased muscle mass accompanies increases in protein turnover that may be stimulated or inhibited by humoral factors. Humoral factors are primarily cytokines that affect neuropeptides that promote or inhibit appetite, stimulate metabolic alterations in the human body, or act through an unknown mechanism. The most thoroughly researched cytokines in regard to cachexia are tumor necrosis factor (TNF), interleukin-6 (IL-6), interferon-γ (IFN-γ), leukemia inhibiting factor (LIF), and ciliary neurotrophic factor (CNTF). Cytokines such as tumor necrosis factor has been shown to stimulate proteolysis (Argiles et al., 1999). Investigators have found that protein depletion may be a result of both muscle breakdown and decreased rates of synthesis; however, the relative contribution of these abnormalities is unknown. It is likely that protein metabolism is affected by tumor biology and may vary slightly depending on the biological characteristics of the tumor.

2.1.d Cancer on Resting Energy Expenditure (REE)

Tumor cells have an inherent ability to alter the energy metabolism of the host. Alterations in energy metabolism have been suggested as one of the causes of severe weight loss in patients with cancer. One clinical study in children with sarcomas suggests that alterations in REE may precipitate the onset of cachexia (Peacock et al., 1987). However, there are limitations to evaluating alterations in energy expenditure in children with cancer. Formulas to estimate energy intakes in children who are malnourished have not been thoroughly designed and tested. Therefore, clinicians extrapolate the formulas reflective of healthy children to those of children with cancer. The use of these equations in children and adolescents who are with a serious medical condition may underestimate individual dietary needs (Galati et al., 2011). Most of the published studies exploring energy expenditure is limited to older children and is not reflective of younger children. Understanding changes in activity must also be controlled for as reduced REE may also be explained by more sedentary behavior during cancer treatment.

Although limited, the available studies reporting on REE in children with cancer have attempted to control for each of the aforementioned variables to varying degrees. In one of the first studies exploring energy expenditure and nutrient turnover, Kien and Camitta studied rates of whole body protein synthesis and breakdown by indirect calorimetry in children with leukemia or lymphoma (age range 3-14 years; gender- NR) at diagnosis and compared the results to reference values (Kien et al., 1987). The authors found energy expenditure was 50% higher in cases compared to reference values. Protein breakdown and synthesis were significantly related to basal metabolic rate ($r= 0.925$, $P< 0.001$; $r = 0.91$; $P< 0.01$, respectively), which may be related to increased energy expenditure. This study is often referenced as support that children with cancer have increased basal metabolic rate, but the study has several flaws in its design which

limit the interpretation of the results (Bond et al., 1992). The study measured basal metabolic rate for a short period of time (five minutes) during sleeping hours and the timing of the administration of chemotherapy was not controlled for in the study. Comparison of cases to controls was not reported.

Stallings *et al.* conducted a subsequent study that addressed many of the weaknesses in the study completed by Kein and Camitta by performing measurements for 60 minutes and controlling for disease status and the administration and phase of chemotherapy (Stallings et al., 1989). REE was evaluated at diagnosis, Day 7 and Day 14 of induction therapy in nine children with ALL (age range 6-15 years/male=3;female=6). The authors found that before the initiation of chemotherapy, patients with a higher tumor burden (Group 1) had a significantly different REE (Mean kcal 1951) when compared to children with lower tumor burden (Group 2; Mean 1222 kcal), $P<0.02$. Percent predicted REE (131% of predicted; $P<0.004$) was higher in the group with higher tumor burden compared to the group with low tumor burden (96% of REE); however this difference was no longer apparent at Day 7 or 14 thus likely reflecting disease status. Carbohydrate utilization increased significantly from diagnosis to Day 7 ($P<0.009$) and fat utilization decreased ($P<0.009$) but these differences were no longer apparent at Day 14. The thermic effect of food, the amount of energy an individual expends to process and metabolize food, increased over the study ($P<0.016$) and the thermic effect of food as a percentage of REE also significantly increased ($P< 0.026$) in all patients. In a later study, this same group of investigators obtained energy assessments in eight children with ALL (age range 7-18 years/male=5; female=3) in the final three months of chemotherapy (continuation phase) (Vaisman et al., 1993). No difference on REE was observed during or after treatment with 6-

mercaptopurine or methotrexate infusion. Utilization of fat increased after methotrexate, but not after 6-mercaptopurine. No effects were observed on carbohydrate or protein utilization. The findings of these two studies provide insight as to whether changes in nutrient metabolism and REE are a result of 1) the cancer cell itself, 2) the action of chemotherapy agents on host metabolism, or 3) tumor burden (Vaisman et al., 1993). The study suggests that alterations in REE may be more strongly related to tumor burden, as demonstrated by REE resuming to normal by Day 14 of therapy and that reducing tumor burden through the administration of anticancer therapy restores metabolic activity to rates prior to the development of a tumor. The variations in substrate utilization may be related to the administration and dose of chemotherapy agents, particularly the role of high-dose steroids during the induction phase of therapy. Subjects did not receive steroids in the latter study.

Reilly *et al.* explored the changes in resting metabolic rate during the continuation phase of therapy (third year of treatment) in 27 children (age range 7.4-12 years/male=15;female=20) with ALL who did not receive cranial radiation and compared them to 27 age-matched controls (Reilly et al., 1996). BMI, weight, and height were collected at diagnosis and two years post diagnosis. No significant differences in resting metabolic rate or respiratory quotient between study groups were observed. There was a significant increase in mean BMI standard deviation score +1.0 (95% CI 0.4-1.7, $P<0.01$) in boys (n=15) and girls (n=17) 1.0 (95% CI 0.3-1.6; $P<0.01$) from baseline to the continuation phase of therapy however it should be noted the confidence interval includes the value of one. This study supports the findings of Vaisman *et al.* in that REE is not altered during the continuation phase of therapy in patients who have not received cranial radiation. Finally, in a small study exploring both energy expenditure and

dietary intake, REE and dietary intake was found to be reduced in 20 children with ALL who had undergone treatment compared to age-matched healthy controls (Reilly et al., 1998).

Although the available studies are limited, these results suggest that aberrations in nutrient metabolism and REE may contribute to changes in body weight but other factors such as diet or other lifestyle behaviors may also have an active role. This effect is most notable in patients who have not received cranial radiation. The results of these studies suggest that changes in nutrition status are caused by multiple factors of which dietary intake are only one component of a multi-faceted model that may lead to malnutrition. Although these studies identified aberrations in some biochemical nutrient pathways, their combined effect is still not entirely clear. These studies are able to merely suggest that changes in nutrient metabolism is likely occur during cancer therapy and should be recognized when providing nutrition therapy to children with cancer.

2.1.e Clinical Conditions Associated with Metabolic Aberrations

Cachexia has long been a hallmark of cancer therapy in both children and adults and is often mistaken for severe malnutrition. Cachexia is a distinct clinical condition that is associated with altered nutrition metabolism in patients with cancer and is most common in patients with advanced disease or with heavy tumor burden. Conversely, severe malnutrition may be diagnosed with significant weight loss but is often not associated with alterations in nutrition metabolism. Symptoms of cachexia include reduced appetite, early satiety, weight loss, and reduced energy (Langer et al., 2001). Although cachexia is similar in presentation to starvation (or severe malnutrition), metabolically it is a different condition. Patients with cachexia often

are hypermetabolic coinciding with a reduction in appetite. This is evidenced by persistent weight loss with a marked reduction in total calories. Patients with cachexia often consume as little as 10-25% of total caloric needs. In contrast, patients experiencing starvation have weight loss that is accompanied by a conservation of energy metabolism and a robust appetite.

Most of the research investigating the process of cachexia has been conducted in animal models with few studies replicated in human trials. Cachexia is a complicated physiological process that varies by stage and site of the tumor. Investigations have identified both humoral and tumor-secreting factors as primary inducers of the cachexia process (Argiles et al., 1999; Argiles et al., 2003; Van Eys, 1985). Humoral factors are primarily cytokines that affect anorexigenic neuropeptides, stimulate metabolic alterations in the human body, or act through an unknown mechanism. The most thoroughly researched cytokines in regard to cachexia are tumor necrosis factor, interleukin-6, interferon-γ, leukemia inhibiting factor, and ciliary neurotrophic factor. The interaction of these factors appear to be related to one another, possibly exerting a synergistic effect in the individual with cancer (Argiles et al., 1999). Individually, tumor necrosis factor has been shown to induce cachexia in animal models. Tumor necrosis factor has also been found in the plasma of children with leukemia; however, elevated serum levels do not appear to be the cause of the development of cachexia (Saarinen et al., 1990). Significant strides have been made in understanding cytokines such as interferon-γ, leukemia inhibitory factor, interluekin-6, administration of antagonists has not been successful in remediating the development of cachexia (Argiles et al., 2003; Ramos et al., 2004). A clear cause and effect pathway has not yet been identified for any humoural factor causing cachexia. Tumor-secreting compounds may also contribute to the complex physiologic process of cachexia although the

effect is also not clear. Some of the earliest theorists proposed that tumor-secreting compounds induce metabolic abnormalities in the human body thereby resulting in increased metabolic activity and decreased appetite however based upon the literature reporting on REE this is likely not the sole effect (Theologides, 1976). Others have suggested tumor-releasing compounds act directly on the liver thereby stimulating inefficient production of substrates used for energy in the body (Van Eys, 1985).

Laboratory investigations have also revealed that cancer cells release compounds that lead to aberrations in the appetite regulating network. This has been supported by a few small studies published in children with cancer (Hagan et al., 2012). Laboratory investigations have suggested that the development of cachexia may be a result of cytokines exerting a stimulant or inhibitory effect on appetite, an action similar to that of neuropeptides. Leptin is secreted by adipose tissue and stimulates anorexigenic compounds while simultaneously inhibiting the release of neuropeptide Y (appetite stimulant). It is unknown if cytokines act in an unknown fashion mimicking the effects of neuropeptide Y and leptin, or stimulate the neuropeptides directly. Alterations in serum levels of leptin have been observed in children with cancer (Karaman et al., 2010). Future studies are needed to elucidate the precise mechanism of action.

2.2 Early Studies on Nutrition Status in Children with Cancer

Initial evaluation of nutrition status and dietary intake among children and adolescents with cancer dates back to the 1960's. Studies performed in this era explored the use of sterile diets, also referred to low bacterial diets or a cooked foods diet, to promote gut sterilization (removal of all gut bacteria) prior to the administration of immunosuppressive agents (chemotherapy and

radiation) (Moody et al., 2002). Investigators hypothesized that reducing the risk of bacterial exposure through food would reduce the risk of developing an infection. Study outcomes were focused on the incidence of infection and survival with no consideration to the impact of these rigorous diets on the nutrition well being of the patient. Mixed results were reported in these trials with later studies reporting that these extreme diets were unnecessary during cancer therapy and had no effect on the incidence of infections (Gardner et al., 2008; Moody et al., 2006).

It was not until the late 1970's that the role of dietary intake and clinical nutrition intervention came under scrutiny. Driving this research were clinicians reporting associations between weight loss, reduced tolerance to therapy, poor quality of life, and frustration on behalf of the patient and parent without data substantiating these clinical observations (Donaldson et al., 1981). It was not until a small pilot in 41 children with cancer was published that medical nutrition therapy emerged as a component of supportive care. Filler *et al.* was the first to report that total parenteral nutrition (TPN) was found to be safe with no adverse events (Filler et al., 1977). Prior to this, administration of medical nutrition therapy was limited due to concerns that TPN would increase the risk of developing an infection, a life-threatening complication. Proponents of nutrition support argued that malnutrition is an independent risk factor for infection and by improving nutrition status through nutrition intervention a reduction in the incidence of infection may be observed. This hypothesis served as a catalyst for subsequent studies exploring the effect of nutrition interventions on therapy-related side effects, infection, and overall survival in children and adolescents undergoing treatment for cancer.

2.2.a Total Parenteral Nutrition (TPN)

Initial studies systematically evaluating nutrition status explored the safety of TPN over the standard of care, which at the time was no nutrition intervention (e.g. no provision of TPN or enteral feeding). In one of the first randomized studies exploring a nutrition intervention in pediatric oncology, 35 children (Age=NR/Gender=NR) with heterogeneous cancers were randomized to TPN or dietary advice (Van Eys et al., 1980). Children who were malnourished received TPN (n=15) while well-nourished patients (n=20) were randomized to diet advice or TPN. The primary outcome in this study was the effect of TPN on nutrition status and weight for height (WFH) (< 80% = malnourished). Among patients who were well-nourished, two of ten patients in the diet advice group and two of ten patients in the TPN group developed malnutrition; however, these patients also had progressive disease diminishing the ability to look at the effect of TPN. Dietary intake was 22% and 16% of recommended dietary allowance (RDA) for calories and 55% and 34% of protein, in the TPN compared to diet advice group, respectively demonstrating the effectiveness of TPN in augmenting dietary intake during cancer therapy. TPN was also effective at enhancing nutrient intake among children and adolescents who were malnourished group demonstrated by 45% of calories and 85% of protein delivered by TPN.

The study also explored the effect of TPN on tolerance to chemotherapy (measured by incidence of side effects), dose reductions, and survival. Does reductions or dose adjustments during cancer therapy are only considered when clinically indicated as reductions in the recommended doses of therapy may affect overall survival. This study found that there were no differences in dose adjustments (reductions in therapy due to clinical conditions) between well-nourished (n=20) and malnourished (n=15) patients during the first course of chemotherapy. However,

when all the control patients were compared to all TPN patients, 45% of controls and 22% of TPN patients experienced dose reductions ($P<0.01$) in the first course. After adjusting for the length of treatment, malnourished patients had fewer dose reductions (13 courses per 100 days) than well-nourished patients (16 courses adjusted over 100 days) but this difference was not significant. Importantly, this study demonstrated that well-nourished patients in this study experienced significantly fewer infections (9/21) compared to malnourished (14/15) ($P<0.002$). The study found 19 episodes of infection in 22 patients who were on TPN and malnourished whereas well-nourished patients experienced five episodes of infection ($P<0.002$). After controlling for the number of days of therapy, the sepsis rate (rate of sepsis was calculated per 100 patient days), in malnourished compared to well-nourished patients was higher ($P<0.001$). Infections were also higher among malnourished patients on TPN than well-nourished on TPN ($P<0.05$). It is possible that TPN may elevate the risk of infection in patients who are already malnourished and begin treatment with TPN however a causal effect of TPN cannot be concluded from this study. Administration of TPN as a prophylaxis of malnutrition does not appear to alter risk of infection as no increased risk of infection among well-nourished patients on TPN.

Building upon the findings of van Eys *et al.,* a retrospective review of 244 children with heterogeneous diagnosis (age:NR/gender: NR) with cancer was performed (Donaldson et al., 1981). Measurement of nutrition status was determined by weight, height, WFH < 80%, and albumin. Patients were followed at the time of first referral until death, loss to follow-up, or most recent visit. Poor nutrition status (WFH or low albumin) was significantly correlated with weight loss, fever, and fatigue ($P<0.01$). However when these variables were stratified by

diagnosis, no significant relationships were observed. Nutrition status at time of referral was related to subsequent relapse, which was most evident for children with a solid tumor (P=0.007). The relationship remained after stratification by stage (P=0.04). At time of first referral, well-nourished children with lymphoma (P=0.02) and solid tumors (P=0.03) with localized disease experienced improved survival. Survival of patients with advanced disease did not correlate with nutrition status at time of referral. The authors concluded that a relationship between nutrition status and survival may exist among patients with solid tumors.

Despite the inherent weaknesses in the study designs, these landmark studies brought nutrition status and intervention into the vernacular of pediatric oncology. Infections are a life threatening complication in children with cancer especially in children undergoing treatment for ALL. Infections contribute to 50% of complications and lead to death if intervention is not administered immediately. These were among the first studies to suggest that nutrition status may impact therapy-related side effects among children with cancer, especially life threatening toxicities such as infection and sepsis. The studies suggested that malnutrition may be a risk factor for increased therapy-related side effects and that minimizing the development of malnutrition may improve quality of life over the course of cancer therapy along with improved outcomes. Finally, they demonstrated that feeding a child with cancer, through intravenous source, is safe and does not promote cancer cell growth. Reductions in survival were not observed.

Later studies with improved study designs and performed in uniform populations replicated these initial findings. Rickard *et al.* evaluated nutrition status in 18 children (age range= 6-10 years/

male=9; female-9) with Stage IV neuroblastoma at diagnosis and during the first few courses of therapy (Rickard et al., 1983). Malnutrition was defined as weight loss > 5% of body weight, WFH < 5th %, or serum albumin < 3.2 grams per deciliter. Of the well-nourished group (n=9), six children received TPN after failing to maintain nutrition status with oral intake, one patient was placed on TPN, and one died. Children with malnutrition were randomized to TPN (n=4) or peripheral parenteral nutrition (n=4) group. Differences in therapy-related side effects and dose reductions were only observed during the first course of therapy. One of nine children in Group 1 (well-nourished group) and six of seven children in Group 2 (malnourished group) experienced a delay in therapy (P<0.01). In course 2, Group 1 received 97% +/- 8% of recommended dose and Group 2 85% +/-10, (P=0.02). At the 3rd course, Group 1 received 94% +/-10% and Group 2 82% +/-14% (P=0.07). When all courses are evaluated together, children in Group 1 received more recommended doses compared to Group 2 (P=0.04). This is an important finding as lower than the recommended dose of therapy or delays in the timing of therapy can have an adverse effect on survival. In concordance with van Eys *et al.*, the authors found that response to therapy was not related to nutrition status. However, the number of days to first event (relapse or death) was greater for the well-nourished compared to the malnourished (P<0.01) and median survival for the well-nourished was 12 months compared to five months for the malnourished (P=0.08) suggesting prolonged survival among patients who were well-nourished. However, change in nutrition status over therapy did not impact overall survival at one year. A follow-up study in 32 children with Stage III/IV neuroblastoma confirmed these findings (Rickard et al., 1985).

2.3 Assessment of Nutrition Status in Children with Cancer

Measurement of nutrition status is variable in children as there are many indices that can be applied to categorize patients as malnourished. Each of these has its strengths and limitations (Mosby et al., 2009). The use of weight alone as a marker of nutrition status is of limited use within the context of pediatric oncology as it is frequently altered by hydration status, the tumor mass, infection, or an amputation which reduce the sensitivity of weight as an indicator of nutrition status (Barr et al., 2011). Biochemical indices of nutrition status are also of limited use in children undergoing treatment for cancer as there is no biochemical marker that is not altered by the effects of cancer therapy. Albumin has limitations as disease status, infections, and therapy related side effects reduce the sensitivity and specificity of albumin. While pre-albumin has been promoted as a more sensitive indice of nutrition status, it is not without limitations and is not routinely collected in the absence of overt malnutrition.

The commonly reported indice to describe changes in nutrition status include weight, height, WFH, BMI, BMI percentile, mid-upper-arm circumference (MUAC), and triceps skin fold (TSF) thickness. The gold standard of nutrition assessment in children with cancer is largely unknown however a recent study suggests that skinfold tests are the most sensitive indice for the measurement of nutrition status among children with cancer (Barr et al., 2011). Investigators have also relied upon fluctuations in fat and fat free mass to gauge nutrition status (Murphy et al., 2010). While the application of this advanced technology to measure fat versus fat free mass is ideal in providing clinicians with a comprehensive understanding of nutrition status, the expense required to evaluate body composition limits its use in the clinical setting. Unfortunately, there is no unanimous agreement on the gold standard therefore the available literature must be viewed considering these limitations. A summary of the literature whose

primary aim was to document the prevalence of malnutrition in children with cancer is provided below.

2.3.a Nutrition Status in Children and Adolescents with Solid Tumors

In a cross-sectional study among 36 patients (age range 4.8-15 years; female=15/male=21) with solid tumors, nutrition status was assessed in 19 children during therapy and 17 children in short term follow up (1-24 months post completion of therapy) (Schiavetti et al., 2002). Weight, height, BMI, and relative body weight percentage (RBW) were collected on each patient. In patients on therapy, 26% of patients were underweight as per %RBW, and 15.8% according to BMI. 36.9% of patients were overweight or obese as per %RBW and 21% as per BMI. Among the patients off therapy, 52.9% were overweight or obese by %RBW and 35.3% as per BMI. Both were significantly different than those patients on therapy $P<0.05$; P=0.05, respectively. The correlation between %RBW and BMI was $r=0.83$, $P<0.001$, demonstrating differences in reporting frequencies between nutrition indices.

2.3.b Nutrition Status in Children and Adolescents with ALL

Children with ALL rarely present at diagnosis with overt malnutrition in developed countries (Ladas et al., 2005). The development of malnutrition is often a consequence of therapy and may vacillate between weight loss and excessive weight gain. Weight loss is typical during the more intensive phases of therapy whereas weight gain is often associated with the continuation phase of therapy (Baillargeon et al., 2007; Withycombe et al., 2009). Weight gain is also a late-effect of childhood ALL with survivors experiencing uncontrollable weight gain within two to

four years after completion of therapy, a phenomenon that has been well-described in the literature with an unknown etiology (Oeffinger et al., 2003).

Reilly *et al.* were one of the first groups to describe weight changes in children diagnosed with ALL (Reilly et al., 1994). This study explored the prognostic impact of WFH in 78 children (age range 1.1-13.3 years;male=47/female=31) with ALL. WFH Z-score at diagnosis was significantly related to survival (P=0.012). This was not influenced by age at diagnosis, intensification schedule, white blood cell count, or gender as evidenced by a X^2 test. The probability of no relapse within five years of diagnosis was approximately 80% in children with WFH Z score > -0.5 and 50% for children with a WFH Z score < -0.5, indicating that the higher the deviation from the mean (represented by a Z score of > -.05), the higher the risk of relapse. The authors propose that undernutrition may be a nonspecific marker of disease by impairing immune function or surveillance and hematopoiesis, reduce the tolerance to anticancer therapy, or alter the pharmacokinetics of drugs.

The findings of this study have been followed up by several other retrospective studies. In a follow-up study by the same group of investigators, Reilly *et al.* explored the prevalence of protein-energy malnutrition in 1019 children (age range 0.2-14.9 years; male=767/female=252) with standard-risk ALL treated on a uniform protocol (Reilly et al., 1999). The authors found that the observed frequency of BMI standard deviation score < -2.0 (indicated 2 standard deviations below the mean) was 7.6% of boys and 6.7% of girls. The observed frequency was significantly different than the expected frequency of 2.3% in both girls and boys (P<0.0001). The frequency of obesity (> 2 standard deviations above the mean) was 2.6% for boys and 3.2%

for girls, which was not statistically different than expected. Evidence revealed that BMI standard deviation scores differed significantly from 1.0 ($P<0.001$ for both sexes). The authors concluded that undernutrition at diagnosis is three times higher than expected.

Uderzo *et al.* evaluated 173 newly diagnosed children with ALL (age range 2-15 years; male=90/ female=83) residing in Italy and compared them to 307 children admitted to the hospital for non-malignant conditions (Uderzo et al., 1996). Nutrition status was evaluated at diagnosis by dietary history, anthropometric measures (weight, height, WFH, MUAC, and TSF), and biochemical indices (prealbumin, retinolbinding protein, albumin, ceruloplasmin, mucoprotein, transferrin, ferritin, zinc, and C3 complement fraction). No significant differences were observed between the two groups in any of the nutrition indices. In 25 children with ALL between the ages of 1-14 years, nutrition status, defined by WFH, weight, height, albumin, MUAC, TSF, was observed at various timepoints in therapy. The authors did not find any cases of malnutrition (Yu et al., 1994).

In one of the only studies describing patterns of weight gain and loss in children with high-risk ALL (n=1,638), BMI percentile was found to decrease over the course of therapy ($P<0.014$ to $P<0.0001$) (Withycombe et al., 2009). By the continuation phase of therapy, BMI percentile increased and was higher compared to diagnosis. This may be related to prolonged exposure to steroids as studies have found an increase in caloric intake coincides with steroid medications among children with ALL (Reilly, 2001). The data presented provides evidence that children with ALL are at increased risk of obesity from diagnosis to the end of treatment. Whether this is

due to increased caloric intake, reduced energy expenditure, metabolic aberrations, or other unknown factors remains unknown.

2.4 Dietary Intake in Children with Cancer

The challenges of conducting dietary studies among healthy and ill individuals have been well described (Freudenheim, 1993; Kushi, 1994). Issues such as adherence to the methodology of dietary collection, loss to follow up, incomplete data collection, and the cost of large studies are frequently encountered and reduce the investigators ability to evaluate meaningful changes in diet over time. The relatively low incidence of childhood cancer, (approximately 12,000 children each year in the United States) makes data collection in a large homogenous patient group difficult. Ideally, an understanding of caloric needs would be complemented with measures of basal metabolic rate and energy expenditure as these are the largest influences on dietary needs and have been found to be modified by a malignancy (Galati et al., 2011). To date, no study has comprehensively evaluated dietary intake in combination with assessment of energy expenditure, nutrient utilization, and basal metabolic rate. A review of the available data is described below and presented in Table 3.

Dietary intake in 26 children (age range 5-16 years; male=16/female=10) with heterogeneous diagnoses was compared to 26 unmatched healthy controls (Bond et al., 1992). Dietary intake was collected with a weighed food record and basal metabolic rate was evaluated one week before chemotherapy. Energy intake was below the RDA in children with ALL, children with solid tumors, and healthy controls (Mean=1822 kcal per day (SEM=140); Mean=1877 kcal per day (SEM= 187); Mean=1860 kcal per day (SEM=62)). The authors did not find any significant

differences in basal metabolic rate between cases and controls suggesting that dietary intake and energy expenditure is similar to that of healthy children. A later study included measures of body composition, (weight, height, MAUC, TSF, and bioelectrical impedance assay (BIA)) along with dietary intake (24-hour recall for children with ALL; 7-day food record for controls) in 15 children (age range 2-16 years; gender-NR) with standard risk ALL and 15 age-matched controls. Dietary data was collected at diagnosis, Day 22, Day 36, and Day 71 of treatment (Delbecque-Boussard et al., 1997). Two of 15 patients were malnourished at diagnosis as defined by WFH a finding that contradicted studies performed by Reilly *et al*. At each of the four timepoints, the caloric intake of children with ALL was 47%, 58%, 85%, and 85% of the French RDA, respectively (mean intakes not reported). Total calorie intake in controls was 104% of the French RDA. For protein, children with ALL reported 1.7, 2.9, 2.5, and 2.7 times the RDA, which was less than controls (3.4 grams per day), although no *P* value was reported. Children with ALL had significantly lower respiratory quotient compared to controls at diagnosis ($P<0.02$) however this difference was not observed at Day 71. This finding confirmed earlier work suggesting that disease status contributes to alterations in energy expenditure among individuals with cancer. No significant differences in REE were observed between the two groups. Although caloric intake was below while intake of protein was above the French RDA in cases compared to controls, the difference in the methodology collecting dietary intake between the two groups limits the interpretation of these results.

Table 3.
Summary of Dietary Studies

Author/Year (Study Design)	Patients	Diagnosis	Dietary Assessment Tool	Reference Value	Results
Bond, 1992 (cross-sectional)	Cases: N=26 Age 5-16 M=16/F=10 Controls: N=26 (healthy, unmatched)	ALL and Solid	Weighed food record	RDA	Children with ALL: 83% of RDA (Mean=1822 kcal per day). Children with Solid Tumors: 89% of the RDA (Mean=1877 kcal per day). Controls: 87% of RDA (Mean=1860 kcal per day).
Galati, 2011 (cross-sectional)	Cases: N=16/ M=7; 9 Controls: N=19 age- and gender-matched	Multiple	Cases: FFQ Controls: FFQ	NA	Cases and controls reported similar calorie intakes. Children with cancer reported significantly higher intakes of potassium compared to controls. The control group reported significantly higher intakes of protein, zinc, phosphorous, riboflavin, and B12 compared to cases.
Delbecque-Boussard, 1997 (cross-sectional study)	Cases: 15 children (Age range 2-16 years/M;F-NR) Controls:15 age-matched controls	ALL	Cases: 24-hour recall Controls: 7-day food record	French RDA	Children with ALL: calorie intakes 47%-85% of RDA. Protein: 1.7-2.9 times the RDA. Controls: calorie intakes 104% of RDA.
Halton, 1998 (cross-sectional study)	Cases: 19 (age 2-15 y; 8M/11F	ALL	3-day food record	Canadian RNI	Total calorie intake 66% above the RNI. Protein > 100% of the RNI.

List of Abbreviations: ALL-Acute Lymphoblastic Leukemia; FFQ- Food Frequency Questionnaire, NR-Not reported; RDA- Recommended Dietary Allowances; RNI- Recommended Nutrient Intakes

Dietary intake and body composition was evaluated in 16 consecutive children (age range 2-15 years; male=8/female=11) undergoing treatment for ALL (Halton et al., 1998). Dietary intake was measured with a 3-day food record. Total caloric intake was averaged for each of the collected timepoints, diagnosis and every 6 months of therapy (averaging about 5-7 food records per patient). Dietary intakes were grouped as mean intakes by age. Total calorie intake was above the Canadian Recommended Nutrient Intake (RNI)) in 70% of children. In all but one child, protein intake was greater than 100% of the RNI. Mean change in the ratio of lean mass to total body weight was reduced by 5% by six months of therapy. Body fat increased from diagnosis to completion of therapy from a mean of 22% to 28%, respectively. Statistical significance was not reported.

In a small cross sectional study, dietary intake obtained with a FFQ in 16 (male=7/female=9) children between 6-15 years of age with varying cancers and at different stages of therapy were compared to 19 healthy controls matched by age and gender (Galati et al., 2011). Energy expenditure was measured by indirect calorimetry, controlling for recent dietary intake with a 3-hour recall. Body composition was measured with BIA. The authors found no significant difference in anthropometric measures (BMI, weight, height), body composition (lean body mass, fat mass), REE, or average respiratory quotient between cases and controls, a finding that was also reported in another study in 13 children (age range10-15 years; male=4/female=9) with solid tumors (den Broeder et al., 2001). Dietary intake also revealed no significant differences in macronutrient intake. Results obtained from a food frequency questionnaire revealed that children with ALL had lower intakes of protein (P=0.027), zinc (P=0.01), phosphorous

(P=0.038), riboflavin (P=0.013), and B12 (P=0.00) and higher intakes of potassium (P=0.017) compared to controls. Both groups did not meet the recommended number of servings for milk, cereal, and vegetables. Children with cancer had increased intake of meat compared to recommended intakes. Both groups met the recommendation for fruits servings. Intakes exceeded the recommended portions for meat, sugar, and beans. There were no significant differences between the groups.

The studies reporting on changes in REE and energy expenditure suggest fluctuations occur over cancer care but the direction of change is not consistent and likely not directly related to either a decrease or increase in dietary intake. Phases of therapy were not controlled for in most of the available studies, which attributes to the inconsistencies among studies. An increase or decrease in dietary intake may be more reflective of the phase of therapy and disease status rather than the disease itself or may be related to reductions in daily function as most patients experience a decline in day-to-day activities when undergoing treatment for cancer. Each of the small studies presented suggest that patients with cancer are either under or over the recommended dietary intakes and one study suggested that children were not adhering to recommended dietary patterns. Protein intake appears to exceed recommendations. The overall impact of less than optimal dietary intake remains largely unknown. In each of the aforementioned studies, confounding variables such as diagnosis, phase of therapy, or class of anticancer drug were not controlled for in a systematic manner rendering the findings to scientific scrutiny. The weaknesses of the available studies underscore the need for prospective studies exploring dietary intake in homogenous populations at systematic timepoints thereby improving the power to detect differences between populations.

2.5 Nutrition status and Therapy-Related Side Effects and Overall Survival

The overarching aim of understanding nutrition status among children with cancer is to identify timely nutrition interventions that can be designed and tested to minimize the progression and severity of malnutrition and the associated clinical outcomes. Severe acute malnutrition is the cause of more than two million deaths worldwide (Talbert et al., 2012). It has been well established that children who are malnourished experience impaired growth and development, reduced academic success, impaired physical function, and physical deformities (Black et al., 2008). Malnutrition is a risk factor for susceptibility to infections and remediation of malnutrition reduces the risk of developing an infection. In a recent review exploring 31 pediatric intensive care units centers in eight countries, optimizing nutrition therapy improves overall outcomes in children, including overall survival (Mehta et al., 2012). Preliminary research suggests that benefits may also be realized for children with cancer if timely and effective interventions are designed, tested, and implemented into clinical practice.

The effect of nutrition status on therapy-related side effects and survival has been investigated in multiple studies with varying scientific rigor. The effect of TPN on tolerance to therapy (measured by therapy-related side effects) was evaluated in ten well-nourished patients (age range 2.5-12 years; gender-NR) with acute nonlymphocytic leukemia. Children were randomly assigned to prophylactic TPN or standard oral nutrition during the induction phase of therapy (Hays et al., 1983). Patients in the TPN group received significantly more calories (63.4 cal/kg/day vs. 41.4 cal/kg/day) and protein (1.9 gm/kg/day vs. 1.1 gm/kg/day) compared to the control group. All patients in the TPN group experienced an increase in weight whereas only one patient in the control group experienced weight gain ($X^2 < .05$). No significant differences

between groups in arm muscle area or serum proteins were observed. In the TPN group, patients were febrile for a mean of 20.5% days compared to 18.2% days in the control group. Patients in the TPN group received antibiotics for a mean of 13.2 days (23.4%) compared to a mean of 36.8 days (51%) in controls. None of these differences were significant; a mere association between the provision of TPN and infection was suggested.

In a slightly larger study these same relationships were not observed. 27 patients (age range 11-33 years) with weight between 65-124% of pre-illness weight received TPN (n=12) or oral nutrition (n=15) (Shamberger et al., 1983). Among the patients receiving TPN, total calorie intake was two times the control group and the protein intake was five times the control group demonstrating the effectiveness of TPN in augmenting oral dietary intake (methodology of measuring dietary intake was NR). However, no benefit on myelosupression, period of granulocytopenia (absolute neutrophil count) ($<500mm^3$), thrombocytopenia, severe thrombocytopenia, or duration of thrombocytopenia were observed. Transfusion requirements (less accurate measure of myelosupression) favored oral nutrition compared to TPN (P=0.05) bringing into question the benefit of TPN. In this study, participants were generally free of bulk disease and well-nourished. It is possible that different results may be observed in patients with established malnutrition who may have increased susceptibility to therapy-related side effects, especially infections.

The final small study was a randomized study conducted in 27 well-nourished children (age range 2.5-17 years; gender-NR) receiving radiation to the abdomen. Participants were randomized to TPN (beginning 2-4 days prior to radiation) (n=11) or dietary advice (n=13)

(Ghavimi et al., 1982). Nutrition status was indicated by height, weight, TSF, and MUAC. Patients in the TPN group gained significantly more weight than controls, 12.3% vs. 1.4% (P=0.006). Four of the fourteen patients in the control group became malnourished and TPN was initiated. MUAC was significantly different at the initiation of the study (P=0.002) and at the end of the study (P=0.018) however controls had higher TSF at initiation compared to the TPN group (P=0.018). This difference was not apparent at the end of the study. No differences in biochemical parameters, dietary intake, or anthropometric measures were observed after three months. Dietary intake did not correlate with weight changes suggesting it may be unreliable. The methodology in the collection of dietary data was not reported. The TPN group experienced an increase in therapy-related side effects as measured by reduced frequency of bowel movements (P=0.007), lower white blood cell count and hemoglobin (P=0.002), and increased number of days with fever (P<0.001). The TPN group experienced fewer dose reductions (P=0.034) suggesting some benefit. No difference in survival was observed between the two groups. Consistent themes among these early studies are difficult to describe as the studies were limited, small, and heterogeneous. It is possible that a ceiling effect may exist with the provision of TPN in that improved weight and reductions in therapy-related side effects may only benefit those patients who are malnourished as has been observed in other clinical conditions.

Recent studies have acknowledged the weaknesses in the early nutrition literature and have begun to evaluate nutrition status in children with a homogenous diagnosis and larger sample sizes. Lange *et al.* demonstrated a relationship between BMI percentile at diagnosis and survival in 768 children with acute myeloid leukemia (AML) (age range= 2-19 years; male=406/female=362) (Lange et al., 2005). At diagnosis, 10.9% of patients were underweight

and 14.8% of patients were obese. After controlling for age, race, leukocyte count, cytogenetics, and stem cell transplant, underweight patients (HR, 1.85; 95% CI, 1.19-2.87; *P*=0.06) were more likely to experience treatment-related mortality (HR, 2.66; 95% CI, 1.38-5.11; *P*=0.03) while obese patients experienced poor outcomes (HR, 1.88; 95% CI, 1.25-2.83; *P*=0.02) and increased treatment-related mortality (HR, 3.49; 95% CI, 1.99-6.10; *P*<0.001). The hazard ratios observed in this study are not trivial. The authors conclude that the observed reduction in survival is equal to the advances in the survival of AML over the past ten years. In a more recent study performed in 314 children with AML, patients with a healthy weight experienced a superior survival compared to patients who were under- or over-weight (*P*=0.01) Treatment-related mortality was also higher in patients under- or over-weight (*P*=0.009) (Inaba et al., 2012). These studies underscore that although significant advances in overall survival have been achieved in children with cancer, addressing supportive care is crucial in order to sustain current achievements and further improve outcomes.

Three smaller studies performed in children with solid tumors explored the effects of nutrition status on therapy-related side effects and survival. One study incorporated measures of dietary intake into the study design. In a retrospective review of 139 children (age range 9-18 years; male=77/female=62) with either Ewing's or osteosarcoma, nutrition status (measured by BMI percentile) was collected at diagnosis and at six timepoints in therapy (diagnosis, 3, 6, 9, 12, and 24 months) (Tenardi et al., 2011). At baseline, 10.1% of patients were underweight, and 17.2% were overweight. Weight significantly declined during therapy as measured by BMI Z-score (-0.57 for weight and -0.73 for BMI Z-scores, *P*<0.001), reaching a nadir at 12-months. Children with increased number of hospital days, more than 170 days, had lower weight (*P*=0.025)

compared to children with less than 108 hospital days. No significant differences in survival were observed. Hingorini *et al.* evaluated nutrition status in 498 children (age range 3.7-30 yeras; male=274/female=224) with osteosarcoma at diagnosis and evaluated changes in BMI on therapy-related side effects (Hingorani et al., 2011). At diagnosis, 73 patients (14.7%) had a low BMI, 382 patients (76.7%) had middle BMI, and 43 patients (8.6%) had a high BMI. There was a trend towards wound infection and slough in patients with a low BMI (OR= 2.0; *P*=0.07). Finally, in 468 patients with rhabdomyosarcoma (age range=2-21 years; male=296/female=172), greater than ten percent weight loss at 24 weeks was associated with more therapy-related side effects and hospital days but not infection rate, failure free survival (interval between diagnosis and progression or death) or overall survival (interval between diagnosis and death) (Burke et al., 2012). Baseline obese patients (>95th percentile BMI) had inferior failure free survival but not overall survival while underweight patients (<5th percentile BMI) had borderline inferior failure free survival and overall survival compared with baseline average weight patients. These differential findings of the effect of nutrition status on therapy-related side effects and survival in children with solid tumors compared to AML suggest that other medical conditions, type of anticancer therapy, or the natural progression of the disease may be influencing the observed effects of nutrition. Despite a better understanding is clearly needed, these studies do provide preliminary evidence that nutrition status may impact therapy-related side effects or overall survival in children with AML and solid tumors underscoring the importance of tailored and effective nutrition interventions and counseling for children with cancer.

Three studies have explored the effect of nutrition status on survival and therapy-related side effects in children with ALL. After controlling for white blood cell count at diagnosis, gender,

intensification (early vs. late), and age, BMI standard deviation score was not related to relapse (P=0.553) or outcome (P=0.720) in 1025 children with standard risk ALL (age range 0.2-14.9 years; male=772/female=253) (Weir et al., 1998). In contrast, Butturini *et al.* reported inferior survival in children and adolescents (n=4,260) who were obese at diagnosis, a finding that was especially prominent among children greater than or equal to ten years of age (Butturini et al., 2007). It should be noted that the latter study was performed in children with both low- and high-risk ALL, possibly explaining the differential findings reported in the initial study. Most recently, a retrospective study exploring the effect of nutrition status at diagnosis and throughout therapy in children with high risk ALL found that those who remained malnourished for the majority of treatment experienced increased toxicity and reduced survival (Orgel et al., 2011).

Taken together, these studies suggest that nutrition status may alter the risk of developing a therapy-related side effects but this is likely dependent on diagnosis and nutrition status at presentation. Most recent studies suggest that sequential measurements of nutrition status may be necessary to understand the impact of poor nutrition on therapy-related side effects or outcome as the duration and severity of malnutrition or excess weight may be a better indicator of the effects rather than a single assessment at diagnosis. It is likely that the effect of nutrition status is multifactorial and that increased vulnerability to therapy-related side effects may be dependent on pathological features of the tumor or the necessary cancer therapy as evidenced by differential findings in the studies exploring the effect of nutrition status in standard compared to high risk ALL. Differences in tumor pathology alters the treatment schema and dosing which may necessitate the need for patients to be “nutritionally fit” in order to withstand the rigorous therapy.

2.6. Dietary Intake of Micronutrients and Therapy-Related Side Effects

Few studies have evaluated the role of dietary intake of specific micronutrients and their relationship on therapy-related side effects. Rather than consider the comprehensive effects of diet, most of the studies have explored the effect of dietary intake or supplementation with a single nutrient on the effect of a specified clinical condition. Micronutrients of interest have been those associated with depletion as a result of cancer therapy (e.g. bone depletion and dietary intake of bone-metabolizing nutrients), antioxidants (micronutrients with antioxidant properties such as vitamin C, vitamin E, and selenium), and B vitamins.

2.6.a Antioxidants

Antioxidants are a class of micronutrients that exert antioxidant properties either through serving as cofactors in for enzymes (selenium, zinc) or by directly quenching free radicals (vitamin C, vitamin E). Numerous studies have explored the effect of antioxidant status, measured by serum nutrient concentrations, in both adults and children with cancer. A comprehensive review of these studies may be found elsewhere (Ladas et al., 2004). Only one study has explored the effect of dietary intake of antioxidants on therapy-related side effects and survival in children with cancer. The first prospective study was completed in 103 children with ALL (age range 2.1-15.1 years; male=60/female=43) and collected dietary intake at three timepoints in therapy diagnosis, Day 28 of induction therapy, and 6-months after diagnosis. The primary aim of this study was to explore the relationship of dietary intake, measured by a food frequency questionnaire and 24-hour recall, of antioxidants on therapy-related side effects in children undergoing treatment for ALL (Kennedy et al., 2004). The authors found that children with increased intake of beta-carotene at 6-months experienced reduced hematologic or non-

hematologic side effect (P=0.04), greater intakes of vitamin C were associated with lower risk of hematologic or nonhematologic side effect (P=0.01), fewer delays in administration of scheduled chemotherapy (dietary intake: P=0.04), and fewer days spent in the hospital (dietary intake: P=0.04). At diagnosis, those with higher vitamin A intakes (P=0.05) were more likely to have a slow response to treatment, whereas those with higher vitamin E intakes (P=0.05) were more likely to have a rapid response to treatment. As this study was a small pilot in children with ALL, the study was exploratory in nature. The authors concluded intakes were below recommendations and poor intake was associated with therapy-related side effects. The authors suggest a larger study is needed to confirm the preliminary findings and explore intakes throughout the course of cancer therapy. This was one of the first studies to also highlight the need for dietary counseling during cancer therapy so as to minimize the effects of identified nutrient deficiencies.

2.6.b Bone-Metabolizing Nutrients

Nutrients related to bone metabolism have been a target area of research due to the observation of increased incidence of bone fractures during and after treatment for ALL (Kaste et al., 2001). While the contribution of cancer therapy, the cancer itself, or lack of dietary intake results in children with ALL experiencing increased fractures is still undergoing scientific inquiry, studies have reported on the contribution of diet. No study has investigated dietary intake of bone-metabolizing nutrients during therapy, one study has reported in dietary intake among survivors of ALL (Tylavsky et al., 2010). Children and adolescent survivors of ALL (n=164) reported on dietary intake with a food frequency questionnaire. The authors reported on the percentage of patients that met or exceeded recommendations for calcium, vitamin D, phosphorous,

magnesium, and fiber. As well, the authors reported on the percentage of patients who met or exceeded the acceptable macronutrient distribution range (ADMR). All patients were within the ADMR for protein, 36% for fat, and 92% for carbohydrate. The authors explored mean intakes to the adequate intake (AI) for all bone-metabolizing micronutrients. When evaluated by AI age group, the majority of survivors between the age of 9-13, 14-18, and 19-30 years of age did not meet the AI for vitamin D, 15%, 15%, and 34%. For calcium, 17%, 16%, and 34% were below the AI for calcium. While the prevalence of poor intake was below that expected, it should be acknowledged that vitamin D and calcium have undergone revision since the publication of this article and a significant increase in the daily recommendation for vitamin D has been set forth by the National Academy of Sciences (e.g. AI=200 IU compared to RDA= 600 IU vitamin D/day). With the increased risk of bone morbidities among children and adolescents with ALL, this study promotes the need for a comprehensive approach to cancer care in which the integration of dietary counseling are woven into standards of care. Consideration for supplementation of bone-metabolizing nutrients may be required for this group of patients in hopes of minimizing the long-term effects of cancer or cancer therapy.

2.6.b B Vitamins

A final area of focus in the nutrition literature is that of B vitamins and the role deficiencies or excesses may have on the efficacy of cancer therapy as well as therapy-related side effects. Within the class of B vitamins, folate has received the most attention due to the inclusion of anti-folate medications used for the treatment of ALL. The importance of dietary folate consumption in patients receiving methotrexate (MTX) has been widely debated as the avoidance of folate and folate-containing foods is often recommended during phases of therapy that include anti-folates.

A heightened interest in this recommendation has emerged as a result of the FDA mandate, effective January 1998, that all grain products (enriched breads, flours, corn meals, rice, noodles, etc) be fortified with 400 mcg of folic acid. A serving of these products will yield about 10% of Daily Value (about 40 mcg). In a post-hoc analysis, dietary folate intake was explored among 107 children with ALL (Ladas, 2003). Fortification significantly increased the amount of folate in the subjects' diets ($P<0.0001$). Mean daily intakes increased by 29.6% (345 μg compared to 491 μg). Mean dietary folate values were compared among subjects who incurred therapy-related side effects (n=17) and compared to subjects who did not experience a side effect (n=61). Dietary folate did not have a significant effect on the incidence of side effects between the two groups ($P<0.70$). Therapy-related side effects related to anti-folates such as gastrointestinal sores did not demonstrate a significance difference. The influence of dietary intake of folate is likely dependent host genetics and red blood cell folate levels (Robien et al., 2003).

The family of B-complex vitamins have also been investigated for the prevention of neuropathy, a common side effect of cancer therapy have been published. Deficiencies in B vitamins have been correlated with a compromised neurological status and an increased incidence of neuropathy in other clinical conditions, including diabetes and HIV (Abbas et al., 1997; Ang et al., 2008). B vitamins are a prescribed treatment in adults with other neuropathic conditions, including diabetes, HIV-treatment related, and alcohol-induced neuropathy (Ang et al., 2008; Peters et al., 2006). Inadequate intake of B vitamins is associated in neurological dysfunction and has been associated with the development of neuropathy in other clinical conditions (Beltramo et al., 2008; Gorson et al., 2006). Case reports and clinical studies have found that administration of B vitamins is effective in managing neuropathy. One case report describes the

use of vitamin B6 in a four year old with ALL with moderate-severe neuropathy (Ozyurek et al., 2007). Administration of B6 (150mg/m^2/day, orally) with pyridostigmine (3 mg/kg/day) during the maintenance phase of therapy was associated with resolution of neuropathy, and allowed for optimal doses of chemotherapy to be administered. Randomized, controlled clinical studies have reported a beneficial effect of B vitamins for the prevention of neuropathy in other clinical settings with few adverse events (Youssef et al., 2008). A recent Cochrane Review found that administration of B vitamins in the setting of neuropathy is encouraging, but not conclusive (Ang et al., 2008). While supplementation has been an area of interest, there are no published reports exploring dietary intake of B vitamins during cancer therapy in children with ALL. Large, epidemiologic studies are needed to accomplish this goal.

2.7 Dietary Recommendations for Children Undergoing Treatment for Cancer

In children with cancer, nutrition intervention and education is primarily based upon the expert opinion of the physician, dietician, and nurse with efforts focused on the treatment of malnutrition and prevention of cachexia. Little consideration is given to the broader scope of nutrition education, especially during cancer therapy (Ladas et al., 2005). Optimizing cancer care includes placing emphasis on all aspects of supportive care interventions that include nutrition education. This is especially important for the child with cancer as clinicians have the additional challenge of supporting growth and development while delivering the recommended doses of anticancer therapy. Clinicians should be compelled to include this into the scope of cancer care however the paucity of data has prevented nutrition intervention and education from being systematically incorporated into cancer care.

Presently, dietary guidelines for children during and after cancer therapy are generally centered on the prevention of cancer and are reflective of those guidelines set forth for healthy children (www.choosemyplate.gov) without a history of cancer or for survivors of adult malignancies (www.aicr.org or www.cancer.gov) (American Institute for Cancer Research, 2012; Chlebowski, 2003) These guidelines include the importance of weight management, fruits and vegetables, whole grains, and lean protein however do not address potential nutrient deficiencies that may develop as a result of cancer therapy. Moreover, the guidelines are not modified to reflect the increased risk of nutrition-related conditions such as heart disease, metabolic disease, or obesity that are widely prevalent among survivors of childhood cancer. In adults, adherence to a cancer prevention diet is estimated to reduce cancer mortality by 22% (Balter et al., 2012). The existence of such a relationship in pediatrics is unknown. A void in data has resulted in extreme variation in the nutrition management and education for children with cancer (Ladas et al., 2005). Often, nutrition management and education mirror the recommendations for healthy children, are extrapolated from guidelines developed for other pediatric conditions, or are adapted from the adult literature. It is reasonable to hypothesize that nutrition intervention and education guidelines may require modification for children with cancer especially given the extensive duration of cytotoxic therapy and myriad of nutrition-related side effects that are frequently encountered by children.

However before epidemiologic studies investigating the benefit of revised nutrition practice and education for children receiving cancer therapy can be undertaken, current guidelines require standardization and modification considering the unique nutrition needs of this vulnerable population. A better understanding of variations in dietary intake during cancer therapy and the

degree to which children deviate from Dietary Reference Intakes will serve as to guide in developing standardized guidelines. Understanding the degree at which intakes are below or exceed the DRIs will aid in the identification of priority areas and serve as a reference so that current guidelines are evidence-based rather than based on empirical data. To undertake such a task, a comprehensive understanding of fluctuations in dietary intake over the course of cancer therapy must be understood. To date, only one small study exploring diet quality has been conducted in a homogenous group children with cancer (Kennedy et al., 2004).

The present study builds upon the existing science by exploring dietary intake among children and adolescents with ALL representing a large homogenous population of children with cancer. The data collected with allow for comparisons among patients withholding the variation of various cancer regimens, a variable that has limited previous studies. The present study will evaluate fluctuations in dietary intake by exploring changes in both macronutrient and micronutrients as compared to healthy children as well as reference values set forth by the National Academy of Science. The data collected from this study will help to close a gap in the scientific literature and begin to provide a foundation for the development of nutrition guidelines for children and adolescents undergoing treatment for cancer.

Chapter 3: Methods

This chapter will provide the reader with details of the study design, data collection methods, and statistical considerations for the current study.

3.0 Study Overview

This study is a cohort study describing changes in dietary intake over the course of a standardized cancer therapy protocol in children diagnosed with ALL. Dietary intake was measured at three timepoints in therapy (Time 1- no therapy (diagnosis); Time 2- high dose therapy (referred to as the induction phase); Time 3-low dose therapy (referred to as the continuation phase)). Dietary intake was measured at each of the timepoints with a food frequency questionnaire (FFQ) that was completed by the parent or patient. Macronutrient and micronutrient values were then compared to: 1) Data from the National Health and Nutrition Examination Survey (NHANES)- representing normative data of dietary intake in children residing in the United States; (U. S.Department of Health Human Services, 2007) and 2) The Dietary Reference Intakes (DRIs) which are recommended nutrient intakes for individuals set forth by the National Academy of Sciences (Otten et al., 2006). Children and adolescents are described as being below, meeting, or above the DRIs. Dietary intakes in children with ALL are described and compared to NHANES data and the DRIs in an effort to identify and recommend priority areas for nutrition intervention that could potentially minimize therapy-related side effects and maximize survival.

The objectives of the study were as follows:

Study Objective 1: To describe macronutrient and micronutrient dietary intakes at three different time points: Time 1 (diagnosis (no therapy)); Time 2 (end of induction (high dose therapy)); Time 3 (continuation (low dose therapy)) in children undergoing treatment for ALL.

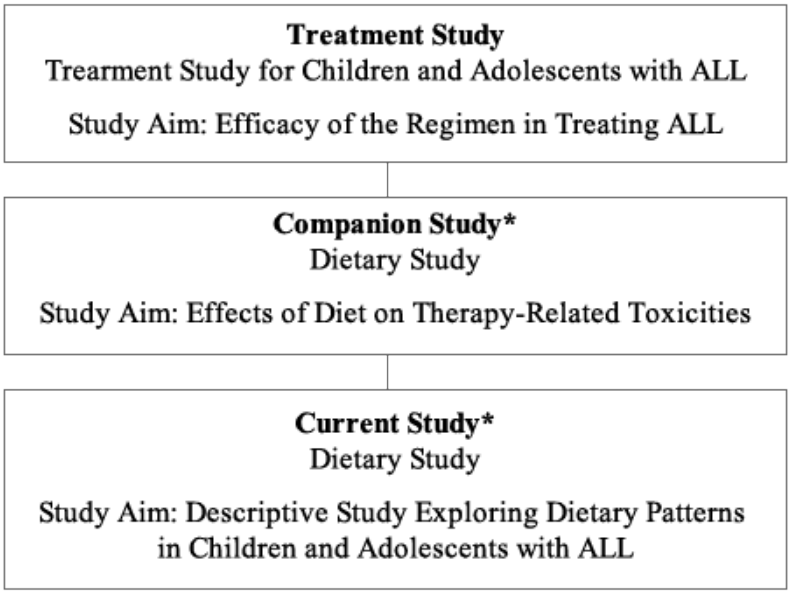
Study Objective 2: To compare mean dietary intake of macronutrients and micronutrients at three different time points: Time 1 (diagnosis (no therapy)); Time 2 (end of induction (high dose therapy)); Time 3 (continuation (low dose therapy)), in children undergoing treatment for ALL to dietary intakes of children reported in National Health and Nutrition Examination Survey (NHANES).

Study Objective 3: To describe the percentage of children undergoing treatment for ALL that are below, meet, or exceed the dietary recommended intakes (DRIs) for macronutrients and micronutrients at three different timepoints in therapy: Time 1 (diagnosis (no therapy)); Time 2 (end of induction (high dose therapy)); Time 3 (continuation (low dose therapy)).

3.0.a Treatment Study

All patients that were enrolled on a Dana Farber Cancer Institute (DFCI) treatment study for ALL were eligible for participation in the current study. The association of the treatment study and current study is described in Figure 1.

Figure 1.
Association of the Treatment, Companion, and Current Study



**Patient participation is optional*

All children and adolescents participating in the current study are undergoing treatment for ALL and being treated on a therapeutic protocol that was developed by the DFCI ALL consortium. The DFCI ALL consortium is one of the largest research consortiums in North America with members from institutions located in the United States, Canada, and Puerto Rico. Participation in the companion study was optional for the children and adolescents and did not require an additional consent process. Participation in the companion study provided the data for the current study, no additional consent process was required. Eleven institutions representing the United States, Canada, and Puerto Rico recruited participants to the treatment as well as companion study. The institutions and location are listed in Table 4.

Table 4. Participating Institutions		
Institution	City	Country
1. Dana Farber Cancer Institute	Boston, MA	USA
2. San Jorge	San Juan, Puerto Rico	USA
3. Tulane	No longer active	No longer active
4. St Justine	Montreal, Quebec	Canada
5. Laval	Saint-Foy, Quebec	Canada
6. McMaster	Hamilton, Ontario	Canada
7. Columbia	New York, NY	USA
8. Rochester	Rochester, NY	USA
9. Rhode Island	Providence, RI	USA
10. Montefiore	Bronx, NY	USA
11. Fairfax INOVA	Falls Church, VA	USA

The aim of the treatment study is to investigate the efficacy of a specific treatment regimen for ALL. The treatment study consists of six different phases of therapy that are delivered over a two-year period and administer high- or low-dose chemotherapy (Chapter 2, Table 1). Some phases of therapy are more intensive for those patients with ALL that are classified as high risk ALL. Classification of high risk ALL is based upon features of the leukemia present at diagnosis (Stanulla et al., 2009).

The first phase of therapy is referred to as the prophase and administers high dose steroids. The second phase of therapy, referred to as the induction phase, delivers high dose chemotherapy and its purpose is to kill the leukemia cells and achieve remission. The third phase of therapy is the consolidation phase of therapy and continues to deliver high dose chemotherapy to kill any remaining leukemia cells. The final phase of therapy is the continuation phase of therapy in which cancer therapy is administered in lower doses than prior phases. Each phase of therapy is

slightly different in its length and can be a minimum of 32 days (induction phase) to 15 months (continuation phase).

3.0.b Companion Study

Several adjunct studies, also referred to as companion studies, are available for participation only to children enrolled on the treatment study. Since all patients that participate in companion studies are treated on the same protocol, companion studies offer the benefit of having all patients receive the same cancer treatment. Large samples are also easier to obtain when conducting companion studies. The dietary information used for the current study was available to the investigator from a companion study that is investigating the associations between dietary intake and therapy-related side effects from cancer therapy in children with ALL. In the companion study, FFQs were administered to patients at three timepoints in therapy. The primary aims of the companion study are to investigate the relationship between dietary intake of select micronutrients and their relationship with therapy-related side effects. Specifically, the companion study will investigate the following three relationships: (1) the association between dietary folate intake, serum folate values, and methotrexate-related side effects (e.g. mouth sores); (2) the association between dietary intake of antioxidants and incidence of infections; and (3) The association between dietary intake of bone-related nutrients and incidence of bone fractures.

3.0. c Current Study

The current study utilizes data obtained in the companion study and reports on change in dietary intake of macronutrients and micronutrients in children and adolescents undergoing treatment for

ALL. Information on dietary intake is collected at Time 1 (diagnosis), Time 2 (Day 32 of induction therapy), and Time 3 (15 months post-diagnosis (continuation therapy)). These time points were selected to reflect varying levels of chemotherapy exposure; Time 1 (no exposure to therapy), Time 2 (exposure to high dose therapy (induction); and Time 3 (exposure to low dose chemotherapy (continuation)). Time 1 reflects no exposure to chemotherapy as the survey reflects dietary intake for the month preceding the diagnosis of cancer. The schedule and timing of administration of dietary surveys are described in Table 5. In the current study, intakes of children with ALL were compared with those of children, as reported in NHANES (U. S.Department of Health Human Services, 2007). The study also examined the proportion of children below, meeting or exceeding the recommended values for dietary intake, based on the DRIs (Otten et al., 2006).

Table 5.
Overview of Companion Study

Phase	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
Duration	3 Days	4 Weeks	3 Weeks	3 Weeks	27 Weeks	~ 70 Weeks
Name of Phase	Prophase	Induction	Consolidation	CNS Therapy	Consolidation II	Continuation
Type/Intensity of Therapy	Steroids	High-Dose Therapy	High-Dose Therapy	Central Nervous System Therapy	High-Dose Therapy	Low-Dose Therapy
Food Frequency Administration	FFQTime1	FFQTime2				FFQTime3

3.1. Subjects

Children and adolescents between the ages of 1 and 18, with newly diagnosed ALL (n=799) were recruited to the study. Eligible participants for the described study were children and adolescents receiving treatment for ALL as per the DFCI treatment study. The treatment study was open to recruitment in May 2005 and closed to accrual in December of 2011. Completion of all study datapoints is expected in the Spring of 2013. Consent to the treatment study was obtained as per the Institutional Review Board of all participating centers (table 4) and served as

consent to the companion study. For the dietary study, participation at each timepoint was optional. Participants or their parents could accept or decline participation in the dietary study and continue to receive treatment for ALL as per the treatment study. Patients declining participation were documented as such and coded as missing data (refer to section 4.0, table 7).

3.2 Study Measurements

3.2.a Demographics

Demographic data was limited to those variables being collected as part of the treatment study. Information on demographics were provided by the participating institutions and collected from the medical chart. The demographic variables provided were: type of ALL (low- risk or high-risk), country of residence (table 4), date of birth, gender (male or female), and ethnicity (White; White, Hispanic; Other, Hispanic; Black; Black, Non-Hispanic; Black, African-American; Asian; American Indian/Alaska; Other).

3.2.b Dietary Intake

Three dietary tools were administered during the study period, The Youth and Adolescent Questionnaire (Appendix A), The Harvard Food Service Questionnaire (Appendix B), and the medical nutrition support form (Appendix C).

3.2.b.1 Dietary Intake: Macronutrients and Micronutrients

The Harvard Food Services Questionnaire (HSFFQ) for children ages 1-5 years and the Youth and Adolescent Food Frequency Questionnaire (YAFFQ) for children ages 6-18 years were administered to study participants at Time 1 (no therapy), Time 2 (high dose therapy), and Time

3 (low dose therapy). In the current study, administration of the YAFFQ and HSFFQ requires children and adolescents or their parents to recall their average intake of foods over a specified period of time. For the current study it was one month. The nutrients of interest retrieved from the data output from the YAFFQ and HSFFQ were the following: total calories, macronutrients (fat (grams), carbohydrate (grams), protein (grams)), antioxidant vitamins (vitamins C (mg), vitamin E (mg), zinc (mg), B vitamins (folate (mcg), pantothenic acid (mg), thiamin (mg), riboflavin (mg), vitamin B12 (mcg), vitamin B6 (mg), niacin (mg)) and bone-metabolizing vitamins (calcium (mg), vitamin D (IU), vitamin K (mcg)). The use of dietary supplements was self-reported and was added into the dietary intakes from both dietary surveys.

For children and adolescents 6-18 years of age, the YAFFQ was administered. The YAFFQ asks participants how often, on average, they consume each of the 131 foods listed (such as mixed vegetables, macaroni and cheese, and peanut butter sandwich). Food portion sizes are determined by comparison with national standard surveys; such as, Nationwide Food Consumption Survey Foods Commonly Eaten by Individuals (specifically for ages 9–18 years), and the 'natural' serving size of foods (e.g. bread slice, apple) (Pao et al., 1982). Additional questions are asked about the frequency of snacks on school days and weekends, and the frequency of eating meals and snacks away from home. Respondents indicate use of dietary supplements in the form of multivitamins/minerals or single nutrients. Administration of the dietary questionnaire requires about 10-15 minutes of the respondent's time and was completed by the patient or parent. The survey was available in English, Spanish, and French.

The HSFFQ was administered to children less than or equal to five years of age. The HSFFQ contains 103 items, including 84 foods and 19 questions about food habits and supplements. In addition to the questions about intake of specific foods, the HSFFQ also collects information on infant feeding habits such as the type and frequency of formula or milk. The HSFFQ inquires about foods commonly eaten by small children and includes a range of questions on fruits, vegetables, simple and complex carbohydrates, dietary sources of protein, and sweets. The HSFFQ is completed by parent or guardian. Questions about food preparation, condiments, and the use of multivitamins are included in the dietary survey tool. This survey was also available in English, Spanish, or French.

Both the HSFFQ and YAFFQ have been tested for reliability and validity in children and adolescence (Blum et al., 1999; Rockett et al., 1997; Rockett et al., 1995). The results revealed by both the YAFFQ and HSFFQ were similar to those in other studies reporting on the reliability and validity of food frequency surveys (Rimm et al., 1992; Suitor et al., 1989; Willett et al., 1985).

YAFFQ: Reliability and Validity

The reliability of the YAFFQ has been established in 179 children between 9-18 years of age (44% M / 56% F) (Rockett et al., 1995). Participants completed two YAFFQs one year apart. Pearson correlations were reported for selected nutrients that included total calories, protein, total fat, carbohydrate, fiber, and calcium. Correlation between the two surveys was .41 indicating moderate reliability (Kushi, 1994). For total calories, the correlation was .49. Correlations for calcium and fiber were .58 and .51 respectively indicating moderate to high correlation for

dietary surveys (Kushi, 1994). However, age and ethnicity were not significantly related to reliability.

This study also reported on the validity of the YAFFQ. The data obtained from the YAFFQ was compared to normative data reported by the Nationwide Food Consumption Survey (NFCS) and NHANES II. When compared to NFCS, mean caloric intakes were within 25% of one another. When the data obtained from YAFFQ was compared to NHANES, mean intakes were within 20% for males. A slightly wider range in nutrient values was observed for females. Overall, these data suggest that validity of the survey is moderate but in line with previously reported tests (Kushi, 1994). The results of these studies are presented below. Pearson correlation coefficients for individual nutrient are presented in Table 6.

A second study reported on the validity of the YAFFQ in 261 children age 9-18 years of age (47% M / 53% F) (Rockett et al., 1997). The majority of the population was Caucasian (96%) with 4% representing African-American, Hispanic, Asian or other ethnicities. Participants completed two YAFFQs over a one-year period and three 24-hour dietary recalls over the same time period. Mean intakes from the three 24-hour recalls were compared to the mean intakes obtained from each of the two YAFFQs. Energy-adjusted correlation coefficients for select nutrients are reported in Table 6. Overall, Pearson correlations between the first YAFFQ and the mean of three 24-hour recalls was .45. Correlation for the second YAFFQ and the three 24-hour

Table 6.
Summary of Validation Studies for YAFFQ and HSFFQ

	$YAFFQ_1$[a]	$YAFFQ_2$[b]	HSFFQ[c]
Overall	0.45	0.42	0.52
Macronutrients			
Calories	0.37	.039	NR
Protein (g)	0.37	0.38	0.43
Carbohydrate (g)	0.40	0.41	0.52
Fat (g)	0.49	0.48	0.62
Fiber (g)	0.46	0.40	0.26
Antioxidants			
Vitamin E (mg)	0.51	0.45	0.56
Vitamin C (mg)	0.54	0.51	0.58
Zinc	0.46	0.41	0.31
B Vitamins			
Thiamin	0.51	0.40	0.57
Riboflavin	0.56	0.47	0.56
Niacin	0.47	0.39	0.55
Folate	0.58	0.52	0.55
Vitamin B12	0.39	0.45	0.58
Vitamin B6	0.52	0.45	0.58
Bone Nutrients			
Calcium	0.55	0.52	0.60

[a] *Comparison of $YAFFQ_1$ to three 24 hour recall (Rocket, et al., 1997)*
[b] *Comparison of $YAFFQ_2$ to three 24 hour recall (Rocket, et al., 1997)*
[c] *Comparison of two HSFFQ to three 24 hour recall (Blum, et al., 1999)*

recall was .42. A slightly higher correlation was observed in males (.47) compared to females (.44). While these correlations may be low, the correlations are still within acceptable ranges for dietary surveys. Additionally, the reported correlations reflect those of other biological tests such as blood pressure and skinfold tests (Kushi, 1994).

This study also compared mean values obtained from the YAFFQ to energy intakes observed from national surveys, NFCS and NHANES II. Males reported slightly higher total caloric intake on the 24-hour recalls whereas females reported slightly higher intakes on the YAFFQ.

Younger children (9-13 years of age) tended to report higher intakes on the YAFFQ. In contrast, older children (14-18 years of age) reported higher intakes on the 24-hour recalls. Overall, the authors reported that energy intakes obtained from the YAFFQ were estimated to be 5-10% less for males and 12-21% higher for females compared to national surveys. The authors suggest that this is within acceptable ranges of other dietary surveys.

HSFFQ: Validity

The HSFFQ has been validated in 233 children between the ages of 1-5 and visiting a WIC clinic in North Dakota (Blum et al., 1999). Fifty six percent of the population was Native American and 44% were Caucasian. Correlations between the average intakes of the two HSFFQ and three 24-hour recalls were reported. The average Pearson correlation coefficient for the entire cohort was 0.52 (table 6). Nutrient correlations were variable and ranged from poor to moderate. Poor correlations were observed for dietary fiber (0.26) whereas moderate to good correlations were observed for fat (0.62), vitamin E (0.56), vitamin C (0.58), and folate (0.60) along with a few other select nutrients (table 5). Pearson correlations were also reported by ethnicity. This analysis revealed similar correlations between ethnic groups, 0.49 among Caucasians and 0.51 among Native-Americans suggesting moderate validity for a dietary tool (Subar et al., 2001). The HSFFQ has not been tested for reliability.

3.2.b.2 Diet Intake: Total Parenteral Nutrition (TPN) and Enteral Feeding

The provision of medical nutrition therapy is often a consequence of anticancer therapy. For standardization of data collection, a medical nutrition therapy form (Appendix C) was developed to collect information on the provision of enteral feeds (nasogastric feeds, gastronomy tubes),

oral nutrition supplements (e.g. Pediasure, Ensure, and Boost) and TPN at each of the designated timepoints. Research assistants at each of the participating institutions completed the medical nutrition therapy form for each patient, regardless of whether received TPN or EN, at each of the three timepoints. The medical nutrition therapy form provided information on the brand of nutrition formula and the prescribed dose (e.g. number of cans of supplement per day). If enteral feeds were administered, the formula, rate, and duration were reported. The nutrients delivered by the scheduled dose were then calculated by the nutritionist at Columbia University and manually added into the individual's dietary analysis produced by the FFQ. Due to institution limitations, the study was not able to collect detailed nutrient information on patients who received TPN. Use of TPN was captured by institutions indicating its administration during the timepoint as 'yes' or 'no'. Medical nutrition therapy forms accompanied each FFQ. Institutions were contacted if the data collection form for enteral nutrition was not received in order to limit missing data.

3.2.c Reference Values for Dietary Intake

Dietary intake obtained from FFQs was compared to two values, the Dietary References Intakes (Otten et al., 2006) and normative data from The National Health and Nutrition Examination Survey (U. S.Department of Health Human Services, 2007).

3.2.c.1 National Health and Nutrition Examination Survey (NHANES)

NHANES is a national survey that began in 1999 and currently collects dietary information annually. NHANES provides information on the mean intakes of most dietary nutrients for children residing in the United States. NHANES is a collaboration between the U.S. Department

of Health and Human Services (HHS) and the U.S. Department of Agriculture. The Center for Disease Control, a division of HHS, is responsible for the sample design and data collection of the dietary survey and the USDA is responsible for the methodology employed in the collection of dietary data and the maintenance of the food and nutrient databases (U. S.Department of Health Human Services, 2007). The survey examines a nationally representative sample of about 5,000 persons each year across the United States. Dietary data is collected by an in-person interview or over the phone by two non-consecutive 24-hour recalls. Interviewers conduct the surveys at a mobile exam center and rely upon the five-step USDA Automated Multiple-Pass Method used for collecting interviewer-administered 24-hour recalls. Data are reported as mean intakes by gender, age group, and race (U.S.Department of Agriculture, 2010). A summary of the normative data reported by NHANES (2005-2006) may be found in Appendix E. In this report, data is not reported for children under the age of two.

3.2.c.2 Dietary Reference Intakes (DRIs)

Dietary intakes were compared to the DRIs. The DRIs are recommendations designed to serve as a reference to guide health professionals in the assessment and planning for the dietary needs of individuals and groups. For total calories, the DRIs define the recommended energy intake as "the amounts of energy that need to be consumed by individuals to sustain stable body weights in the range desired for good health (BMI from 18.5 up to 25 kg/m^2) while maintaining lifestyles that include adequate levels of physical activity to maintain social, cultural, and economic activity" (National Academy of Sciences et al., 2002). Recommended calorie intakes have been developed by age and gender. For the macronutrients, fat, protein and carbohydrate, the acceptable macronutrient dietary ranges (AMDR) (Appendix D) were developed which are

macronutrient distribution ranges as a percentage of total calories (National Academy of Sciences et al., 2002).

For micronutrients, the DRIs consist of four categories: Estimated Average Requirement (EAR), the Recommended Dietary Allowance (RDA), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL). The DRIs were designed to meet the needs of seemingly healthy individuals and are not meant to be applied to those with acute or chronic disease or for the repletion of nutrients in patients who are malnourished. It is not known if these values are applicable to individuals with a chronic condition however other reference values are not available for clinical practice. The DRIs are based upon scientific research and clinical trials documenting safety or efficacy of a specified nutrient. For nutrients without clinical trials to guide practice, an AI is developed and is largely based in empirical knowledge. The DRIs are the most widely used reference guide to determine the adequacy of individual and group diets and provides a systematic framework in which dietary data, obtained in individuals or groups, may be compared. Summary tables of the DRIs may be found in Appendix D.

3.3 Data Collection Procedures

For this study, a designated research assistant at each of the participating institutions administered the age-appropriate FFQ to study participants. Administration of dietary surveys was given to patients during a routine clinic visit to the outpatient center. For patients that were in the hospital at the time of the datapoint, the FFQ survey was administered while they were at the hospital. For each institution, the training of research assistants was provided by the nutritionist and co-investigator of the study (E.L.) at the lead institution of the diet study (Columbia University). Institutions were trained in person, over the phone, or at annual DFCI

consortium group meetings. Institutions were advised to administer the dietary survey to the parent or patient within three working days of the designated timepoint. If the child or adolescent were not willing, interested, or too young to complete the survey, the parent or legal guardian would complete the survey instrument. Surveys not completed within this timeframe were documented as missing data. Research assistants were instructed to advise participants that responses should reflect the previous month's dietary intake. The information was disseminated to each of the research assistants and was also included in a brief cover letter delivered to the patient at the time of administration of the FFQ.

Upon collection of dietary surveys, research assistants were advised to ensure that the FFQ was complete. Blank questions were reviewed with the respondent. Surveys were then batched by each institution and sent to Columbia University for preparation for data analysis at intervals convenient for the participating institution. The lead institution notified institutions if surveys were incomplete or clarifications were needed. Once completed, surveys were then processed by the research group at Columbia University, in accordance with the guidelines set forth by the Channing Laboratory at Harvard University. The YAFFQs are bubble-coded surveys that were coded and copied and sent by parcel post to the Channing Laboratory at Harvard University for scanning and analysis. The HSFFQ are written surveys in which respondents indicate food frequency with a check mark. Completed surveys were entered into a DOS-based data system (provided by the Channing Laboratory) by the team at Columbia University. Surveys were then batched and sent by electronic mail for dietary analysis.

The investigative team followed a standardized protocol to reduce the possibility of processing error. For the HSFFQ, input of the dietary data into the database system was vulnerable to improper data entry, which may lead to misclassification. To minimize this risk, a research assistant, who was not involved with the collection of dietary data, reviewed all data. If improper data entry was identified, the data system was corrected and reviewed a third time for accuracy of data input before proceeding to data analysis.

3.4 Statistical Analysis

Dietary intakes at three different timepoints in therapy are included in the dietary analysis for the described study. Mean intakes are reported adjusting for total caloric intake. Adjusted nutrient intakes are reported for the described analysis despite controversy on the utility of reporting absolute or energy adjusted nutrient intakes (Block, 2001; Willett, 2001). Studies have found that energy adjusted intakes correlate better with biological markers of a specified micronutrient (Willett, 2001). Holding energy constant allows the investigator to observe changes in the composition of the diet, however small they may be on disease risk (Willett, 2001).

Categorization of patients into DRI categories were based on absolute intakes in which patients were categorized as below, meeting, or exceeding the recommended nutrient intake as denoted by the DRI by gender and age (Appendix D). For calories, reference values for dietary intakes were calculated for each age and gender category assuming a sedentary activity level for all three timepoints. Caloric intake for each patient was classified into four groups: (1) as below the recommended intake, (2) met (caloric intake that was at or within 10% of recommended intake), (3) exceed by 10-24% (caloric intakes that exceeded recommendations by 10-24%), and (4) exceed by 25% or more (caloric intakes that exceeded recommendations by 25% or more). The two classification of excess caloric intake were based upon the clinical expertise of the

investigator of the current study. Categorization of the percent of calories for dietary intakes of fat, protein, and carbohydrates were classified as below, met, or above the AMDR for the specified nutrient.

Micronutrient intakes were also classified as below, met, or above for each nutrient. The RDA served as the reference point for each micronutrient. For those micronutrients, pantothenic acid and vitamin K, in which an RDA was not set, the AI served as the reference value. Micronutrient intakes that were below the RDA were classified at below. Micronutrient intakes that were at the RDA and below the upper intake level (UL) were classified as met. Micronutrient intakes that were at or above the UL were classified as exceeding the recommended intakes. For micronutrients in which an upper limit was not set (thiamin, riboflavin, B12, vitamin K, and pantothenic acid), micronutrient intakes were classified only as below or met the RDA or AI for each nutrient.

Normality

The distribution of mean intakes was explored by age and by timepoint for normality by skewness and kurtosis before and after the removal of outliers. Non-normality was defined if the skewness (or kurtosis) statistic were +/- 3 times its standard error. Outliers were defined as cases that were more than three standard deviations away from the mean for age. Fifteen patients met this criterion for exclusion. An additional three patients were removed from the analysis due to dietary intakes below 100 calories per day or exceeding 5000 calories per day. Re-evaluation of skewness and kurtosis resulted in most age groups meeting the normality assumption. However, the model used for the current analysis, the linear mixed-effects model, is robust against violation of normality assumptions.

3.4.a Sample Size

A total of 799 children were recruited to the treatment study and enrollment is now complete. A total of 615 surveys at Time 1 and 556 for Time 2 was collected and analyzed. Collection of dietary surveys for Time 3 is still ongoing as the observation for the final patient will occur in the Spring of 2013. Complete dietary data will not be available for analysis until late Fall of 2013. As of June 2012, the point at which data collection for this analysis was closed, 417 surveys had been collected and analyzed for Time 3. All analysis was performed in SPSS (version 18.0) (SPSS Inc. Released 2009, 2009).

3.4.b Analysis Plan

Study Objective 1: To describe macronutrient and micronutrient dietary intakes at three different time points (Time 1 (diagnosis-no therapy); Time 2 (end of induction-high dose therapy); Time 3 (continuation-low dose therapy) in children undergoing treatment for acute lymphoblastic leukemia

A linear mixed-effects model method was used for analysis of changes in dietary intake over the three study timepoints. Diagnosis (Time 1) served as the base of which subsequent analysis were compared. The linear mixed-effects model was performed due to: (1) datapoints are not exclusive of one another—the same subject was measured repeatedly, (2) linear mixed-effects model provides more flexibility in handling unequal variances and missing data, and (3) the models presented in this study required controlling for time varying covariates (mean intake of calories change at each timepoint and analysis was adjusted for calories for macronutrients and micronutrients). The linear mixed-effects model allows for time-dependent covariates

(predictors measured over time). In summary, mixed model analysis provides a general, flexible approach in these situations.

Study Objective 2: To compare mean dietary intake of macronutrients and micronutrients at three different time points, (Time 1 (diagnosis (no therapy)); Time 2 (end of induction (high dose therapy)); Time 3 (continuation (low dose therapy)), in children undergoing treatment for acute lymphoblastic leukemia to dietary intakes of children reported in National Health and Nutrition Examination Survey (NHANES).

Descriptive statistics were used to explore differences between children with cancer and children as reported in the NHANES dataset. The cohort was categorized by age groups as reported by NHANES. Group mean intakes of the cohort were reported as a percentage below or above NHANES data.

Study Objective 3: To describe the percentage of children undergoing treatment for acute lymphoblastic leukemia that are below, meet, or exceed the dietary recommended intakes for macronutrients and micronutrients at three different timepoints in therapy: Time 1 (diagnosis-no therapy); Time 2 (end of induction-high dose therapy); Time 3 (continuation-low dose therapy).

Participants were classified as under, met, or exceed the DRI and the proportion of patients in each group by timepoint was statistically evaluated. Three comparisons of the categorical data were performed: 1) Time 1 to Time 2, 2) Time 2 to Time 3, and 3) Time 1 to Time 3. The Wilcoxon Signed-Rank Test, the non-parametric test equivalent to the dependent t-test, was used

to compare the nutrient intake categories from one time point to another. Dietary intake for the cohort was not normally distributed when intakes were evaluated by nutrient, age, and timepoint (refer to section on normality). The Wilcoxon Signed-Ranks Test does not assume normality in the data therefore it can be used when this assumption has been violated and the use of the dependent t-test is inappropriate. *P* values used in Wilcoxon signed-rank test are adjusted according to the Bonferroni correction. The Bonferroni correction reduces the chances of obtaining false-positive results (Type I errors) when multiple pair wise tests are performed on a single set of data. Instead using the *P* value of $\leq .05$ to determine statistical significance, *P* values $\leq .017$ (e.g. .05/3=.017) are used to assess statistical significance of the results of the Bonferroni-adjusted Wilcoxon signed-rank test.

3.4.c Statistical Considerations

The data are unbalanced repeated measures data, meaning that dietary data was not available for each patient at each datapoint. Of the 615 subjects, 358 subjects have dietary data at all three time points. To control for this unbalanced design, a mixed linear model was used to conduct the analysis as this is a fairly robust model to control for this weakness in the study design.

The analysis assumed the data was missing at random. To support this assumption, both listwise and pairwise deletions were performed to confirm the direction of effects were consistent. The listwise deletion resulted in the inclusion of only those subjects in which dietary data for all three timepoints was available for analysis. After listwise deletion, dietary data on 358 participants was available for all three timepoints. Analysis on these 358 participants did not differ significantly in regards to the observations that were presented in the current study, suggesting

that the data were missing at random. Thus, the data was evaluated utilizing the larger sample size, of 667 participants.

Chapter 4: Results

This chapter will present the results for the current study. The chapter will highlight significant findings that are especially relevant to directing change in clinical practice and identifying future opportunities for research.

4.0 Completed and Missing Data

Dietary data was completed and analyzed for 623 (78%), 563 (70%), and 422 (53%) patients at Time 1, Time 2, and Time 3, respectively (table 7). Dietary data collection for Time 3 is ongoing and is represented by the 20% of datapoints classified as pending. The 53% represents those data collected up through June 2012 when data collection for this study was closed. A small percent of patients (5-6%) declined participation at each timepoint. Two percent of surveys at Time 1, 5% of surveys at Time 2, and 10% at Time 3 of surveys were not collected due to death or change in clinical condition resulting in removal from the treatment protocol. Administrative errors (Time 1, 12%; Time 2, 15%; Time 3, 12%) consisted of improper completion by respondent or institution, institution failed to administer, or patient did not complete within three working days of the timepoint.

Table 7. Dietary Surveys: Completed and Missing Data						
	Time 1		Time 2		Time 3	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Completed [a]	623	78%	563	70%	422	53%
Analyzed [b]	615	77%	556	70%	417	52%
Patient Declined	39	5%	50	6%	42	5%
Medical	16	2%	41	5%	81	10%
Administrative Error	92	12%	122	15%	97	12%
Other	29	4%	23	3%	0	0%
Pending[c]	0	0%	0	0%	157	20%
Outlier	8	1%	7	0.9%	5	0.6%
Total	799	100%	799	100%	799	100%

[a] Represents the total surveys completed out of the 799 eligible patients; [b] 8 surveys at Time 1, 7 surveys at Time 2, and 5 surveys at Time 3 were removed due to data meeting outlier criteria; [c] Pending surveys are either in data cleaning, or patient has not reached the Time 3 data point as of June 2012.

4.1 Demographics

The demographics of the study participants are described in Table 8. A slightly larger proportion of patients were males (56.4%) than females. The mean age at diagnosis was 6.6 years with the majority of patients Caucasian (67%) or Hispanic (18.7%). The remaining ethnicities included: other (8.1%), Black/African-American (3.7%), Asian (2.1%), and American Indian/Alaska (.3%), representing a small proportion of patients. The majority of patients were diagnosed with low risk ALL (58.6%). The demographics of this sample reflect the typical demographics of children and adolescents with ALL (Stanulla et al., 2009).

Table 8. Demographics of Study at Time 1		
Total Sample	667*	
Age (Mean/SD)	6.6 years (SD 4.6)	
Age Range	1 to 17.9 years	
Gender	**N**	**Percent**
Male	376	56%
Female	291	44%
Total	**667**	**100%**
Race	**N**	**Percent**
White	447	67%
Hispanic	125	18.7%
Other	54	8.1%
Black	25	3.7%
Asian	14	2.1%
American Indian/Alaska	2	.3%
Total	**667**	**100%**
Risk Group	**N**	**Percent**
Low Risk	391	58.6%
High Risk	276	41.4%
Total	**667**	**100%**

**Represents the number of unique patients in the current study resulting from pair wise deletion.*

4.2 Nutrition Support

Table 9 describes the proportion of patients that received either enteral feeding (oral or nasogastric) or total parental nutrition (TPN) at each of the timepoints. At diagnosis (Time 1), few patients were receiving any form of nutrition support with only .3% of patients receiving TPN and 1.9% receiving enteral nutrition. By Time 2, there is an increase in the number of patients receiving nutrition support with 6.8% receiving TPN and 11.5% receiving enteral nutrition, an expected finding due to the initiation of high-dose cancer therapy (table 1). By Time 3, few patients received enteral nutrition (3.8%) while no patients received TPN. The use of nutrition support was also reported by age group. Administration of nutrition support was most frequent among the youngest patients. At Time 2, 15.6% and 7.2% of patients 1-1.99 and 2-5 years old, respectively, were administered TPN. Administration of enteral feeds was also

more frequent among these age groups with 25% and 11.4% of patients, respectively, receiving enteral nutrition at Time 2. By Time 3, TPN was not administered to any participant however the use of enteral nutrition was still administered to a small percentage of participants.

Table 9.
Percentage of Patients Receiving Nutrition Support by Timepoint

Age Group	Time 1			Time 2			Time 3		
	TPN	Enteral Nutrition	No Support	TPN	Enteral Nutrition	No Support	TPN	Enteral Nutrition	No Support
1-1.99 years	0%	5.1%	94.9%	15.6%	25%	59.4%	*	*	*
2-5 years	0%	2.2%	97.8%	7.2%	11.4%	81.4%	0%	4.5%	95.5%
6-11 years	.7%	1.3%	98%	3.7%	9%	87.3%	0%	4%	96%
12-19 years	1%	2%	97%	7.1%	10.6%	82.3%	0%	2.2%	97.8%
Total	.3%	1.9%	97.8%	6.8%	11.5%	81.7%	0%	3.8%	96.2%

**No patients in this age group at Time 3*

4.3 Macronutrients

4.3.a Calories

Table 10 compares the mean caloric intake across three timepoints by gender and age group. Overall, mean intake of total calories was significantly different between the three timepoints (P=0.003). When evaluated by age group, children 6-11 years of age reported significantly different mean caloric intake values between the three timepoints (P=0.000). Among adolescents (12-19 years of age), mean caloric intakes were also different between the three timepoints (P=0.000), but only among males (P=0.002). In general, calories are lower at Time 3 as compared to Time 1 in children greater than or equal to six years of age.

Table 10.
Mean Caloric Intake by Timepoint and Compared to NHANES

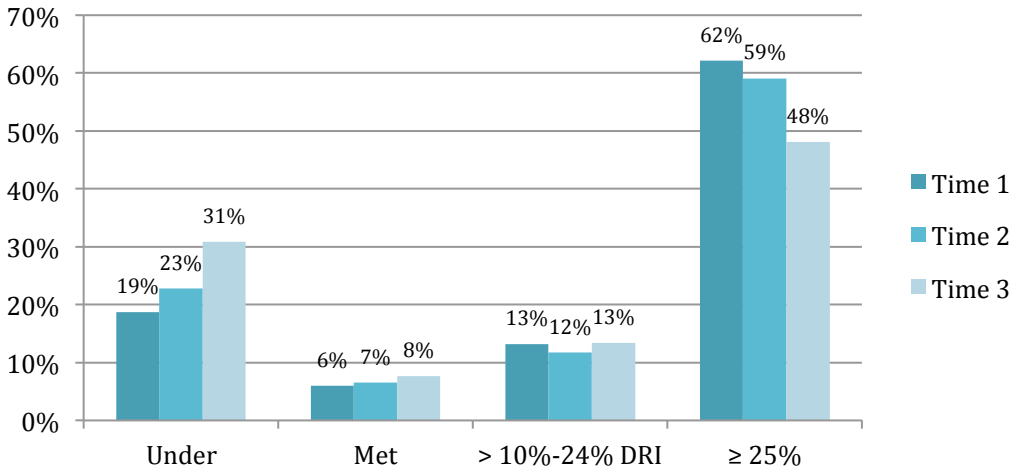
Age Group	N	Time 1		Time 2		Time 3		*P* Value	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	1896	29.8	1843	32.1	1782	30.1	*P*=.003	
Female	291	1839	44.5	1751	45.9	1721	43.4	*P*=.024	
Male	376	1940	40	1917	44	1828	41.2	*P*=.056	
1-1.99 years	50	1463	98	1423	97.5	1682	131.2	*P*=.148	*
Female	30	1330	120.5	1340	102.6	1683	178.8	*P*=.125	*
Male	20	1666	149.2	1567	193.2	1768	187.8	*P*=.613	*
2-5 years	352	1558	29.1	1557	36.7	1641	41.5	*P*=.135	
Female	152	1546	45.7	1504	55.1	1586	53.7	*P*=.451	1486
Male	200	1568	37.2	1598	49.3	1686	60.1	*P*=.179	1641
6-11 years	157	2441	52.4	2262	59.5	1990	50.7	*P*=.000	
Female	74	2527	78.6	2274	83	1975	81.9	*P*=.000	1879
Male	83	2363	68.8	2253	84	1992	62.1	*P*=.000	2092
12-19 years	108	2369	79.3	2373	82.4	2037	72.9	*P*=.000	
Female	35	2074	104	2130	128.8	1906	123.5	*P*=.262	1906
Male	73	2507	101.4	2497	100.4	2126	85.4	*P*=.002	2707

**For children 1-1.99, NHANES data not reported.*

Table 10 also presents mean caloric intakes reported by NHANES for children 2 years of age and older. Contrary to expectations, dietary intake both early on in the disease process (Time 1) and during treatment (Time 2 and 3) appears to be similar to normative values as reported by NHANES. Exceptions were for female children 6-11 years of age with higher intakes than normative values and 12-19 year old males with lower caloric intakes compared to normative values.

Figure 2 presents the proportion of patients below, meeting, or exceeding the DRI for calories. The majority of patients exceeded the DRI for calories by age and gender while a smaller proportion were below the DRI for calories (19 – 31%) at any given timepoint.

Figure 2.
Proportion of Patients Under, Meeting, or Exceeding DRI for Calories*



**Categorized by RDA by age, gender*

At Time 1, 6% of the population was meeting the DRI for calories whereas more than half of the patients (62%) exceeded the DRI by at least 25%. Conversely, nearly 20% were below the DRI for total caloric intake at diagnosis. The percentage of patients above the DRI by at least 25% or more of caloric intake was reduced from 62% to 48% by Time 3, an unexpected finding. This observation coincided with an increase in the proportion of patients under the DRI for calories by Time 1 to Time 3, 19% compared to 31%, respectively. There was a significant difference in the distribution of patients under, meeting, or exceeding the DRI for calories between Time 1 and Time 2 (P=0.016), Time 2 and Time 3 (P=0.000), and Time 1 and Time 3 (P=0.000). Patients tended to be in a higher category (e.g. consuming more calories) at Time 1 compared to Time 2 and 3 and Time 2 compared to Time 3.

Comparison to the DRI was also analyzed by age group (table 11). The finding that the majority of patients exceeded the DRI by at least 25% was also apparent across all age groups and at each

timepoint (25 – 81%). Despite the use of nutrition support, 13-29% of patients between one to five years of age were below the DRI, an alarming finding as this represents the time at which growth velocity is at its peak. The study also found that 58% of males 12 – 19 years old at Time 3 were under recommendations for calories.

Table 11.
Percentage of Patients Under, Meeting, or Exceeding DRI Calories by Age Group and Timepoint

	Under	Met	> 10%-24%	≥ 25%
Time 1				
1-1.99	13%	8%	10%	69%
2-5	21%	6%	15%	57%
6-11	6%	3%	10%	81%
12-19	32%	9%	13%	46%
Time 2				
1-1.99	28%	0%	16%	56%
2-5	24%	7%	12%	58%
6-11	14%	6%	7%	72%
12-19	29%	9%	16%	45%
Time 3				
1-1.99*	-	-	-	-
2-5	29%	5%	17%	49%
6-11	14%	10%	12%	63%
12-19	58%	10%	7%	25%

**No patients in this age group at Time 3*

4.3.b Fat

Overall, dietary intake of fat was not significantly different between timepoints (P=0.175) (table 12). When evaluated by age group, there were significant differences in fat intake between timepoints for males 1-1.99 (P=0.01), males 2-5 (P=0.01), and females 2-5 (P=0.003) years of age.

Table 12.
Mean Intake of Fat (grams) by Timepoint and Compared to NHANES*

Age Group	N	Time 1		Time 2		Time 3		*P* Value	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	64	0.39	69	0.47	64	0.48	*P*=.175	
Female	291	61	0.514	66	0.681	61	0.69	*P*=.223	
Male	377	66	0.57	72	0.65	66	0.57	*P*=.489	
1-1.99 years	50	50	1.2	52	1.4	55	1.2	*P*=.145	
Female	30	50	1.2	49	1.7	51	1.5	*P*=.201	**
Male	20	52	2.4	57	2.4	64	1.9	*P*=.010	**
2-5 years	352	54	0.46	60	0.62	54	0.68	*P*=.000	
Female	152	53	0.635	58	0.89	53	1	*P*=.003	52.2
Male	200	54	0.65	62	0.87	55	0.93	*P*=.010	58.4
6-11 years	157	79	0.96	83	0.96	78	1	*P*=.639	
Female	74	79	1.3	83	1.4	79	1.3	*P*=.692	71.6
Male	83	79	1.4	83	1.2	76	1.5	*P*=.183	79.4
12-19 years	108	82	1.1	85	1.3	81	1.2	*P*=.761	
Female	35	71	1.6	73	1.8	71	2.1	*P*=.612	72.3
Male	73	88	1.4	91	1.6	85	1.5	*P*=.685	100.9

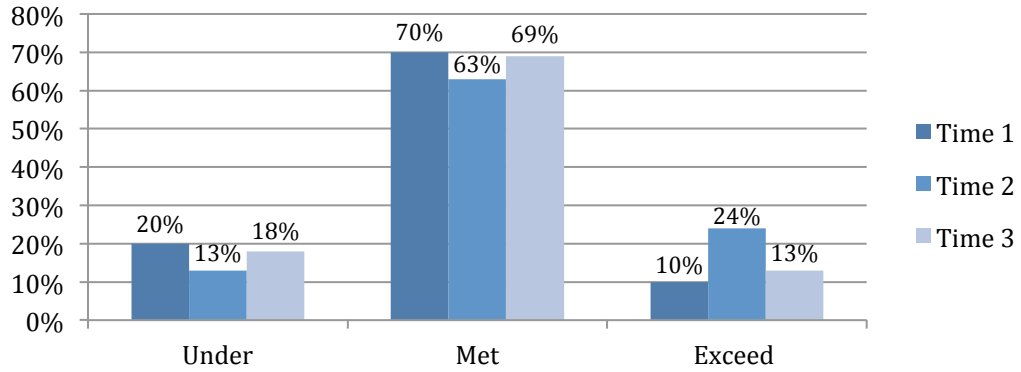
**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

The mean intake of grams of fat by the cohort was compared to normative values reported by NHANES. Dietary intake of fat was similar to normative values for all age groups except females 6-11 years and males 12-19 years of age. Mean intakes of fat were above normative values at Time 2, compared to Time 1 and Time 3. An exception were males 12-19 years of age, dietary intake of fat was lower than normative values at all timepoints.

Dietary intake of fat was also compared to the DRI (figure 3). The percentage of patients meeting the DRI decreased from Time 1 (70%) to Time 2 (63%) but returned to values observed at diagnosis by Time 3 (69%). An increase in the percentage of patients that exceeded the DRI was observed between Time 1 to Time 2, 10% compared to 24%. This observation was

statistically significant. Patients tended to be in a higher category at Time 2 compared to Time 1 (*P*=0.000). Patients tended to be in a higher category at Time 2 compared to Time 3 (*P*=0.000).

Figure 3.
Proportion of Patients Under, Meeting, or Exceeding DRI for Fat (% of Calories)*



* *Categorized by the AMDR*

The proportion of patients under, meeting, or exceeding the DRI for fat was further evaluated by by age group (table 13). At each timepoint and age group, most patients were within the recommended values for fat. However, dietary intake of fat above the DRI was most frequently reported at Time 2, with this most evident among older children compared to younger children. At the same time, nearly a third of patients particularly children less than two years of age were under the recommendations for fat at each timepoint.

Table 13. Percentage of Patients Under, Meeting, or Exceeding % of Calories from Fat by Age Group and Timepoint			
	Under	**Met**	**Exceed**
Time 1			
1-1.99	33%	64%	3%
2-5	30%	66%	5%
6-11	6%	79%	15%
12-19	4%	75%	21%
Time 2			
1-1.99	35%	61%	3%
2-5	17%	61%	22%
6-11	3%	71%	26%
12-19	4%	62%	34%
Time 3			
1-1.99*	-	-	-
2-5	27%	63%	10%
6-11	11%	75%	13%
12-19	8%	75%	18%

**No patients in this age group at Time 3*

4.3.c Protein

Among the cohort, significant differences for dietary intake of protein were observed (P=0.003); however, this appears to be due to changes in dietary intake of protein in males (P=0.006) not females (P=0.144) (table 14). By age group, significant differences were only observed for children between the age of 2-5 years (P=0.000). Although statistically significant, the differences at each timepoint reflected only one to three grams variations in daily protein intake, which would not be considered clinically meaningful.

Table 14.
Mean Intake of Protein (grams) by Timepoint and Compared to NHANES*

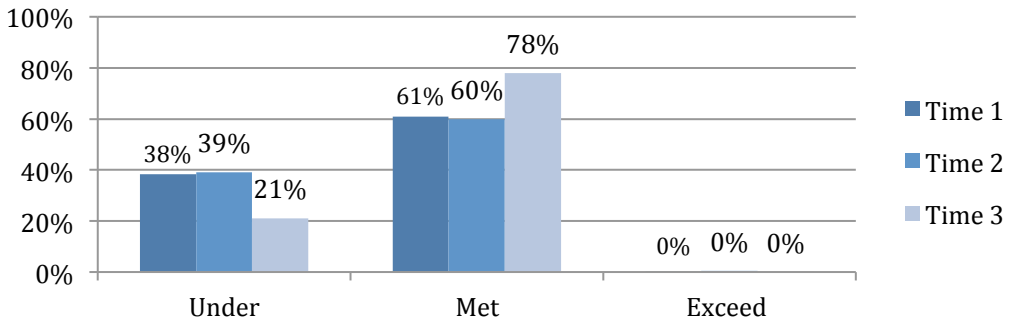
Age Group	N	Time 1		Time 2		Time 3		*P* Value	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall (cal)	667	70	0.47	72	0.52	72	0.62	*P*=.003	
Female	291	68	0.65	71	0.79	69	0.89	*P*=.144	
Male	376	72	0.67	74	0.68	74	0.84	*P*=.006	
1-1.99 years	50	55	1.4	58	3	55	1.9	*P*=.149	
Female	30	53	1.2	61	4.2	55	2	*P*=.332	* *
Male	20	58	2.7	58	2.5	60	1.9	*P*=.000	* *
2-5 years	352	58	0.5	60	0.6	59	0.76	*P*=.000	
Female	152	58	0.70	60	0.91	59	1.1	*P*=.000	51.9
Male	200	57	0.70	60	0.8	59	1	*P*=.004	56.3
6-11 years	157	90	1.10	92	1	93	1.6	*P*=.187	
Female	74	90	1.5	93	1.3	91	2	*P*=.720	63.4
Male	83	89	1.6	91	1.6	94	2.3	*P*=.077	70.9
12-19 years	108	90	1.4	92	1.3	91	1.6	*P*=.131	
Female	35	77	2.5	82	2.5	73	2.6	*P*=.040	64.2
Male	73	95	1.6	96	1.6	98	1.8	*P*=.109	99.1

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

In comparison to NHANES data, children and adolescents with ALL appear to consume more protein than normative data. This was most evident for children between 6-11 years of age in which mean intake of protein was consistently higher than normative values at each timepoint. Females, 12-19 years of age, were generally above (114-127%) whereas males 12-19 years of age were generally within normative values.

Despite intake of protein being above normative values, the majority of patients (60-78%) met the DRI at each timepoint with a smaller percentage (21-39%) under the DRI (figure 4). No intakes above the DRI were observed. Dietary intake of protein appears to be consistent at Time 1 and Time 2 but there is a significant differences in the distribution of patients under or meeting the DRI for all timepoints, Time 1 and Time 2 (P=0.03), Time 2 and Time 3 (P=0.00), and Time 1 and Time 3 (P=0.00). Patients tend to move from a lower to a higher category.

Figure 4.
Proportion of Patients Under, Meeting, or Exceeding DRI for Protein (% calories)*



* *Categorized by the AMDR*

4.3.d Carbohydrate and Fiber

Overall, intake of carbohydrates was significantly different between the three timepoints (*P*=0.027) (table 15). The differences between timepoints were only significantly different in children 2-5 years of age (*P*=0.000) in both females (*P*=0.000) and males (*P*=0.000). Similar to dietary intake of protein, significant differences in the reported mean intakes of carbohydrate were small and probably not clinically meaningful.

For most age groups, mean intake of grams of carbohydrates was near normative data based on NHANES. The exception was females between 6-11 years of age who reported intakes 20-25% above normative values.

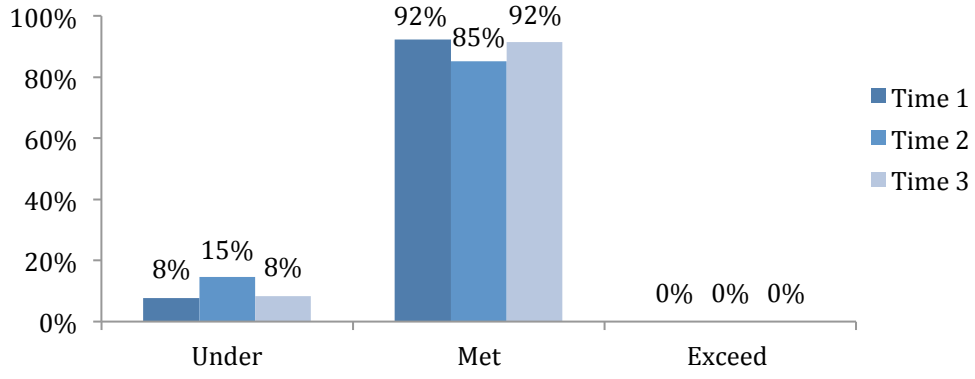
Table 15.
Mean Intake of Carbohydrate (grams) by Timepoint and Compared to NHANES*

Age Group	N	Time 1		Time 2		Time 3		*P* Value	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall (cal)	667	253	1.1	238	1.3	252	1.4	*P*=.027	
Female	291	244	1.50	230	1.9	243	1.9	*P*=.104	
Male	376	261	1.60	246	1.8	258	1.9	*P*=.248	
1-1.99 years	50	205	3.70	197	5.3	193	3.4	*P*=.249	
Female	30	191	3.40	183	6.8	184	2.9	*P*=.961	* *
Male	20	229	10.60	216	8.1	197	4.4	*P*=.000	* *
2-5 years	352	221	1.30	202	1.7	219	1.9	*P*=.000	
Female	152	214	1.8	197	2.4	212	2.8	*P*=.000	207
Male	200	228	1.9	207	2.3	223	2.6	*P*=.000	228
6-11 years	157	305	2.6	293	2.6	304	3	*P*=.280	
Female	74	315	3.7	303	3.8	313	3.9	*P*=.955	251
Male	83	297	3.5	285	3.6	298	4.5	*P*=.046	280
12-19 years	108	303	3.1	295	3.3	307	3.5	*P*=.460	
Female	35	269	4.9	258	5.3	274	5.4	*P*=.177	253
Male	73	318	3.9	310	4.1	321	4.4	*P*=.698	352

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

Mean intake of grams of carbohydrate was compared to the DRI for age and gender at each of the timepoints (figure 5). The majority of children and adolescents met the DRI for carbohydrate (85-92%). Significant differences in the distribution of patients who were under or met the DRI was observed between Time 1 and Time 3 (P=0.009), and Time 2 and Time 3 (P=0.003). No significant difference was observed between Time 1 and Time 2 (P=0.078).

Figure 5.
Proportion of Patients Under, Meeting, or Exceeding DRI for Carbohydrate (% calories)*



* *Categorized by the AMDR*

No significant differences in the intake of fiber (reported as grams of fiber) was observed for the cohort (*P*=0.082) (data not shown). Mean intakes of fiber was one to three grams above normative data for each age group. When fiber intake was evaluated by the percentage of patients meeting the DRI, most patients were not meeting recommended intakes for fiber. At each timepoint, 91%, 93%, and 94% were below the DRI (data not shown). No significant differences between timepoints were observed at any of the timepoints, Time 1 and Time 2 (*P*=0.307); Time 2 and Time 3 (*P*=0.353): Time 1 and Time 3 (*P*=0.160).

4.4 Micronutrients

4.4.a Antioxidants

Mean intakes of vitamin C were significantly different between the timepoints for the cohort (*P*=0.004). This was due to females (*P*=0.043), but not males (*P*=0.065) (table 16). In general, mean intakes of vitamin C were lower at Time 2 than Time 3. For children between

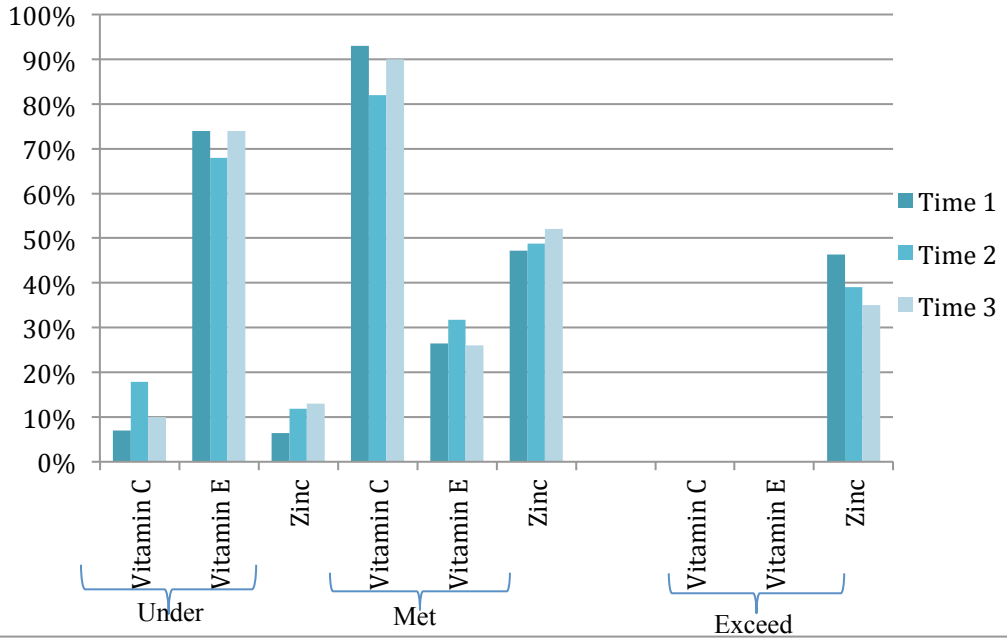
Table 16.
Mean Intake of Vitamin C (milligrams) by Timepoint and Compared to NHANES*

Age Group	N	Time 1		Time 2		Time 3		*P* Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	108	2.6	88	2.4	113	3	*P*=.004	
Female	291	104.4	3.9	81.9	3.4	107.3	4.6	*P*=.043	
Male	376	110.7	3.5	92.9	3.3	117.6	3.9	*P*=.065	
1-1.99 years	50	58.4	5.5	73.7	9.3	74.9	8.5	*P*=.041	
Female	30	60.1	6.7	75.8	13.5	69.7	10.5	*P*=.099	**
Male	20	55.3	9.4	74.6	8	89.2	12.3	*P*=.102	**
2-5 years	352	76	2.7	60.7	2.7	86.3	3.6	*P*=.081	
Female	152	75.4	4.2	57.1	3.8	79.9	5.1	*P*=.425	86.7
Male	200	76.2	3.4	63.6	3.7	91.8	5	*P*=.075	104
6-11 years	157	154.9	6.6	126.5	5.4	154.8	7.4	*P*=.262	
Female	74	164.6	9.6	127	7.3	169.6	11.2	*P*=.821	75.4
Male	83	147.3	9	126	8	142	9.6	*P*=.108	87
12-19 years	108	159.6	7.3	129.5	6.9	165	8.5	*P*=.629	
Female	35	133.9	13.7	99.4	10.8	157.6	16.4	*P*=.259	73.8
Male	73	170.3	8.6	140.9	8.5	169	10	*P*=.786	86.6

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

2-5 years of age, mean intakes at each of the timepoints were below (8-64% of reported values) normative values. However, for older children and adolescents, mean intakes were above normative values (125-156%) at each timepoint. When evaluated by the percentage of patients meeting the DRI (figure 6), patients tended to move from the met to the under category from Time 1 to Time 2 (P=0.000) and move back to the met category between Time 2 and Time 3 (P=0.001). There was not a significant difference in the distribution of patients by category between Time 2 and Time 3 (P=0.199).

Figure 6.
Antioxidant Nutrients
Percent of Patients by DRI Category*



** Under= Intakes below the RDA; Met= Intakes at the RDA but below the UL; Exceed= Intakes at or above the UL*

Mean intakes of vitamin E remained stable over the three timepoints and did not vary significantly over time (*P*=0.195) (table 17). Although significant differences were observed for some age groups and gender (table 16), no consistent themes appeared in the data. Similar to vitamin C, mean intakes were above those reported by NHANES at each of the study data points with this most evident in older children and adolescents (6-19 years of age). Dietary intake of vitamin E for some age groups were near double that of normative data.

Table 17.
Mean Intake of Vitamin E (milligrams) by Timepoint and Compared to NHANES*

Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	7	0.202	8	0.19	8	0.26	*P*=.195	
Female	291	7.1	0.32	7.1	0.25	7.2	0.39	*P* =.076	
Male	376	7.3	0.26	7.9	0.26	7.8	0.33	*P* =.351	
1-1.99 years	50	4.8	0.35	7.2	0.83	7.2	0.8	*P* =.904	
Female	30	4.6	0.52	5.4	0.84	5.8	0.72	*P* =.793	* *
Male	20	5	0.4	10.2	1.5	8.5	1.6	*P* =.006	* *
2-5 years	352	5	0.15	6.1	0.22	5.6	0.27	*P* =.218	
Female	152	4.8	0.26	6.1	0.37	5.8	0.52	*P* =.764	4.4
Male	200	5	0.16	6.1	0.29	5.5	0.28	*P* =.039	4.6
6-11 years	157	11.2	0.59	9.5	0.38	9.5	0.62	*P* =.180	
Female	74	12.1	0.89	10	0.5	9.3	0.94	*P* =.037	6
Male	83	10.6	0.79	9	0.59	9.7	0.78	*P* =.560	6
12-19 years	108	10.3	0.64	9.5	0.53	11.3	0.96	*P* =.121	
Female	35	10	1.3	7.1	0.48	9.2	0.99	*P* =.085	6
Male	73	10.3	0.7	10.4	0.71	11.9	1.3	*P* =.420	7.7

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

Despite intakes being above normative values, the majority of patients, 74%, 68%, and 74% at Time 1, 2, and 3, respectively, did not meet the DRI for vitamin E (figure 6). No patients exceeded the recommended values for vitamin E at any of the timepoints. A significant difference in the distribution of patients under or meeting the DRI was observed between Time 1 and Time 2 (*P*=0.014) represented by an increase in the percentage of patients meeting the DRI from Time 1 (26%) to Time 2 (36%). No significant differences were observed between any of the other timepoints for vitamin E.

For zinc, mean intakes were significantly different between timepoints (*P*=0.052) (table 18). When evaluated by age group, significant differences between timepoints was observed for

younger males aged 1-1.99 and 2-5, *P*=0.007; *P*=0.045, respectively. Mean intakes were also significantly different between timepoints for older females, 6-11 and 12-19 years of age, *P*=0.005; *P*=0.017, respectively. For each group, mean intakes at each timepoint exceeded those values reported by NHANES. Reported intakes in children with ALL were 10%-100% above normative values.

Table 18.
Mean Intake of Zinc (milligrams) by Timepoint and Compared to NHANES*

Zinc	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	12	0.21	11	0.12	12	0.26	*P* =.052	
Female	291	11.9	0.32	10.8	0.18	11.9	0.4	*P* =.136	
Male	376	12.3	0.284	11.4	0.15	12.5	0.35	*P* =.331	
1-1.99 years	50	8.7	0.3	9.2	0.38	9.3	0.45	*P* =.111	
Female	30	8.5	0.4	8.8	0.39	9.4	0.7	*P* =.657	**
Male	20	9	0.42	10	0.77	9.3	0.39	*P* =.007	**
2-5 years	352	9.2	0.11	9.5	0.14	9.8	0.25	*P* =.103	
Female	152	9.3	0.16	9.6	0.23	10.2	0.48	*P* =.202	7
Male	200	9.1	0.14	9.5	0.18	9.4	0.24	*P* =.045	8
6-11 years	157	17.4	0.64	13.7	0.28	15.4	0.7	*P* =.067	
Female	74	18	0.96	14	0.39	14.9	1	*P* =.005	9
Male	83	16.9	0.87	14	0.4	16.1	0.91	*P* =.288	11
12-19 years	108	15.7	0.72	13.5	0.31	16.4	1	*P* =.724	
Female	35	14.5	1.5	11.4	0.48	14	1.2	*P* =.017	9
Male	73	16.5	0.8	14.3	0.39	17.3	1.4	*P*=.962	13

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

High intakes of zinc were also reflected when the data was evaluated by the DRIs. At timepoints 1, 2, and 3, 46%, 39%, and 35% of patients exceeded the DRI for zinc, respectively (figure 6). More participants moved from a higher intake category to a lower intake category (e.g. moved from met/exceed to met/under) from Time 1 compared to Time 2 (*P*=0.000) and Time 1 to Time 3 (*P*=0.001). No significant difference between Time 2 and Time 3 was observed (*P*=0.188).

4.4.b B Vitamins

The study evaluated changes in mean intake between the three timepoints in B vitamins that included analysis of folate, pantothenic acid, niacin, thiamin, riboflavin, vitamin B6, and vitamin B12, adjusting for total caloric intake. Mean intakes are presented for the entire cohort and by age and gender.

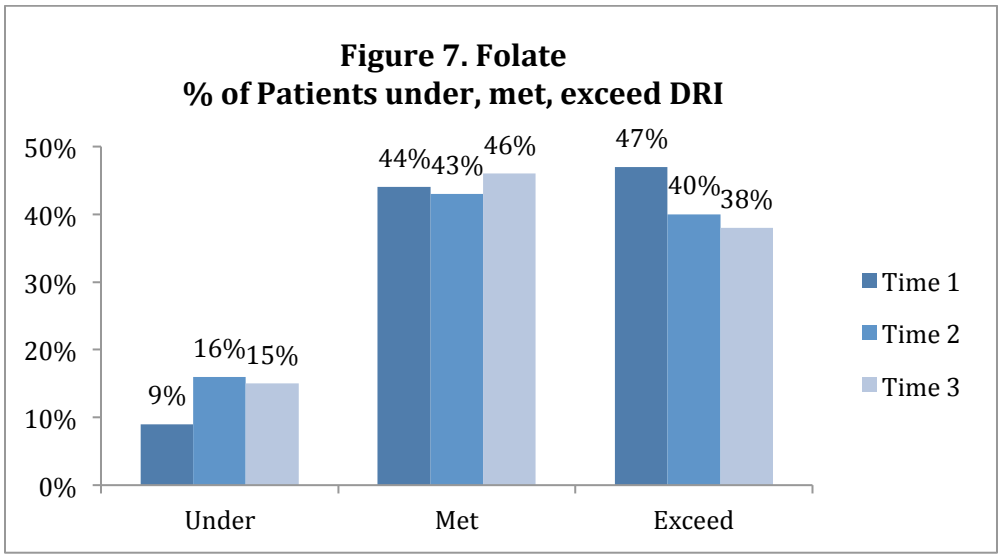
Fluctuations in the intake of folate are especially relevant for children with ALL due to the administration of anti-folate medications (methotrexate). Significant differences between timepoints were only found for children less than 2 years of age ($P<0.05$) with this only evident in females ($P<0.05$), not males ($P=0.603$) (table 19). When compared to normative data, mean reported intakes of folate were 11-22% below NHANES for younger children whereas older children were within at or near normative values, generally within 18%.

Table 19.
Mean Intake of Folate (micrograms) by Timepoint and Compared to NHANES*

Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	431	6.7	403	4.5	445	8.5	*P*=.383	
Female	291	424.6	10.3	390.9	6.8	432.2	13.4	*P* =.464	
Male	376	434.6	8.8	411.6	6.1	454.2	10.9	*P* =.704	
1-1.99 years	50	299.4	14.7	327.3	15	319.8	22.1	*P* =.035	
Female	30	291	22.5	314.1	20.6	349.9	27	*P* =.007	**
Male	20	307.9	22.1	346.5	23.1	303.2	29.4	*P* =.603	**
2-5 years	352	339.5	5.4	339.2	6	359.3	9.7	*P* =.227	
Female	152	345.4	7.8	342.5	9	359.9	16.6	*P* =.590	401
Male	200	334.1	7.4	337.4	7.9	358.9	11.2	*P* =.219	427
6-11 years	157	588.3	19.1	501.8	9.8	560.9	20	*P* =.152	
Female	74	613.2	28.6	505	15	556.6	32	*P* =.069	470
Male	83	568.5	25.6	501	13	567.5	24.2	*P* =.353	530
12-19 years	108	561.6	20.9	494.2	12.3	592.3	30.1	*P* =.748	
Female	35	515	45.2	426.3	17.6	496.6	39.5	*P* =.404	509
Male	73	585.3	22	523.8	15.5	628.1	39.2	*P* =.934	610

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

In comparison to the DRIs, 47%, 40%, and 38%, at each of the respective timepoints exceeded the recommended DRI for folate (figure 7).



** Under= Intakes below the RDA; Met= Intakes at the RDA but below the UL; Exceed= Intakes at or above the UL*

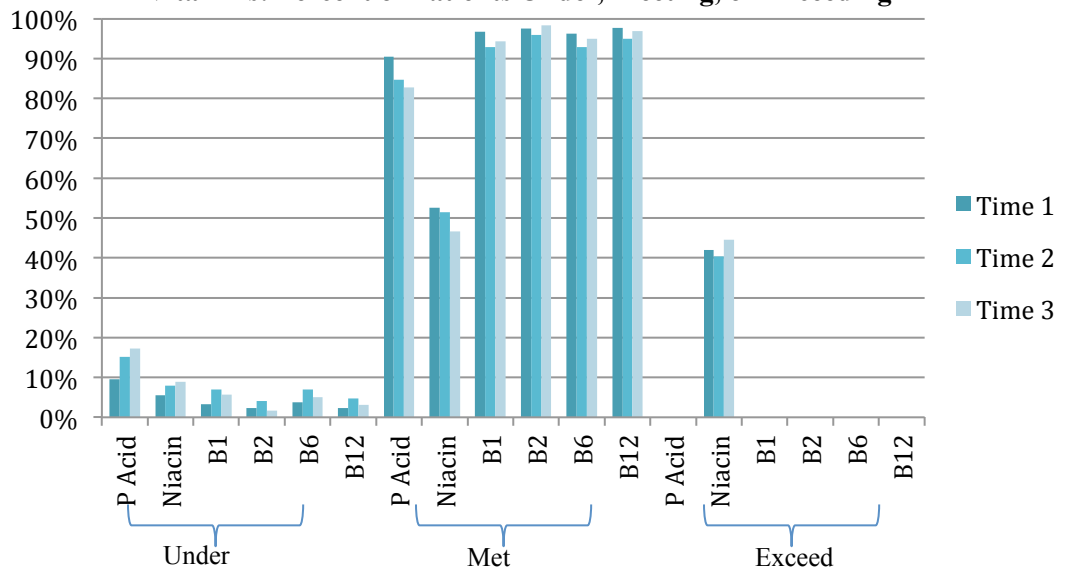
Participants tended to move from a higher to a lower DRI category from Time 1 to Time 2 (*P*=0.000). More patients were categorized in a higher DRI category at Time 1 compared to Time 3 (*P*=0.001). No significant difference was observed between Time 2 and Time 3 (*P*=0.828).

For the entire cohort, no significant differences between timepoints were observed for any of the B vitamins including pantothenic acid, niacin, thiamin, riboflavin, B6, and B12 (refer to Appendix F). While some significant values were observed for select age groups and timepoints, there was not a consistent theme in terms of gender or group identified within the class of B

vitamins. Mean intakes for males and females in all age groups were at or above those reported by NHANES.

In comparison to the DRIs, adequate intake of B vitamins was also reflected in the proportion of patients meeting the DRI for each nutrient (figure 8). As Figure 8 depicts, most patients were within the recommended DRI at each of the timepoints. Patients exceeded the recommended intake for niacin with 42%, 40%, and 45% of patients above the DRI at Time 1, Time 2, and Time 3, respectively.

Figure 8.
B Vitamins: Percent of Patients Under, Meeting, or Exceeding DRI



** Under= Intakes below the RDA; Met= Intakes at the RDA but below the UL; Exceed= Intakes at or above the UL*

4.4.c Bone Metabolizing Nutrients

For the cohort, mean adjusted intake of calcium was significantly different between timepoints (P=0.021) (table 20). Borderline significance was observed in males (P=0.055), not females

(*P*=0.285). When evaluated by age groups, significant differences were only observed for children 6-11 years of age (*P*=0.021), which was only evident for females (*P*=0.005), not males (*P*=0.650). Comparison of mean intakes to normative data revealed children 2-5 years of age, reported mean intakes within 5% of normative values. For children and adolescents between the age of 6-11 and 12-19, mean intakes were above those reported by NHANES with intakes 15-51% higher than normative values.

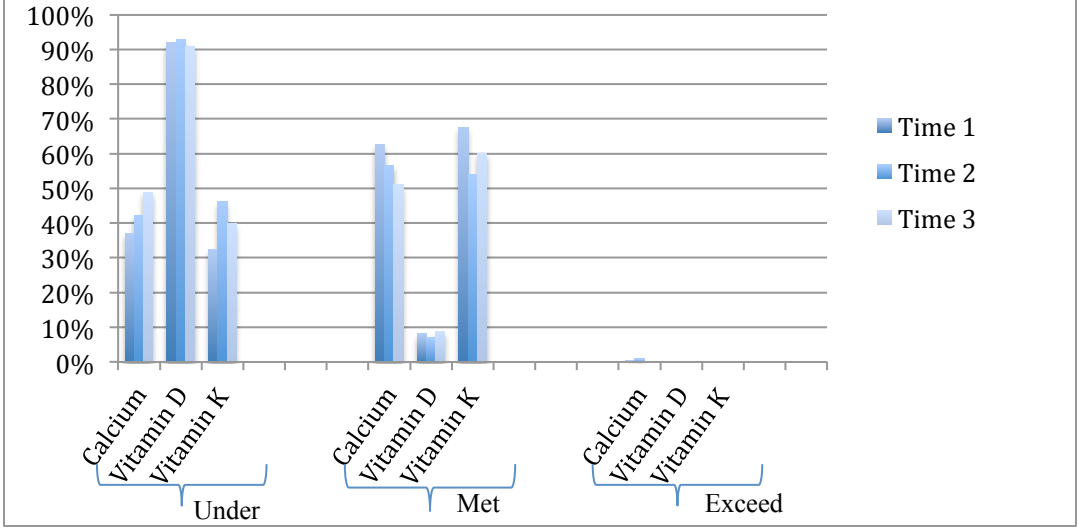
Table 20.
Mean Intake of Calcium (milligrams) by Timepoint and Compared to NHANES*

Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall (cal)	667	1097	12.40	1098	14.8	1115	15	*P* =.021	
Female	291	1079	18	1075	22.2	1076	22.7	*P* =.285	
Male	376	1111	17.1	1114	19.8	1144	19.9	*P* =.055	
1-1.99 years	50	932	54.9	1040	51.9	972	48.1	*P* =.282	
Female	30	908	65	1041	61.6	965	55.2	*P* =.182	**
Male	20	998	92.9	1006	88.9	1019	85.3	*P* =.370	**
2-5 years	352	991	14.8	959	19.9	1007	20.1	*P* =.562	
Female	152	993	21.70	948	29.1	996	30.7	*P* =.536	957
Male	200	987	20.10	967	26.9	1015	26.5	*P* =.143	1009
6-11 years	157	1303	28.40	1311	30.4	1307	33.4	*P* =.021	
Female	74	1318	41.2	1339	45.6	1287	47.4	*P* =.005	885
Male	83	1291	38.4	1289	40.5	1331	45.9	*P* =.650	1034
12-19 years	108	1210	34	1269	38.2	1238	40.6	*P* =.755	
Female	35	1079	56.5	1129	68.6	1015	70.8	*P* =.917	878
Male	73	1263	42.1	1329	45.6	1302	48.3	*P* =.247	1173

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

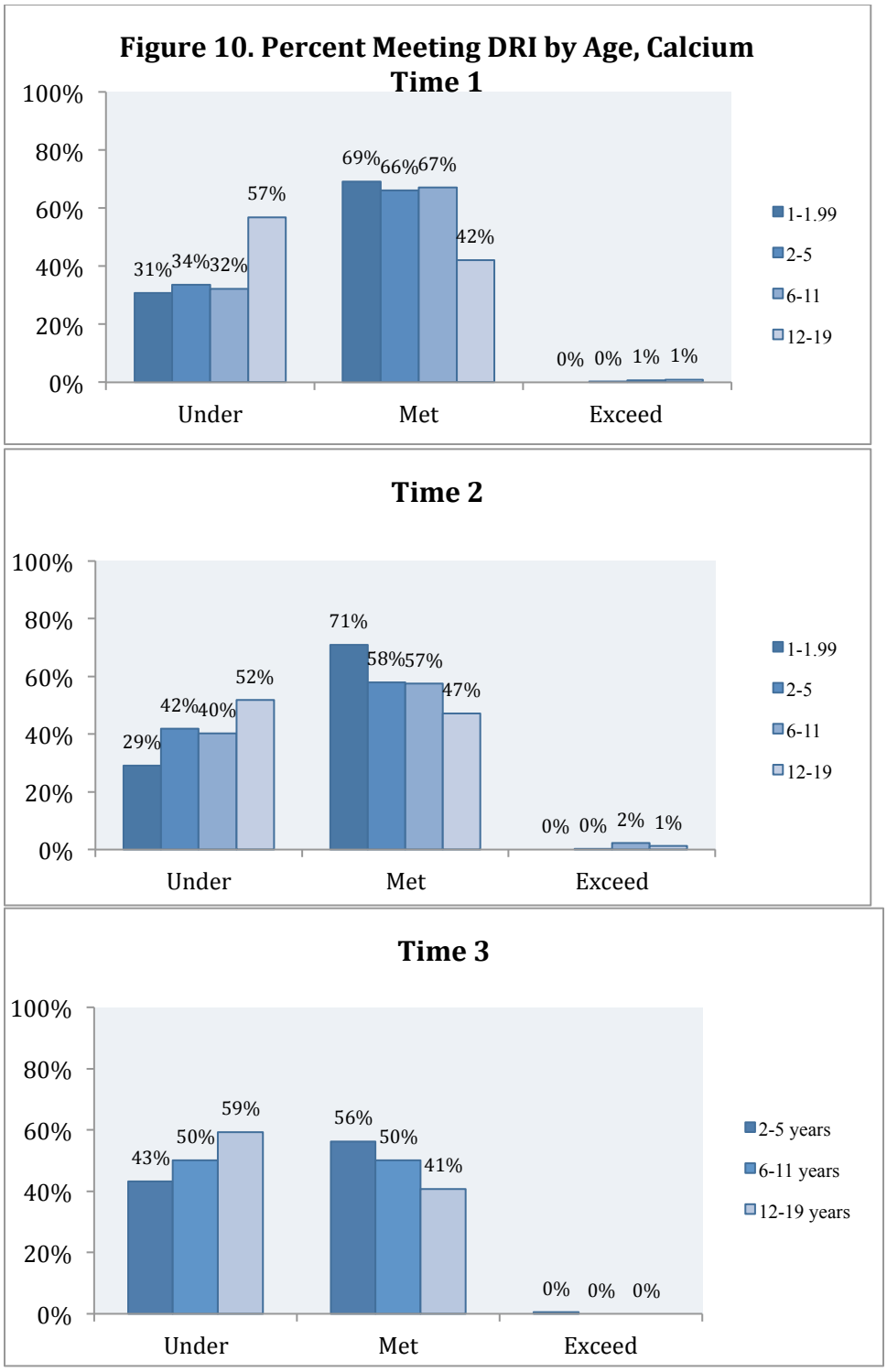
Comparison of intakes to the DRI for calcium revealed that the majority of patients did not meet the DRI for age and gender (figure 9). The data revealed that 37%, 42%, 49% at Time 1, 2, and 3, respectively were not meeting the DRI for calcium.

Figure 9.
Bone Nutrients Number of Patients by DRI Category



** Under= Intakes below the RDA; Met= Intakes at the RDA but below the UL; Exceed= Intakes at or above the UL*

There was a significant difference in the categorization of patients between Time 1 and Time 3 (*P*=0.000) and Time 2 and Time 3 (*P*=0.015). No significant difference in the distribution of patients was observed between Time 1 and Time 2 (*P*=0.032). A higher number of patients met the DRI for calcium at Time 2 compared to Time 3. More patients met the DRI for calcium at Time 1 compared to Time 3. Further analysis of calcium intake by age group revealed that deficiencies were observed at each group, with a higher percentage of adolescents 12-19 years of age below the DRI at each timepoint (figure 10).



* *Under= Intakes below the RDA; Met= Intakes at the RDA but below the UL; Exceed= Intakes at or above the UL*

For the cohort, mean intakes of vitamin D did not significantly fluctuate between timepoints (*P*=0.664), reflecting stable intakes of vitamin D over the course of ALL therapy (table 21). As observed with calcium, children between the age of 6-11 years of age reported significantly different mean intake between timepoints (*P*=0.004) however this was only significant for females (*P*=0.001), not males (*P*=0.254), an observation that was also found with mean intake of calcium. Mean intakes at each timepoint exceeded normative values for most age groups. Dietary intake of vitamin D among children with ALL was nearly two times normative data for most age groups and timepoints.

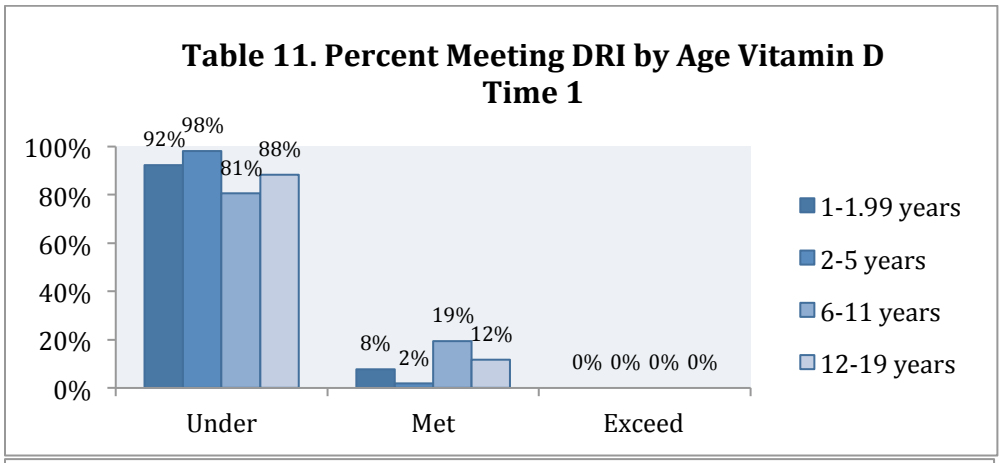
Table 21
Mean Intake of Vitamin D (internation units) by Timepoint and Compared to NHANES*

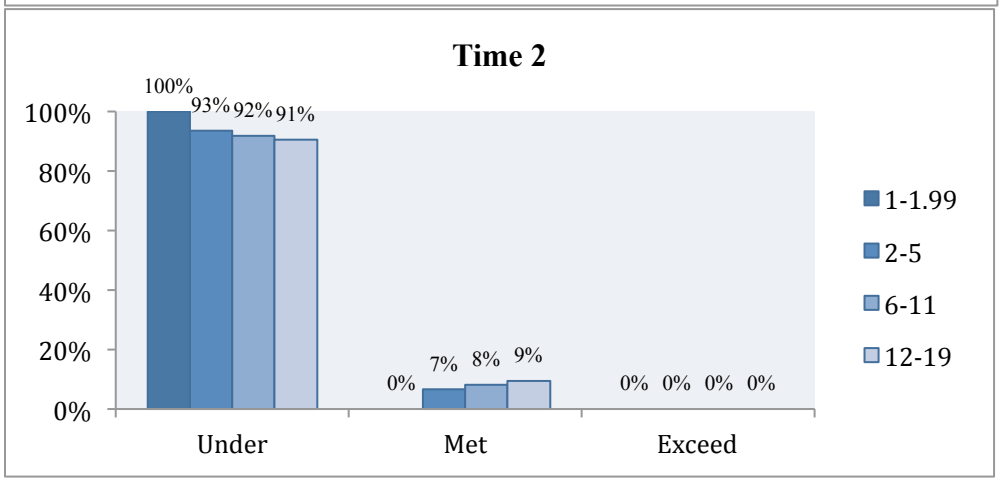
Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall (cal)	667	319.50	6.90	304	6.4	340.3	11.5	p=.664	
Female	291	316.6	10.7	299.8	9.9	333.7	16.9	p=.166	
Male	376	321.6	9.1	307.8	8.4	345.7	15.5	p=.947	
1-1.99 years	50	278.5	23.7	316.9	22.6	389.1	88.7	p=.587	
Female	30	278.9	28.1	328.2	30.4	286	24.5	p=.026	* *
Male	20	298.6	40.9	329.2	32	389	88.9	p=.138	* *
2-5 years	352	272.8	6.4	280	8.5	303.9	13.5	p=.235	
Female	152	271.00	9.40	278.3	13	332.9	25.9	p=.672	244
Male	200	272.80	8.60	281.4	11.3	281.5	12.7	p=.063	260
6-11 years	157	417.90	18.60	338.2	13.2	362.3	22.2	p=.004	
Female	74	432.7	28.7	337	19.3	347.5	30	p=.001	184
Male	83	406.4	24.3	340.5	18.2	379.9	31.3	p=.254	220
12-19 years	108	353.9	22.9	320.4	15.2	399.2	31.4	p=.731	
Female	35	336.9	46.9	306.1	32	321.7	41.4	p=.309	152
Male	73	361.2	25	327.8	16.8	424.6	40.8	p=.913	236

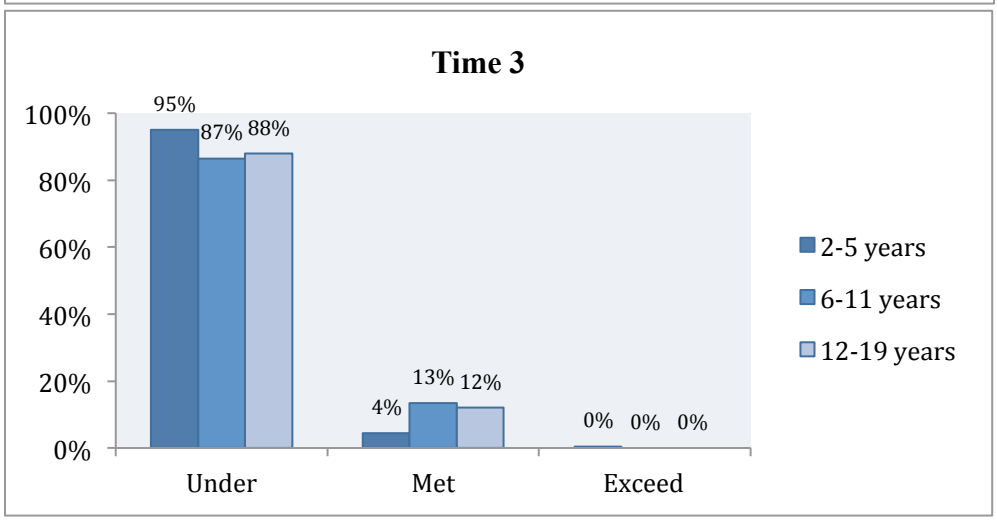
**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

However, the majority of patients were below the DRI for vitamin D (92% at Time 1, 93% at Time 2, and 91% at Time 3) (figure 8). No significant differences between any of the timepoints was observed which is likely due to minimal variability in the intake of vitamin D at each time.

As was observed with intakes of calcium, the distribution of patients under or meeting the DRI for vitamin D was similar across the age groups (figure 11).







** Under= Intakes below the RDA; Met= Intakes at the RDA but below the UL; Exceed= Intakes at or above the UL*

Finally, mean intakes of vitamin K revealed no significant difference in dietary intakes for the entire cohort (*P*=0.311) (table 22). Interestingly, females between 6-11 years of age reported significantly different mean intakes between the timepoints (*P*=0.011). Mean intakes for each age group were near or above values reported by NHANES. This was especially evident for children greater than or equal to 6 years of age. Mean intake for this group were two to three times the values reported by NHANES.

Table 22.
Mean Intake of Vitamin K (micrograms) by Timepoint and Compared to NHANES*

Vitamin K	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall (cal)	667	92.00	3.70	81.4	3.5	103.1	4.8	*P*=.311	
Female	291	84	4.6	75.3	4.7	96.6	6.7	*P* =138	
Male	376	98.6	5.5	86	5	108.2	6.6	*P* =.339	
1-1.99 years	50	57.9	6.9	46.5	6.4	48.9	6	*P* =.816	
Female	30	46.7	6.3	44.4	6.7	40	5.4	*P* =.527	* *
Male	20	72.9	17.2	54.5	15.4	58.9	11	*P* =.000	* *
2-5 years	352	54.6	1.9	45	1.9	58.5	2.9	*P* =.462	
Female	152	57.90	3.10	47.3	3.7	60.4	5	*P* =.601	44
Male	200	52.00	2.20	43.4	1.9	57.1	3.5	*P* =.628	54
6-11 years	157	129.50	9.20	128.1	9.4	156.7	12.1	*P* =.742	
Female	74	123.3	12.3	133.9	13.7	195.7	19.8	*P* =.011	48
Male	83	138.1	13.3	122.7	12.7	122.9	13.1	*P* =.083	52
12-19 years	108	170	15.7	146.8	14.2	224	20.2	*P* =.313	
Female	35	137.6	22.6	101.9	17.3	134.6	26.3	*P* =.658	59
Male	73	185.1	20.2	167.2	18.5	263.2	25.4	*P* =.177	76

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

Most patients met the DRI for vitamin K at each of the timepoints (figure 9). There was only a significant difference in the distribution of patients between Time 1 and Time 2 (*P*=0.000). More patients met the DRI at Time 1 compared to Time 2.

4.5 Summary of Results

Table 23 provides and overview of the summary of results observed for both macronutrients and micronutrients. For each nutrient category, the Table 23 highlights most important findings related to: 1) Mean nutrient intakes at each timepoint; 2) Nutrient comparison to normative data reported by NHANES, and 3) Nutrient comparisons of dietary intake to DRIs. Recommendations for future research and clinical implications of these findings will be presented in the following chapter.

Table 23.
Summary of Findings

Nutrient	Mean Intakes	Comparison to NHANES	Comparison to DRI
Macronutrient			
Calories	For the cohort, significant difference between timepoints. Significant difference in children 6-11 yrs., and males 12-19 yrs.	Time 1: Intakes higher (7-11%). Time 2: Intakes at or above (1-21%). Time 3: Intakes at or above (1-11%). Time 1, 2, and 3: Males, 12-19 yrs., below at each timepoint (8-22%).	At each timepoint: 60-70% exceed DRI. At each timepoint: 19-31% below the DRI. Percentage of patients below the DRI increased from Time 1 to Time 3.
Fat	For the cohort, no significant differences between timepoints. Mean intakes were highest at Time 2. Mean intakes were similar at Time 1 and 3.	Time 1, 2, and 3: Intakes at or near (4-10%). Time 1, 2, and 3: Males, 12-19 yrs., 11-14% below.	Time 1 and 3: Similar distribution in intakes under, met, and exceed. Time 1, 2, 3: 13-20% below the DRI. Time 2: Higher percentage exceeding DRI (24%).
Protein	For the cohort, significant differences observed. Differences not considered clinically significant.	Time 1, 2 and 3: Mean intakes for most age groups above, by at least 46%. Intakes above most apparent for children 6-9 yrs.	Time 1, 2, and 3: The majority of patients met the DRI, 61%, 60%, 78%, respectively. Time 1, 2, and 3: 38%, 39%, and 21%, respectively, were below the DRI.
Carbohydrate	For the cohort, significant differences observed. Differences not considered clinically significant.	Time 1, 2, and 3: Mean intakes were within 25% of normative values.	Time 1, 2, and 3: The majority of patients met the DRI, 92%, 85%, 92%, respectively.

Table 23. Continued

Nutrient	Mean Intakes	Comparison to NHANES	Comparison to DRI
Vitamin C	For the cohort, significant differences observed. Differences not considered clinically significant.	Time 1, 2, and 3: Intakes were below children 2-5 yrs. (8%-39%) Time 1, 2, and 3: In older children, intakes were at or near 2 times above.	Time 1, 2, and 3: 80-93% met the DRI. No patients exceeded the DRI. Small percentage under the DRI.
Vitamin E	Some significant differences observed. Differences were not considered clinically significant.	Time 1, 2, and 3: In all age groups, mean intakes were above (109-200%).	Time 1, 2, and 3: Majority under the DRI, 74%, 68%, 74%, respectively. No patients exceeded the DRI.
Zinc	Some significant differences observed. Differences were not considered clinically significant.	Time 1, 2, and 3: For all age groups, intakes were above (110-200%).	Time 1, 2, and 3: Most patients met the DRI, 47%, 49%, and 52%, respectively. Time 1, 2, and 3: Large proportion exceed DRI, 46%, 39% and 35%, respectively.
Folate	For most age groups, no significant differences were observed.	Time 1, 2, and 3: Intakes within 22% of normative values.	Time 1, 2, and 3: Large proportion met DRI, 44%, 43%, and 46%, respectively. Time 1, 2, and 3: Large proportion exceeded DRI, 47%, 40%, and 38%, respectively.
Niacin, Pantothenic Acid, Riboflavin, Thiamin B6, B12	For most age groups, no significant differences were observed.	Time 1, 2, and 3: Intakes were within normative values for each nutrient.	The majority of patients met the DRI for each B vitamin. Time 1, 2, and 3: A large proportion exceeded the DRI, 42%, 44%, and 45%, respectively.
Calcium	For the cohort, significant differences were observed. For most age groups, no significant differences were observed.	Time 1, 2, and 3: 2-5 yrs, were near normative values. Time 1, 2, and 3: All other groups were above (107-148%).	Time 1, 2, and 3: A large proportion were below DRI, 37%, 42%, and 49%, respectively. Time 1, 2, and 3: 63%, 57%, 51%, respectively, met the DRI.
Vitamin D	For the cohort, no significant differences were observed. Some age groups reported significant differences, no patterns were observed.	Time 1, 2, and 3: For all age groups, intakes were at or above (up to 2 times) normative values.	Time 1, 2, and 3: A large proportion were below DRI, 92%, 93%, and 91%, respectively.
Vitamin K	For the cohort, no significant differences were observed. Some age groups reported significant differences, no patterns were observed.	Time 1, 2, and 3: For all age groups, intakes were at or above (up to 2-3 times) normative values.	Time 1, 2, and 3: A large proportion were below DRI 32%, 46%, and 40%, respectively. The remaining met the DRI.

Chapter 5: Discussion

This chapter will present a summary and discussion of the results of this study. Implications for clinical practice and priority areas for future research will be presented.

5.0 Overall Summary

This study is the first prospective dietary study performed in a large cohort of children and adolescents receiving a uniform treatment for ALL. The study was successful in demonstrating the acceptability and feasibility of performing dietary assessments at systematic timepoints in therapy at multiple institutions. Response rates were reasonable and similar to other studies that assessed diet in cancer patients (Schatzkin et al., 2009).

Findings from this study did not support the hypothesis that the majority of children and adolescents with ALL have total calorie intakes below the DRIs. Contrary to expectations, we found that the majority of patients exceeded the DRI for total calories at all three time points. These findings suggest that, despite receiving anticancer therapy, most children and adolescents with ALL were still able to consume adequate calories.

At the same time, there were a small proportion (19% to 31%) of patients who were below the DRI for total calories and this proportion increased over the course of therapy. This was especially evident for males 12-19 years of age who went from 29% at Time 2 to 58% at Time 3 below the DRI for calories. Subsequent analysis revealed that the majority of these individuals were not receiving total parental nutrition or enteral nutrition support. These findings underscore

the need for careful monitoring of dietary assessment throughout all phases of treatment for ALL as this subgroup of individuals may be at particularly high risk for malnutrition.

Similar to calories, a small proportion of patients were below the DRI for fat and protein, although the majority of patients met the DRI for these macronutrients. There was an interesting finding for fat such that nearly one-quarter of patients exceeded the DRI at Time 2 (high dose phase of therapy). Although practitioners would not likely advise patients to decrease fat intake at this phase of treatment, this may be an opportunity for clinicians to educate families on healthy sources of dietary fat, particularly since children and adolescents with ALL are at increased risk for obesity and cardiovascular disease.

For micronutrients, findings suggest that special attention is warranted for dietary intake of vitamin E, zinc, niacin, folate, calcium, vitamin D and vitamin K in patients with ALL. Dietary intakes in excess of the DRI (i.e. intakes above the ULs) were noted for zinc and niacin in a large proportion of patients. In contrast, dietary intakes were below the DRI for calcium, vitamin D, vitamin K and vitamin E in the majority of patients despite a significant proportion of the population exceeding the DRI for calories.

For folate, it was unexpected that nearly half of children and adolescents with ALL exceeded the DRI at Time 1. The percentage of patients exceeding the DRI decreased over time, which may reflect avoidance of folate-rich foods while on anti-folate medications. This is a dietary counseling approach that is based upon individual clinical practice rather than standardized guidelines. Dietary folate will need to be evaluated within the context of serum folate and

genetic polymorphisms in folate-metabolizing enzymes as these are significant factors in the bioavailability and metabolism of folate (Robien, 2005). For all other B vitamins, no noteworthy observations were found.

This is the first cohort study to compare dietary intakes in a large population of children and adolescents with ALL to normative values reported by NHANES. The hypothesis that dietary intakes in children undergoing treatment with ALL will be different than that of normative data due to receiving cancer therapy was not supported. This study found that, in general, dietary intake of macronutrients and micronutrients in ALL patients were similar to normative values implying that cancer or its treatment does not alter dietary intake in children with ALL. In many cases, mean reported intakes of micronutrients were above normative values.

The finding that the majority of patients are consuming greater than 25% of the recommended calories for age yet deficiencies in key nutrients are still observed suggests that better effort must be placed on the nutrition management of children and adolescents with ALL. These findings suggest potential priority areas for nutrition education and intervention. The effect of these future interventions on the development of therapy-related side effects and survival will be essential to forming nutrition guidelines specific to children with ALL.

5.1 Macronutrients

The results of this study begin to provide an understanding of changes in macronutrient intakes among children and adolescents undergoing treatment for ALL. To date, the ability of clinicians to design and test dietary interventions has been limited due to the lack of descriptive data

exploring the timing and degree of fluctuations in the diet throughout treatment for ALL. This study has helped to close this gap in science.

5.1.a Calories

In this study, children and adolescents with ALL tended to be below or above the DRI for calories with a small percentage of patients within the recommended guidelines.

This study found that a moderate percentage of patients are not meeting the DRI for calories, a finding that has been reported in previous studies (Bond et al., 1992; Delbecque-Boussard et al., 1997). These findings are important in that they suggest that a select group of children and adolescents with ALL may be at increased risk of malnutrition. Subsequent analysis of the current data set revealed that the children below the DRI for calories were least likely to receive enteral support. These findings imply that consistent dietary assessment throughout all phases of therapy is a necessary component of supportive care in order to minimize the risk of malnutrition especially as the *duration* of malnutrition is adversely linked to survival in children with ALL (Orgel et al., 2011). Supplementation with advanced nutrition support such as enteral feeds should be considered for children and adolescents with persistent dietary intake below the DRI, especially in children with clinical confirmation of malnutrition.

This study also found that caloric intake in the majority of patients exceeded the DRI at all timepoints, a finding that is supported by some studies (Halton et al., 1998; Reilly, 2001) but not others (Bond et al., 1992; Delbecque-Boussard et al., 1997). Two important conclusions may be drawn from this finding. The first is that children and adolescents with ALL are consuming excess calories prior to the initiation of cancer therapy (Time 1). Prior to this study, caloric

intake was assumed to be within the recommended range at the initiation and during the early phases of treatment. Increased caloric intake was assumed to occur over the course of therapy. These common assumptions by clinicians were supported by numerous studies describing increases in weight over the course of therapy combined with small studies reporting excess calorie intake during *low dose phases* of therapy. Clinicians hypothesized that prolonged exposure to steroids may lead to dietary behaviors that are associated with excess calorie intake. This study refutes these assumptions. The finding that caloric intake for most age groups is within 10% of normative data at all timepoints does not lend support that children with ALL are eating differently than 'healthy' children residing in the United States. Additionally, children with ALL are consuming excess intakes at diagnosis, supporting the idea that this behavior (i.e. consumption of increased calories) is not learned over therapy. Combined, this suggests that other factors are likely influencing dietary intake that may or may not be the cause of weight gain during therapy for ALL.

The second conclusion that may be gleaned is that while the majority of patients exceeded the DRI for calories during therapy, the proportion decreases rather than increases over the course of therapy, a findings that did not confirm the hypothesis of the current study which was that dietary intake increases rather than decreases over therapy. The reduction in the percentage of patients exceeding the DRI for calories from Time 1 to Time 3 may be related to reduced physical activity rather than the cancer therapy itself. This may be especially relevant for older children who are often advised to avoid sports activity during cancer therapy. Previous studies have reported an association between increased weight during therapy and reduced physical activity (Reilly et al., 1998; Warner et al., 1998). The increase in children who are below the DRI

at Time 3 may be a response to the reduction in physical activity by eating less. The well-documented increase in children who are overweight or obese during therapy may be due to an insufficient reduction in total calories thus not adequately compensating for the reductions in physical activity during treatment. Adolescent males may be especially vulnerable to fluctuations in physical activity due to the avoidance of organized sports during treatment for ALL. Reduced activity that resulted in a reduction in caloric intake may explain the pronounced increase in adolescent males below the DRI for calories at Time 3. It is also plausible that less attention to dietary intake is placed on adolescent males who may be less inclined to discuss nutrition-related issues with family members or clinicians. A combination of factors is likely influencing the clinical picture. Future studies may consider the inclusion of measurement of physical activity into the lifestyle assessment of children and adolescents with and survivors of ALL to gain a better understand of the interaction of these variables.

5.1.b Fat

This study was the first to explore fluctuations in dietary fat intake over the course of therapy in children with ALL. A small percentage of patients at each timepoint were below the DRI for fat. In light of the increased risk of cardiovascular disease and obesity in this patient population, dietary counseling augmenting fat intake among these patients is not clinically indicated. It is plausible that lower intakes of fat may benefit this population and serve to prevent subsequent weight gain. Lower intakes of fat may also serve to prevent the development of nutrition-related side effects, such as hypertriglyceridemia, that may be fostered by excess intake of dietary fat. This study found that a small percentage of patients exceeded the DRI for fat. An increase in the percentage of patients exceeding the DRI for fat at Time 2 is a reasonable observation that is

likely associated with high-dose steroids (Time 2). This observation highlights a teachable moment for clinicians to counsel patients on healthy sources of dietary fat. Dietary intake of fats that are high in unsaturated fat may be of benefit in relation to cardiovascular risk factors associated with treatment for ALL. Dietary education during timepoints in therapy in which patients are at highest risk for nutrition-related conditions may be a cost effective intervention that may also empower families to take an active role in their child's health during treatment.

5.1.c Protein

Previous studies have reported higher intakes of protein among children with cancer compared to recommended values (Delbecque-Boussard et al., 1997; Halton et al., 1998). In the current study, patients did not exceed the DRI at any timepoint with the majority of patients within the DRI for protein. It can be concluded from this study, that most children and adolescents with ALL are within the DRI for protein for each of the timepoints. Although intakes were above normative data, the data does not suggest a concern as no patient met the upper limit for protein at any of the evaluated timepoints. The strengths of the current study design, in comparison to previously reported data, support the findings of the current study.

This study also found that nearly 40% of patients are below the DRI for protein, a figure that has not been previously reported. This was observed during earlier phases of therapy compared to later phases. Emphasizing diets high in protein or providing dietary counseling on strategies to increase intake of protein may be necessary early on in therapy, but not during later phases of therapy among a select group of patients.

5.1.d Carbohydrate

This study found that the majority of patients met the DRI for carbohydrate and were near normative values. This study did not explore the contribution of simple and complex carbohydrates or the glycemic index in the diets of children with ALL, areas that are open for future exploration. Understanding these variables may provide a therapeutic opportunity for the management of medication-induced diabetes, a condition that is encountered by approximately 15% of children with ALL during the first month of therapy (Koltin et al., 2012). Among survivors of ALL, aberrations in glucose metabolism have also been described (Surapolchai et al., 2010). In both of these clinical circumstances, the role of diet, especially variations in dietary intake of carbohydrates, is not known. Until more is understood, dietary counseling should reflect that of healthy children and emphasize a diet that is plentiful in complex carbohydrates from a variety of food sources.

5.2 Micronutrients

Three classes of micronutrients were investigated due to their potential association with therapy-related side effects: antioxidants, B vitamins, and bone-metabolizing nutrients.

5.2.a Antioxidants

Mean intakes of vitamin C were similar to previously reported data in children with ALL (Kennedy et al., 2004) in that around 10% of children were found to be below the RDA for vitamin C. This was a surprising finding as vitamin C is a common self-prescribed supplement during cancer therapy (Kelly et al., 2000). This study did not provide evidence that children with ALL are being exposed to excess intakes of vitamin C at any timepoint. Kennedy *et al.* found

that higher intakes of vitamin C were associated with reduced therapy-related side effects such as suppressed immune system. Subsequent analysis of the current data set will aim to confirm or refute these findings. If a benefit of higher intakes of vitamin C are observed, the implications for dietary counseling may be to consider educating families on foods rich in vitamin C as well as encourage the use of supplementation for a select group of patients. However, until these data are available, dietary strategies focused on increasing intake of vitamin C for those patients below recommendations does not seem warranted.

In contrast to vitamin C, the majority of patients were below the DRI for vitamin E. This study found that the percentage of patients below the DRI for vitamin E is higher than previously reported. The higher incidence in the current study is likely due to different reference values between the two studies (Kennedy et al., 2004). The observation that mean intake of vitamin E were above normative data for each age group and timepoint suggests that this is not a consequence of treatment for ALL. Although low intakes of vitamin E are lower than the DRI, they appear to be reflective of children and adolescents residing in the United States.

Low dietary intake of vitamin E may be of particular concern as reduced intake may exacerbate side effects associated with cancer therapy. For example, depleted levels of vitamin E have been associated with the development of neuropathy, a side effect often observed in children with ALL, especially among older patients (Weijl et al., 1998). Supplementation of vitamin E appears to reduce the incidence of neuropathy (Argyriou et al., 2006). Among children with ALL, greater intakes of vitamin E were associated with reduced infection (Kennedy et al., 2004). The observation that intakes below the DRI were found in the majority of patients underscores the

importance of dietary counseling emphasizing dietary sources of vitamin E such as wheat germ, nuts, broccoli, spinach, and tomato. Supplementation may be indicated if dietary intake is not feasible. Future studies should explore the efficacy of improved intakes on therapy-related side effects, particularly as they relate to vitamin E.

Finally, dietary intake of zinc did not reflect that of vitamin C or vitamin E. An unexpected finding of the study was that a large percentage of patients exceeded the DRI for zinc. The results of this study found that a smaller percentage of patients were below recommended values compared to previously reported data. Sgarbieri *et al.* reported that 24% of Brazilian children undergoing treatment for ALL were below the RDA for zinc (Sgarbieri et al., 1999). Whether this is representative of children residing in the United States is unknown. Dietary intakes above the DRI may be linked to higher intakes of protein as protein intake for the cohort was also consistently above normative values, a finding that was also observed for zinc.

The ramifications, if any, of dietary intake of zinc that exceeds the DRI are unknown. Previous studies have linked decreased serum zinc concentrations with the development of cancer (Alam et al., 2012; Chan et al., 1998) and reduced zinc levels have been associated with the malignant process, thus increased intakes may be compensatory (Gokhale et al., 2007). This study did not collect biological markers of nutrients, thus it is unknown if elevated dietary intake of zinc manifested into elevated serum zinc levels. This is an area that requires further investigation.

5.2.b B-Complex Vitamins

This study is the first study to report on dietary intake of B-complex vitamins during treatment for ALL. With the exception of folate, this investigation was exploratory. For most B vitamins, the ramifications of dietary intakes below or above the RDA among children with cancer are unknown. Supplementation with B vitamins has provided a clinical benefit in select groups of patients, particularly those at increased risk for neuropathy (Ang et al., 2008; Ozyurek et al., 2007). Whether supplementation is beneficial only in patients with low dietary intakes or deficiencies of B vitamins as evidenced by serum analysis remains unknown. This study found that a small percentage of patients were below the RDA for select B vitamins. A previous study performed in healthy children found that 0-10% of healthy children were below the estimated average requirement (EAR) for select B vitamins (Suitor et al., 2002). While this study found that a higher percentage were below the RDA, the reference values between the two studies are not comparable.

Investigation of folate is especially important within the context of ALL therapy as anti-folate drugs are an integral component of treatment. Dietary intakes in excess of the RDA may be related to increased demand of folate due to the leukemic process. Conversely, patients may also be compensating for reduced folate status due to the methotrexate-containing regimen. However, the finding that children tended to be in a higher RDA category at Time 1 compared to Time 2 and 3 suggests that the administration of anti-folates does not precipitate increases in dietary intake. Elevated intakes may mirror that of healthy children due to the fortification of the US food supply in 1998 as was also evidenced by mean intakes of the cohort were reflective of normative values. This legislation has demonstrated success in improving blood folate levels among adults and children (Quinlivan et al., 2003).

The reduction in the percentage of patients that exceeded the RDA over time for folate may be related to dietary counseling advising patients to avoid folate-rich foods or folate-containing supplements during treatment. The assumption that the increased intake of dietary folate will reduce the efficacy of anti-folate medications is a theoretical concern, despite preliminary evidence suggesting that supplemental intakes are safe among children with ALL (Ladas et al., 2003). Until a thorough assessment can be done of folate status that includes assessment of dietary intake, serum folate concentration, and polymorphisms in folate-metabolizing, it appears that it is prudent to continue to avoid supplementation with folate until evidence supporting or refuting high or low dietary intake of folate is obtained.

5.2.c Bone Metabolizing Nutrients

Bone morbidities are a significant therapy-related side effect in children and adolescents with ALL, with up to 21% of patients experiencing reduced bone density, a figure that exceeds the prevalence of 5% among healthy children (Kaste et al., 2001). While previous studies have explored intake of bone-metabolizing nutrients after completion of therapy (Tylavsky et al., 2010), this study is the first to report on dietary intake of bone-metabolizing nutrients during treatment for ALL. This study provides the first line of evidence that dietary intake of bone-metabolizing nutrients at diagnosis and during therapy are below the RDA for most children and adolescents with ALL.

The percentage of patients below the RDA was higher among this cohort compared to previous report among survivors of ALL, likely due to increased attention to supplementation upon cessation of treatment (Tylavsky et al., 2010). However, the findings from the current study are

in line with other studies that have reported on dietary intake of vitamin D and calcium in young children (1-6 years of age). Salvo, *et al* reported that 95% of Hispanic children and 97% of African-America were below the RDA for vitamin D and 31% and 38% were below the RDA for calcium, respectively (Salvo et al., 2012). Dietary intake in that study was collected with a food record lending strong support for the data obtained from the current study. In the current study, the observation that mean intake of bone-metabolizing nutrients were above those reported by NHANES at each timepoint may suggest that clinicians and parents are aware of the risk of bone depletion and that clinicians may be providing dietary counseling emphasizing increased intake of bone-metabolizing nutrients while parents may also be self-prescribing dietary supplementation of bone metabolizing nutrients.

Dietary deficiencies in bone-metabolizing nutrients have significant research and clinical implications both during and after cancer therapy. First, these results endorse the support for proactive dietary counseling at diagnosis and during therapy. Children and adolescents should be counseled on strategies to increase intake of vitamin D, calcium, and vitamin K. Supplementation of bone-metabolizing nutrients should be incorporated into the armamentarium of nutrition interventions, as diet alone may not be sufficient to compensate for low dietary intake. When available, dietary interventions should incorporate biological markers of vitamin status such as vitamin D3 to ensure interventions ensure adequate dosing and effectiveness at improving biological markers of vitamin D. Special attention should be placed on adolescents, as bone accretion is most active in this age group.

5.3 Other Considerations

The current study classified dietary intake as below, met, or exceed the RDA by comparing mean intakes obtained from the FFQ to the RDA for age and gender. Another component of the DRI, the estimated average requirement (EAR), was designed to identify deficient intakes in populations and is the median distribution for population requirements (Kennedy et al., 2005). The EAR was developed to prevent nutrient-induced deficiencies rather than to prevent disease in populations. The EAR is a *minimum requirement* for a group of similar individuals and is applied with the understanding that half the population will require dietary intakes above the established EAR (Yates, 2006). In contrast, the RDA is designed to meet the needs of 97.5% of the healthy population. On average, the RDA is about 20% higher than the EAR for each nutrient, two standard deviations above the EAR. This figure is also not designed to meet populations who are at risk for nutrition-related morbidities but is set as the reference point for individual daily nutrient intakes and is the reference value used when performing individual dietary assessment.

Controversy as to which reference value is best suited for the evaluation of populations has been previously described, yet neither address the best reference value for populations at increased risk for nutrition-related morbidities (Otten et al., 2006; Yates, 2006). Children with ALL are at increased risk for many nutrition-related conditions such as heart disease, osteoporosis, and metabolic disorders. The goal of this study was to highlight priority areas for potential intervention and thus maximize the proportion of patients at risk for deficiencies. In performing the analysis in this manner, an overestimation of children and adolescents below the RDA (versus below the EAR) is likely to occur (refer to Appendix D). A post-hoc analysis of the cohort was conducted explore the proportion of children and adolescents classified as under or

over the DRI as defined by the EAR. While the percentage of patients under the DRI was tempered, dietary intakes below the DRI was still observed in the majority of children and adolescents. For vitamin D, on average across timepoints, 50% of the population was below the EAR compared to slightly over 90% below the RDA for vitamin D. Similar differences were observed for folate, calcium, and most antioxidants. Evaluation of the reported dietary intakes by both the RDA and EAR resulted in similar conclusions however the application of the EAR lessens the magnitude of the need for proactive, systematic nutrition intervention. In developing both the RDA and EAR, neither value considers the unique risk factors attributed to children with ALL. By using the EAR, the magnitude of children and adolescents that may benefit from proactive counseling is lessened while the risks for reduced quality of life and increased medical costs are elevated. With increased attention focused on individualized medicine, it seems reasonable to modify the reference point used for comparison among this cohort as they represent a unique population that is more aligned with the objectives of the RDA rather than the EAR.

5.4 Strengths and Limitations

The study has several limitations. In the current study, administration of the FFQ was administered due to the feasibility of its administration within a multi-site study. The FFQ was designed to be self-administered, which was especially relevant for institutions without access to a trained dietitian or adequate research staff to administer the survey in-person. However, the use of an FFQ may result in over-reporting of dietary nutrients. In this study, over-reporting appears to be limited based upon a number of comparisons. First, nutrient intakes obtained from this study were similar to previous dietary studies performed in children with ALL that collected

diet information with the both a FFQ and 24-hour recall (Kennedy et al., 2004). Second, for several nutrients, the observations were similar to other studies performed in children with cancer (Delbecque-Boussard et al., 1997; Halton et al., 1998; Kennedy et al., 2004). In comparison to the current study, the three aforementioned studies collected dietary data with a 24-hour recall, 3-day food record, and food frequency questionnaire combined with a 24-hour recall, respectively. Third, a previous validation study for the YAFFQ found that males tended to report values under NHANES while females were more often above NHANES, an observation that was also observed in the current study (Rockett et al., 1997). Finally, the percentage of patients below the RDA for vitamin D was within 1-3% of a study that compared intakes among healthy Hispanic or Africa-American school age children to the RDA (Salvo et al., 2012). Similar observations were found for calcium and vitamin E (Suitor et al., 2002). Taken together, these comparisons lend support to the findings of this study and suggest that either over- or under-reporting was comparable to previously published studies.

The study utilized the optimal tool for dietary analysis of a large cohort. An FFQ was selected due to the reasonable cost and previous experience with the instrument on behalf of the investigative team. A major limitation of this tool is that validation studies have not been performed in children with cancer. A previous study utilized the same dietary tool and similar research methodology in children with ALL (Kennedy et al., 2004). In that study, the YAFFQ was validated with a 24-hour recall and agreement was reported between the two survey instruments, but the correlations were not reported.

In the current study, total calorie intake was evaluated by categorizing patients by age and gender. The categorization of the results by age and gender allowed the investigator to control for confounding variables related to energy intake such as gender, age, height, lean mass, physical activity, and metabolic efficiency (Willett, 2001). Due to limited personnel and financial support, the study was unable collect information on other lifestyle factors affecting dietary intake such as physical activity. Comparison of mean intakes to the DRIs assumed a sedentary lifestyle for patients due to the medical recommendation of limited sports activity during cancer therapy. The study was also unable to collect biological markers to correlate with dietary data. Collection of biological markers of nutrient intake would strengthen the results of future studies.

The study was also limited by the lack of variability in all categories of nutrient intakes. For example, the majority of participants exceeded the DRI for calories resulting in little representation of participants meeting or below the recommendations. While this is an important finding for the study objectives of the current study, it reduces the power of the investigator to explore the effects of low and high dietary intake in subsequent analysis. Limited representation of patients below or exceeding the DRI must be considered in future analysis.

This study was unable to collect information on all aspects of medical nutrition therapy, thus it is unknown if the provision of total parenteral nutrition would attenuate the significant relationships observed in this study. At Time 2, the time at which the use of TPN was highest, 38 patients received TPN at some point during the induction phase of therapy. Based on clinical

expertise, it is unlikely that patients received TPN through the entire phase of therapy. Analysis of the data removing these 38 patients did not attenuate the results for total calories.

Finally, the current study required either the parent or child (≥7 years of age) to complete the dietary survey. Limitations in data collection prevented the investigative team to include respondent's relationship to the patient. For the majority of patients, a dedicated parent or legal guardian accompanies the patient however this was an assumption made on behalf of the investigator's clinical experience. This is a potential source of error however studies demonstrate parents are good surrogates for children's dietary intake (Blum et al., 1999; Rockett et al., 1997; Rockett et al., 1995).

There are several strengths of the current study. Most importantly, the study minimized variability in dietary data by collecting information on diet at systematic points in therapy among a cohort of children with a single cancer diagnosis and treated on the same treatment regimen. This is a significant accomplishment as the majority of previous studies have been limited by each of the variables. This study administered a standard dietary tool at systematic timepoints in therapy while also collecting information on enteral nutrition. This is the first study to accomplish a comprehensive dietary assessment during cancer therapy in children with ALL.

Completion of the dietary assessment was also successful in this study. Time 1 and Time 2 represent complete datasets. At each of these timepoints, 77% and 70% of surveys, respectively were completed and analyzed. These figures are at (Johansson et al., 1997; Kuskowska-Wolk et al., 1992), above (Johansson et al., 1997; Subar et al., 2001), or below (Johansson et al., 1997;

Kuskowska-Wolk et al., 1992; Subar et al., 2001) previously published research. It should be recognized that in the current study incentives, a frequent strategy implemented for completion of survey data, was not permitted in accordance with local institutional review boards. Thus, respondents were provided the survey while in the hospital or during a routine outpatient visit. In each of the aforementioned studies, incentives were implemented to enhance survey completion. Parents or children refusing to participate constituted a small percentage of missing data. For Time 3, 20% of surveys were in the data analysis phase or pending completion thus unable to be included in the current study. The inclusion of these surveys has the potential for analyzed surveys at Time 3 to be as high as 72%, a figure in line with Time 1 and Time 2. Taken together, this study demonstrated that the exploration of diet during cancer therapy is feasible among children with cancer. Additionally, the data suggests that parents and children are a motivated audience to participate in dietary studies and may be especially amenable to dietary counseling and intervention.

Finally, this is the first study utilizing dietary intake to categorize the nutritional status of children and adolescents with ALL. Previous studies have relied solely upon anthropometric indices to determine nutrition status despite the numerous limitations of these indices within the setting of cancer therapy, (Barr et al., 2011) which may result in misclassification (Barr et al., 2011; Bliijdorp, 2012). In Latin America, a region with a high prevalence of malnutrition, single assessments of nutrition status was less predictive of survival or therapy-related side effects, especially when relying on BMI alone (Sala et al., 2012). The current study suggests that the addition of diet into the matrix of nutrition assessment may aid clinicians in identifying nutrient intakes below recommended values that may be masked by excess caloric intake BMI. Children

with ALL are at increased risk of many nutrition-related morbidities. While the immediate consequence of dietary intakes below the DRI may not be evident, the short- and long-term effect of persistently low intakes remains unknown. Clinical dietary practice may need to consider a more systematic approach in the nutrition assessment of children with cancer, until a better understanding of the effect dietary intakes below or above the DRIs are understood.

5.5 Clinical Implications

Changes in dietary intake and nutrition status are a hallmark of cancer therapy yet much of the literature describing fluctuations in diet is based on anecdotes and theory rather than evidence-based science. This study was successful in identifying seven priority areas of dietary assessment and counseling for children undergoing treatment for ALL (table 24). These priority areas include: total calories, fat, protein, vitamin E, and bone-metabolizing nutrients (calcium, vitamin D, and vitamin K). There is now clear evidence that routine dietary assessments should occur throughout the course of treatment for ALL. Although interesting results were observed for other nutrients, specifically zinc, folate, and niacin, further information still seems needed prior to advising change in clinical practice.

This study provides evidence that dietary assessment should be performed throughout treatment, even during low dose phases of therapy. This suggests a significant change to the current standard of nutrition practice as routine nutrition assessments are not provided to children and adolescents with cancer (Ladas et al., 2005), but is in accordance with the multi-disciplinary approach that forms the backbone of the delivery of supportive care to children and adolescents with cancer. Dietary assessment with likely require tailoring based upon age and gender as

uniform findings were not observed across all groups. Dietary assessment may include the use of anthropometric data for standard assessments combined with a modified 24-hour recall. In children and adolescents in which poor dietary intake is suspected, a comprehensive 24-hour recall or food record may be clinically indicated. Confirmation of poor dietary intake especially in the presence of clinically confirmed malnutrition should be remediated as per institutional standards of practice. For those patients with excess calorie intakes, dietary counseling may emphasize strategies to minimize excess caloric intake, manage portion control, cravings and taste alterations, and adhere to a low-calorie diet if appropriate for age.

The results of this study suggest there is an opportunity for clinicians to educate patients on dietary fat especially during the phase of therapy in which high-dose steroids are administered. Dietary education on healthy fats may be incorporated into the standard of care as modification of dietary fat has proven to be beneficial in the prevention of cardiovascular disease in other clinical settings.

For protein, careful assessment of intake of dietary protein may be necessary early on in therapy for a select group of patients however this is not necessary for the majority of patients. In patients that are suspected to be consuming low intake of protein, dietary assessments should include careful analysis of protein intake, ideally with either a food record or 24-hour recalls. For patients with persistently low intakes, counseling on increasing protein intake is warranted. Supplementation with protein drinks may be clinically indicated for some patients.

For micronutrients, evidence now exists to develop clinical recommendations for vitamin E, vitamin D, calcium, and vitamin K. Screening guidelines may be developed for vitamin E, vitamin D, calcium, and vitamin K to ascertain an individual's risk of poor dietary intake of these nutrients. When warranted, dietary supplementation may be considered to ensure intakes meet the minimum daily requirement. For vitamin D, serum assessment of vitamin D status may be woven into clinical practice to ensure adequate dosing and duration of supplementation with vitamin D. Screening of serum vitamin D may accompany the systematic monitoring of bone morbidities, a practice that is slowly becoming integrating into the current standard of care for children with ALL.

Table 24. Clinical Implications for Noteworthy Nutrients		
Nutrient	**Focus of Intervention**	**Timing of Intervention**
Dietary Assessment	Ensure intake of macronutrients and micronutrients are not below or above recommended values. Dietary assessment needs to be tailored based upon age, gender, and dietary patterns	At diagnosis and at systematic timepoints during all phases of therapy.
Calories	Dietary counseling should emphasize portion control and healthy food choices in the majority of patients. For patients that are below recommended guidelines, consider nutrition support to maximize caloric intake.	Diagnosis-Initial consultation and assessment of nutrition intake. Patients with caloric intake below or above recommended values should continue to be monitored in a systematic manner during all phases of therapy.
Fat	During induction therapy (Time 2), dietary counseling may emphasize sources of healthy fats such as foods high in unsaturated fatty acids (fish, avocado, nuts, seeds).	Diagnosis through first month of therapy (Induction phase)
Protein	Emphasize protein-rich sources only for children at risk for insufficient protein intake.	At diagnosis and at systematic timepoints in throughout therapy.
Vitamin E	Emphasize foods rich in vitamin E. Foods high in vitamin E include nuts, seeds, kiwi, mango, and tomatoes. Consider supplementation, if dietary intake does not meet the RDA.	Routine assessments through all phases of therapy.
Calcium	Emphasize foods rich in calcium such as dairy and leafy greens. Consider supplementation, if dietary intake does not meet the RDA.	Routine assessments through all phases of therapy.
Vitamin D	Emphasize foods rich in vitamin D such as fortified diary products. Consider supplementation, if dietary intake does not meet the RDA. Evaluation of serum vitamin D status may be considered to direct dosing recommendations.	Routine assessments through all phases of therapy.
Vitamin K	Emphasize foods rich in vitamin K. Consider supplementation, if warranted.	Routine assessments through all phases of therapy.

5. 6 Future Directions

The results of this study have identified a variety of priority areas for future research. As a first step, it will be important to confirm and expand upon the findings of this interim analysis once complete data is available for Time 3. The final analysis should explore if the described relationships remain with the larger data set as well as perform advanced statistical modeling to identify trends over time. For the highlighted micronutrients, subsequent analysis on the complete dataset may consider a thorough evaluation of folate to include genetic polymorphisms of folate-metabolizing genes and biological markers of folate intake. Additional micronutrient analysis may also explore the risks associated with excess intakes of niacin and zinc especially at it relates to therapy-related side effects and survival. The influence of ethnicity, weight, and geographic location on the observed associations may also be explored, as these variables are influential in assessing dietary intake. When possible, the inclusion of socioeconomic status may also provide a comprehensive understanding to nutrition status as this has been linked to reduced outcomes among children with cancer (Lightfoot et al., 2012).

Secondly, the role of dietary patterns on therapy-related side effects during and after completion of therapy is an area for further exploration. For example, while significant associations were not identified for carbohydrates, exploration into the quality of carbohydrates (simple versus complex), especially as intake relates to the glycemic index, may reveal interesting findings that are clinically significant. Future studies may also consider exploring dietary patterns that include the ratio of saturated and unsaturated fat, servings of fruits and vegetables, and dietary exposure to phytonutrients. The understanding of dietary patterns during therapy may aid clinicians in identifying target areas for dietary intervention upon completion of treatment. It is plausible that

children and adolescents may be more amenable to dietary intervention once treatment is complete. This is a time when the focus is turned towards the prevention of late-effects and second malignancies rather than the day-to-day fluctuations that are often encountered during treatment for cancer.

Future investigations need to give consideration to the complexity of dietary intervention during cancer therapy. Dietary interventions targeting children and adolescents with ALL must be designed to be flexible and cognoscente of the side effects that may limit dietary intake such as changes in the taste and desire for food, "fussy eating", and the psychosocial impacts of the diagnosis of cancer (Fleming, 2012; Pizzo, 2011). Each of these factors may limit adherence to any dietary recommendation. Tailored nutrition interventions will likely be required, as food preferences may need to be considered within the findings of dietary assessment. The timing of dietary education and format of intervention is also a fertile area for investigation among children with cancer. For example, distal lifestyle intervention programs are effective at modifying changes in dietary patterns and physical activity among adult survivors of cancer (Mosher et al., 2012). With the increased use of technology among adolescents and young adults, this may be an ideal format to deliver nutrition education both during and after therapy.

Future studies may also consider the investigation of the optimal tool for evaluating diet among children with cancer. The strengths and weaknesses of the available dietary tools should be explored in this setting. The utilization of electronic food records or recalls may ease the burden of data collection for investigators and increase opportunities for subsequent dietary studies in children with cancer. Additionally, practical issues related to the collection of dietary data

among children with cancer may also be considered. The development of a systematic process for the implementation and training of the research and investigative staff will improve the reliability and validity and minimize incomplete data sets in future epidemiologic studies performed in children with cancer.

Finally, this study may serve as a benchmark to direct the formation of dietary goals for children and adolescents with ALL. As well, the reported mean intakes may serve as a reference point for future dietary studies in children with ALL. Whether these results apply children with cancer diagnosed with malignancies outside of ALL remains unknown. The current study design may also serve as a blueprint for exploration of diet in children with other types of malignancies in which malnutrition is thought to be a significant concern due to the nature of anticancer therapy. Future studies should explore this data in children at high risk for malnutrition that include children and adolescents with a brain tumor, undergoing stem cell transplant, or with a solid tumor. The benefit of these scientific efforts will hopefully be more children and adolescents entering survivorship, which is the ultimate goal of medical professionals working in pediatric oncology.

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Appendices

A. The Harvard Youth and Adolescent Survey

B. The Harvard Food Service Survey

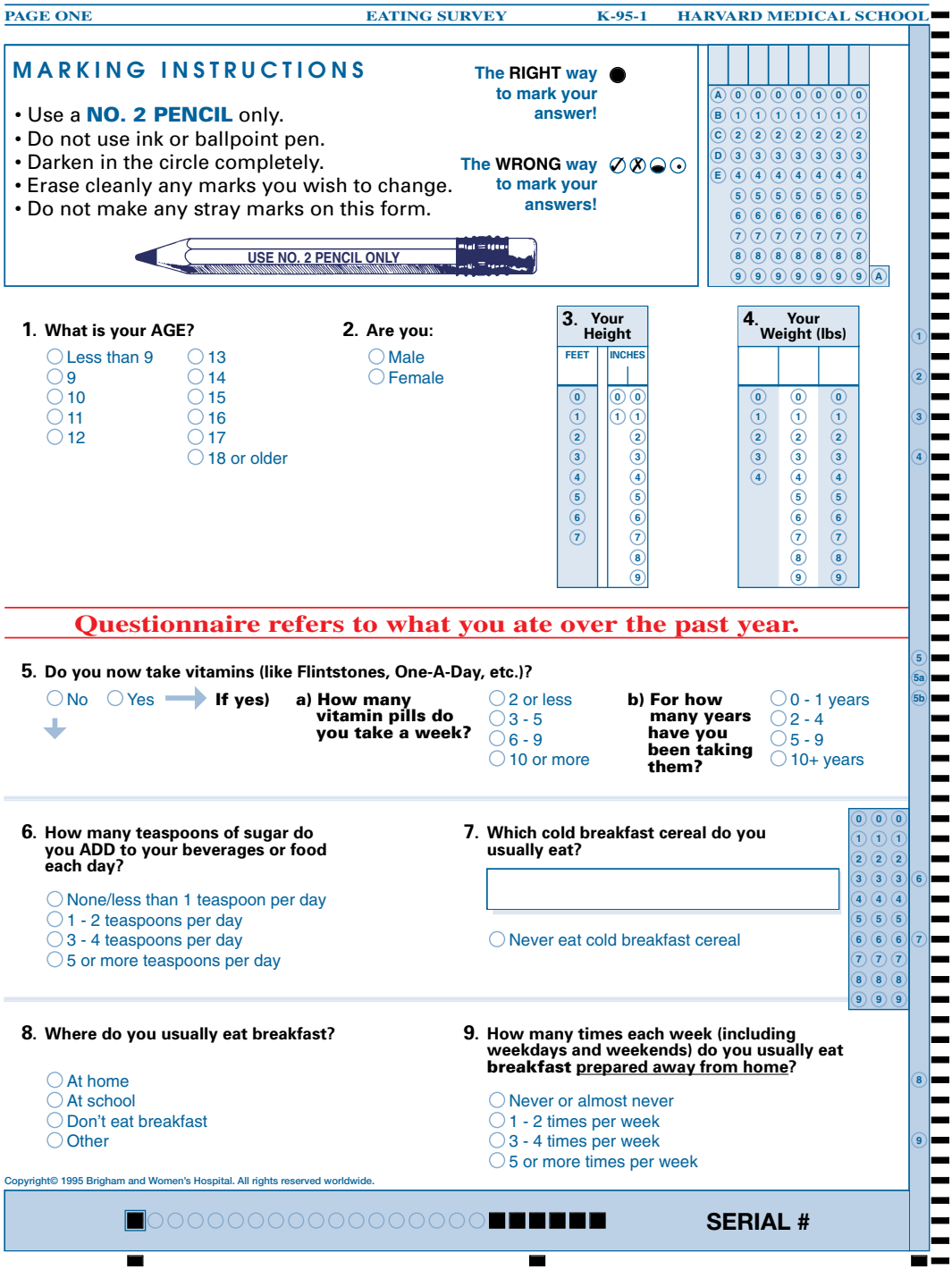
C. Medical Nutrition Support Form

D. Summary Tables: Dietary Reference Intake

E. Summary Tables: National Health and Nutrition Examination Survey (NHANES)

F. Summary Tables: Mean Intakes of B Vitamins

A. The Harvard Youth and Adolescent Survey



PAGE ONE EATING SURVEY K-95-1 HARVARD MEDICAL SCHOOL

MARKING INSTRUCTIONS

- Use a **NO. 2 PENCIL** only.
- Do not use ink or ballpoint pen.
- Darken in the circle completely.
- Erase cleanly any marks you wish to change.
- Do not make any stray marks on this form.

The RIGHT way to mark your answer!

The WRONG way to mark your answers!

USE NO. 2 PENCIL ONLY

1. What is your AGE?
   - Less than 9
   - 9
   - 10
   - 11
   - 12
   - 13
   - 14
   - 15
   - 16
   - 17
   - 18 or older

2. Are you:
   - Male
   - Female

3. Your Height (FEET / INCHES)

4. Your Weight (lbs)

Questionnaire refers to what you ate over the past year.

5. Do you now take vitamins (like Flintstones, One-A-Day, etc.)?
   - No
   - Yes → If yes)
     - a) How many vitamin pills do you take a week?
       - 2 or less
       - 3 - 5
       - 6 - 9
       - 10 or more
     - b) For how many years have you been taking them?
       - 0 - 1 years
       - 2 - 4
       - 5 - 9
       - 10+ years

6. How many teaspoons of sugar do you ADD to your beverages or food each day?
   - None/less than 1 teaspoon per day
   - 1 - 2 teaspoons per day
   - 3 - 4 teaspoons per day
   - 5 or more teaspoons per day

7. Which cold breakfast cereal do you usually eat?
   - Never eat cold breakfast cereal

8. Where do you usually eat breakfast?
   - At home
   - At school
   - Don't eat breakfast
   - Other

9. How many times each week (including weekdays and weekends) do you usually eat breakfast prepared away from home?
   - Never or almost never
   - 1 - 2 times per week
   - 3 - 4 times per week
   - 5 or more times per week

SERIAL #

10. **How many times each week (including weekdays and weekends) do you usually eat lunch prepared away from home?**

- ○ Never or almost never
- ○ 1 - 2 times per week
- ○ 3 - 4 times per week
- ○ 5 or more times per week

11. **How many times each week do you usually eat after-school snacks or foods prepared away from home?**

- ○ Never or almost never
- ○ 1 - 2 times per week
- ○ 3 - 4 times per week
- ○ 5 or more times per week

12. **How many times each week (weekdays and weekends) do you usually eat dinner prepared away from home?**

- ○ Never or almost never
- ○ 1 - 2 times per week
- ○ 3 - 4 times per week
- ○ 5 or more times per week

13. **How many times per week do you prepare dinner for yourself (and/or others in your house)?**

- ○ Never or almost never
- ○ Less than once per week
- ○ 1 - 2 times per week
- ○ 3 - 4 times per week
- ○ 5 or more times per week

14. **How often do you have dinner that is ready made, like frozen dinners, Spaghetti-O's, microwave meals, etc.**

- ○ Never/less than once per month
- ○ 1 - 2 times per week
- ○ 3 - 4 times per week
- ○ 5 or more times per week

15. **How many times each week (including weekdays and weekends) do you eat late night snacks prepared away from home?**

- ○ Never/less than once per month
- ○ 1 - 2 times per week
- ○ 3 - 4 times per week
- ○ 5 or more times per week

16. **How often do you eat food that is fried at home, like fried chicken?**

- ○ Never/less than once per week
- ○ 1 - 3 times per week
- ○ 4 - 6 times per week
- ○ Daily

17. **How often do you eat fried food away from home (like french fries, chicken nuggets)?**

- ○ Never/less than once per week
- ○ 1 - 3 times per week
- ○ 4 - 6 times per week
- ○ Daily

DIETARY INTAKE

How often do you eat the following foods:

Example **If you drink one can of diet soda 2 - 3 times per week, then your answer should look like this:**

E1. **Diet soda (1 can or glass)**

- ○ Never
- ○ 1 - 3 cans per month
- ○ 1 can per week
- ● 2 - 6 cans per week
- ○ 1 can per day
- ○ 2 or more cans per day

PAGE THREE — Questionnaire refers to what you ate over the past year. — HARVARD MEDICAL SCHOOL

BEVERAGES

FILL OUT ONE BUBBLE FOR EACH FOOD ITEM

18. Diet soda (1 can or glass)
- ○ Never/less than 1 per month
- ○ 1 - 3 cans per month
- ○ 1 can per week
- ○ 2 - 6 cans per week
- ○ 1 can per day
- ○ 2 or more cans per day

19. Soda - not diet (1 can or glass)
- ○ Never/less than 1 per month
- ○ 1 - 3 cans per month
- ○ 1 can per week
- ○ 2 - 6 cans per week
- ○ 1 can per day
- ○ 2 or more cans per day

20. Hawaiian Punch, lemonade, Koolaid or other non-carbonated fruit drink (1 glass)
- ○ Never/less than 1 per month
- ○ 1 - 3 glasses per month
- ○ 1 glass per week
- ○ 2 - 4 glasses per week
- ○ 5 - 6 glasses per week
- ○ 1 glass per day
- ○ 2 or more glasses per day

21. Iced Tea - sweetened (1 glass, can or bottle)
- ○ Never/less than 1 per month
- ○ 1 - 3 glasses per month
- ○ 1 - 4 glasses per week
- ○ 5 - 6 glasses per week
- ○ 1 or more glasses per day

22. Tea (1 cup)
- ○ Never/less than 1 per month
- ○ 1 - 3 cups per month
- ○ 1 - 2 cups per week
- ○ 3 - 6 cups per week
- ○ 1 or more cups per day

23. Coffee - not decaf. (1 cup)
- ○ Never/less than 1 per month
- ○ 1 - 3 cups per month
- ○ 1 - 2 cups per week
- ○ 3 - 6 cups per week
- ○ 1 or more cups per day

24. Beer (1 glass, bottle or can)
- ○ Never/less than 1 per month
- ○ 1 - 3 cans per month
- ○ 1 can per week
- ○ 2 or more cans per week

25. Wine or wine coolers (1 glass)
- ○ Never/less than 1 per month
- ○ 1 - 3 glasses per month
- ○ 1 glass per week
- ○ 2 or more glasses per week

26. Liquor, like vodka or rum (1 drink or shot)
- ○ Never/less than 1 per month
- ○ 1 - 3 drinks per month
- ○ 1 drink per week
- ○ 2 or more drinks per week

Example If you eat:

3 pats of margarine on toast
1 - 2 pats of margarine on sandwich
1 pat of margarine on vegetables

5 - 6 pats total all day

then answer this way →

E2. Margarine (1 pat) - not butter
- ○ Never
- ○ 1 - 3 pats per month
- ○ 1 pat per week
- ○ 2 - 6 pats per week
- ○ 1 pat per day
- ○ 2 - 4 pats per day
- ● 5 or more pats per day

DAIRY PRODUCTS

27. What TYPE of milk do you usually drink?
- ○ Whole milk
- ○ 2% milk
- ○ 1% milk
- ○ Skim/nonfat milk
- ○ Don't know
- ○ Don't drink milk

28. Milk (glass or with cereal)
- ○ Never/less than 1 per month
- ○ 1 glass per week or less
- ○ 2 - 6 glasses per week
- ○ 1 glass per day
- ○ 2 - 3 glasses per day
- ○ 4+ glasses per day

29. Chocolate milk (glass)
- ○ Never/less than 1 per month
- ○ 1 - 3 glasses per month
- ○ 1 glass per week
- ○ 2 - 6 glasses per week
- ○ 1 - 2 glasses per day
- ○ 3 or more glasses per day

SERIAL #

PAGE FOUR — Questionnaire refers to what you ate over the past year. — HARVARD MEDICAL SCHOOL

30. Instant Breakfast Drink (1 packet)
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

31. Whipped cream
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

32. Yogurt (1 cup) - Not frozen
- ○ Never/less than 1 per month
- ○ 1 - 3 cups per month
- ○ 1 cup per week
- ○ 2 - 6 cups per week
- ○ 1 cup per day
- ○ 2 or more cups per day

33. Cottage or ricotta cheese
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

34. Cheese (1 slice)
- ○ Never/less than 1 per month
- ○ 1 - 3 slices per month
- ○ 1 slice per week
- ○ 2 - 6 slices per week
- ○ 1 slice per day
- ○ 2 or more slices per day

35. Cream cheese
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

36. What TYPE of yogurt, cottage cheese & dairy products (besides milk) do you use mostly?
- ○ Nonfat
- ○ Lowfat
- ○ Regular
- ○ Don't know

37. Butter (1 pat) - NOT margarine
- ○ Never/less than 1 per month
- ○ 1 - 3 pats per month
- ○ 1 pat per week
- ○ 2 - 6 pats per week
- ○ 1 pat per day
- ○ 2 - 4 pats per day
- ○ 5 or more pats per day

38. Margarine (1 pat) - NOT butter
- ○ Never/less than 1 per month
- ○ 1 - 3 pats per month
- ○ 1 pat per week
- ○ 2 - 6 pats per week
- ○ 1 pat per day
- ○ 2 - 4 pats per day
- ○ 5 or more pats per day

39. What FORM and BRAND of margarine does your family usually use?
- ○ None
- ○ Stick
- ○ Tub
- ○ Squeeze (liquid)

WHAT SPECIFIC BRAND AND TYPE (LIKE "PARKAY CORN OIL SPREAD")?

Leave blank if you don't know.

40. What TYPE of oil does your family use at home?
- ○ Canola oil
- ○ Corn oil
- ○ Safflower oil
- ○ Olive oil
- ○ Vegetable oil
- ○ Don't know

MAIN DISHES

41. Cheeseburger (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ One per week
- ○ 2 - 4 per week
- ○ 5 or more per week

42. Hamburger (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ One per week
- ○ 2 - 4 per week
- ○ 5 or more per week

43. Pizza (2 slices)
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

44. Tacos/burritos (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ One per week
- ○ 2 - 4 per week
- ○ 5 or more per week

45. Which taco filling do you usually have:
- ○ Beef & beans
- ○ Beef
- ○ Chicken
- ○ Beans

46. Chicken nuggets (6)
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

47. Hot dogs (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ One per week
- ◯ 2 - 4 per week
- ◯ 5 or more per week

48. Peanut butter sandwich (1) (plain or with jelly, fluff, etc.)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ One per week
- ◯ 2 - 4 per week
- ◯ 5 or more per week

49. Chicken or turkey sandwich (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ One per week
- ◯ 2 or more per week

50. Roast beef or ham sandwich (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ One per week
- ◯ 2 or more per week

51. Salami, bologna, or other deli meat sandwich (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ One per week
- ◯ 2 or more per week

52. Tuna sandwich (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ One per week
- ◯ 2 or more per week

53. Chicken or turkey as main dish (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

54. Fish sticks, fish cakes or fish sandwich (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 or more times per week

55. Fresh fish as main dish (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

56. Beef (steak, roast) or lamb as main dish (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

57. Pork or ham as main dish (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

58. Meatballs or meatloaf (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

59. Lasagna/baked ziti (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 or more times per week

60. Macaroni and cheese (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 or more times per week

61. Spaghetti with tomato sauce (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

62. Eggs (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 eggs per month
- ◯ One egg per week
- ◯ 2 - 4 eggs per week
- ◯ 5 or more eggs per week

63. Liver: beef, calf, chicken or pork (1 serving)
- ◯ Never/less than 1 per month
- ◯ Less than once per month
- ◯ Once per month
- ◯ 2 - 3 times per month
- ◯ Once per week or more

64. Shrimp, lobster, scallops (1 serving)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 or more times per week

SERIAL #

65. French toast (2 slices)

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

66. Grilled cheese (1)

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

67. Eggrolls (1)

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

MISCELLANEOUS FOODS

68. Brown gravy

- ○ Never/less than 1 per month
- ○ Once per week or less
- ○ 2 - 6 times per week
- ○ Once per day
- ○ 2 or more times per day

69. Ketchup

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

70. Clear soup (with rice, noodles, vegetables) 1 bowl

- ○ Never/less than 1 per month
- ○ 1 - 3 bowls per month
- ○ 1 bowl per week
- ○ 2 or more bowls per week

71. Cream (milk) soups or chowder (1 bowl)

- ○ Never/less than 1 per month
- ○ 1 - 3 bowls per month
- ○ 1 bowl per week
- ○ 2 - 6 bowls per week
- ○ 1 or more bowls per day

72. Mayonnaise

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 6 times per week
- ○ Once per day

73. Low calorie/fat salad dressing

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 6 times per week
- ○ Once or more per day

74. Salad dressing (not low calorie)

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 6 times per week
- ○ Once or more per day

75. Salsa

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 6 times per week
- ○ Once or more per day

76. How much fat on your beef, pork, or lamb do you eat?

- ○ Eat all
- ○ Eat some
- ○ Eat none
- ○ Don't eat meat

77. When you have chicken or turkey, do you eat the skin?

- ○ Yes
- ○ No
- ○ Sometimes

BREADS & CEREALS

78. Cold breakfast cereal (1 bowl)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 bowls per month
- ◯ 1 bowl per week
- ◯ 2 - 4 bowls per week
- ◯ 5 - 7 bowls per week
- ◯ 2 or more bowls per day

79. Hot breakfast cereal, like oatmeal, grits (1 bowl)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 bowls per month
- ◯ 1 bowl per week
- ◯ 2 - 4 bowls per week
- ◯ 5 - 7 bowls per week
- ◯ 2 or more bowls per day

80. White bread, pita bread, or toast (1 slice)

- ◯ Never/less than 1 per month
- ◯ 1 slice per week or less
- ◯ 2 - 4 slices per week
- ◯ 5 - 7 slices per week
- ◯ 2 - 3 slices per day
- ◯ 4+ slices per day

81. Dark bread (1 slice)

- ◯ Never/less than 1 per month
- ◯ 1 slice per week or less
- ◯ 2 - 4 slices per week
- ◯ 5 - 7 slices per week
- ◯ 2 - 3 slices per day
- ◯ 4+ slices per day

82. English muffins or bagels (1)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 4 per week
- ◯ 5 or more per week

83. Muffin (1)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 muffins per month
- ◯ 1 muffin per week
- ◯ 2 - 4 muffins per week
- ◯ 5 or more muffins per week

84. Cornbread (1 square)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more per week

85. Biscuit/roll (1)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 4 per week
- ◯ 5 or more per week

86. Rice

- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

87. Noodles, pasta

- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

88. Tortilla - no filling (1)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 4 per week
- ◯ 5 or more per week

89. Other grains, like kasha, couscous, bulgur

- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 or more times per week

90. Pancakes (2) or waffles (1)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 or more times per week

91. French fries (large order)

- ◯ Never/less than 1 per month
- ◯ 1 - 3 orders per month
- ◯ 1 order per week
- ◯ 2 - 4 orders per week
- ◯ 5 or more orders per week

92. Potatoes - baked, boiled, mashed

- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

FRUITS & VEGETABLES

93. Raisins (small pack)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ 1 per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

94. Grapes (bunch)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

95. Bananas (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 4 per week
- ◯ 5 or more per week

96. Cantaloupe, melons (1/4 melon)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ 1 per week
- ◯ 2 or more times per week

97. Apples (1) or applesauce
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 6 per week
- ◯ 1 or more per day

98. Pears (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 6 per week
- ◯ 1 or more per day

99. Oranges (1), grapefruit (1/2)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 6 per week
- ◯ 1 or more per day

100. Strawberries
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 or more times per week

101. Peaches, plums, apricots (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 or more per week

102. Orange juice (1 glass)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 glasses per month
- ◯ 1 glass per week
- ◯ 2 - 6 glasses per week
- ◯ 1 glass per day
- ◯ 2 or more glasses per day

103. Apple juice and other fruit juices (1 glass)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 glasses per month
- ◯ 1 glass per week
- ◯ 2 - 6 glasses per week
- ◯ 1 glass per day
- ◯ 2 or more glasses per day

104. Tomatoes (1)
- ◯ Never/less than 1 per month
- ◯ 1 - 3 per month
- ◯ 1 per week
- ◯ 2 - 6 per week
- ◯ 1 or more per day

105. Tomato/spaghetti sauce
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

106. Tofu
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

107. String beans
- ◯ Never/less than 1 per month
- ◯ 1 - 3 times per month
- ◯ Once per week
- ◯ 2 - 4 times per week
- ◯ 5 or more times per week

108. Beans/lentils/soybeans
- ○ Never/less than 1 per month
- ○ Once per week or less
- ○ 2 - 6 times per week
- ○ Once per day

109. Broccoli
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

110. Beets (not greens)
- ○ Never/less than 1 per month
- ○ Once per week or less
- ○ 2 or more times per week

111. Corn
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

112. Peas or lima beans
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

113. Mixed vegetables
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

114. Spinach
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once a week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

115. Greens/kale
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

116. Green/red peppers
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once a week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

117. Yams/sweet potatoes (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once a week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

118. Zucchini, summer squash, eggplant
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

119. Carrots, cooked
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

120. Carrots, raw
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

121. Celery
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

122. Lettuce/tossed salad
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 6 times per week
- ○ One or more per day

123. Coleslaw
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

124. Potato salad
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

Think about your usual snacks. How often do you eat each type of snack food.

Example If you eat poptarts rarely (about 6 per year) then your answer should look like this:

E3. Poptarts (1)

- ● Never/less than 1 per month
- ○ 1 - 3 per month
- ○ 1 - 6 per week
- ○ 1 or more per day

SNACK FOODS/DESSERTS

125. Fill in the number of snacks (food or drinks) eaten on school days and weekends/vacation days.

Snacks	School Days					Vacation/Weekend Days				
	NONE	1	2	3	4 OR MORE	NONE	1	2	3	4 OR MORE
Between breakfast and lunch	○	○	○	○	○	○	○	○	○	○
After lunch, before dinner	○	○	○	○	○	○	○	○	○	○
After dinner	○	○	○	○	○	○	○	○	○	○

126. Potato chips (1 small bag)

- ○ Never/less than 1 per month
- ○ 1 - 3 small bags per month
- ○ One small bag per week
- ○ 2 - 6 small bags per week
- ○ 1 or more small bags per day

127. Corn chips/Doritos (small bag)

- ○ Never/less than 1 per month
- ○ 1 - 3 small bags per month
- ○ One small bag per week
- ○ 2 - 6 small bags per week
- ○ 1 or more small bags per day

128. Nachos with cheese (1 serving)

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 or more times per week

129. Popcorn (1 small bag)

- ○ Never/less than 1 per month
- ○ 1 - 3 small bags per month
- ○ 1 - 4 small bags per week
- ○ 5 or more small bags per week

130. Pretzels (1 small bag)

- ○ Never/less than 1 per month
- ○ 1 - 3 small bags per month
- ○ 1 small bags per week
- ○ 2 or more small bags per week

131. Peanuts, nuts (1 small bag)

- ○ Never/less than 1 per month
- ○ 1 - 3 small bags per month
- ○ 1 - 4 small bags per week
- ○ 5 or more small bags per week

132. Fun fruit or fruit rollups (1 pack)

- ○ Never/less than 1 per month
- ○ 1 - 3 packs per month
- ○ 1 - 4 packs per week
- ○ 5 or more packs per week

133. Graham crackers

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ 1 - 4 times per week
- ○ 5 or more times per week

134. Crackers, like saltines or wheat thins

- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ 1 - 4 times per week
- ○ 5 or more times per week

135. Poptarts (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 poptarts per month
- ○ 1 - 6 poptarts per week
- ○ 1 or more poptarts per day

136. Cake (1 slice)
- ○ Never/less than 1 per month
- ○ 1 - 3 slices per month
- ○ 1 slice per week
- ○ 2 or more slices per week

137. Snack cakes, Twinkies (1 package)
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ Once per week
- ○ 2 - 6 per week
- ○ 1 or more per day

138. Danish, sweetrolls, pastry (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ 1 per week
- ○ 2 - 4 per week
- ○ 5 or more per week

139. Donuts (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 donuts per month
- ○ 1 donut per week
- ○ 2 - 6 donuts per week
- ○ 1 or more donuts per day

140. Cookies (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 cookies per month
- ○ 1 cookie per week
- ○ 2 - 6 cookies per week
- ○ 1 - 3 cookies per day
- ○ 4 or more cookies per day

141. Brownies (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ 1 per week
- ○ 2 - 4 per week
- ○ 5 or more per week

142. Pie (1 slice)
- ○ Never/less than 1 per month
- ○ 1 - 3 slices per month
- ○ 1 slice per week
- ○ 2 or more slices per week

143. Chocolate (1 bar or packet) like Hershey's or M & M's
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ 1 per week
- ○ 2 - 6 per week
- ○ 1 or more per day

144. Other candy bars (Milky Way, Snickers)
- ○ Never/less than 1 per month
- ○ 1 - 3 candy bars per month
- ○ 1 candy bar per week
- ○ 2 - 4 candy bars per week
- ○ 5 or more candy bars per week

145. Other candy without chocolate (Skittles) (1 pack)
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

146. Jello
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

147. Pudding
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

148. Frozen yogurt
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

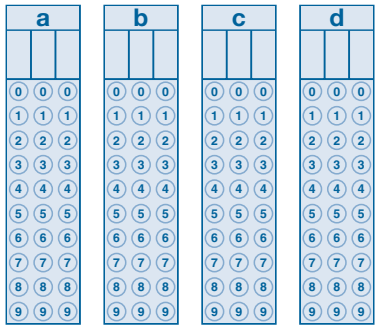
149. Ice cream
- ○ Never/less than 1 per month
- ○ 1 - 3 times per month
- ○ Once per week
- ○ 2 - 4 times per week
- ○ 5 or more times per week

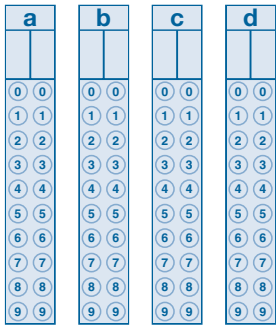
150. Milkshake or frappe (1)
- ○ Never/less than 1 per month
- ○ 1 - 3 per month
- ○ 1 per week
- ○ 2 or more per week

151. Popsicles
- ○ Never/less than 1 per month
- ○ 1 - 3 popsicles per month
- ○ 1 popsicle per week
- ○ 2 - 4 popsicles per week
- ○ 5 or more popsicles per week

152. **Please list any other foods that you usually eat <u>at least once per week</u> that are not listed (for example, coconut, hummus, falafel, chili, plantains, mangoes, etc. . .)**

FOODS	HOW OFTEN?
a) _____	a) _____
b) _____	b) _____
c) _____	c) _____
d) _____	d) _____





THANK YOU FOR COMPLETING THIS SURVEY!

SERIAL #

B. Harvard Food Service Survey

Children's Nutrition Questionnaire

What Have You Been Eating Lately?

"During the past 4 weeks, how often did you eat a serving of each of the foods listed here?"
Mark only one X for each food

Name: _____

ID: _____

Date ____/____/____

DOB: ____/____/____

Age: _____

Respondent: *(please check)*

☐ Mother

☐ Other _____

Example:

	last 4 weeks		each week			each day			
Number of times	0	1–3	1	2–4	5–6	1	2–3	4–5	6+
Milk				X					
Hot chocolate	X								

	last 4 weeks		each week			each day			
Number of times	0	1–3	1	2–4	5–6	1	2–3	4–5	6+
Milk									
Hot chocolate									
Cheese, plain or in sandwiches									
Yogurt									
Ice cream (cones, sandwiches, sundaes)									
Pudding									
	0	1	2	3	4	5	6	7	8

What kind of milk does your child usually drink? (Check one)

1 ☐ breastmilk 3 ☐ whole 5 ☐ 1% 7 ☐ Chocolate Milk

2 ☐ formula 4 ☐ 2% 6 ☐ skim 8 ☐ other _____

	last 4 weeks		each week			each day			
Number of times	0	1–3	1	2–4	5–6	1	2–3	4–5	6+
Orange juice or grapefruit juice									
Other juice									
Fruit drinks (Hi-C, Kool-aid, lemonade, sportsdrink)									
Banana									
Peaches									
Fruit cocktail, mixed fruit									
Orange or grapefruit									
Apple or pear									
Applesauce									
Grapes									
Strawberries									
Melon									
Pineapple									
Raisins or prunes									
	0	1	2	3	4	5	6	7	8

Continued on next page

Mark only one **X** for each food.
How often did you eat a serving of these foods during the past 4 weeks?

	last 4 weeks		each week			each day			
Number of times	0	1-3	1	2-4	5-6	1	2-3	4-5	6+
Corn									
Peas									
Tomatoes, tomato sauce, salsa									
Peppers (green, red or hot)									
Carrots									
Broccoli									
Green beans									
Spinach									
Greens (mustard, turnip, kale)									
Mixed vegetables									
Squash, orange or winter									
Zucchini, yellow squash									
French fries, fried potatoes, tater tots									
Potatoes (baked, boiled, or mashed)									
Sweet potatoes or yams									
Cabbage, coleslaw or cauliflower									
Lettuce salad									
Salad dressing									
Mayonnaise									
	0	1	2	3	4	5	6	7	8

	last 4 weeks		each week			each day			
Number of times	0	1-3	1	2-4	5-6	1	2-3	4-5	6+
Chips (potato, corn or others)									
Popcorn or pretzels									
Crackers									
Nuts									
Cookies or brownies									
Cake or cupcake									
Pie									
Jello									
Chocolate or candy bar									
Other candy (not chocolate)									
Coffee or tea									
Soda, soft drink, pop (not sugar free)									
Soda, soft drink, pop (sugar free)									
	0	1	2	3	4	5	6	7	8

	last 4 weeks		each week			each day			
Number of times	0	1-3	1	2-4	5-6	1	2-3	4-5	6+
Beans (baked, chili, or other)									
Rice									
Spaghetti or other pasta									
Pizza									
Tacos, burritos									
Macaroni and cheese									
Hot dogs									
Sausage									
Hamburger (prepared any way)									
Canned tuna									
Fried fish, fish sticks									
Other fish									
Cold cuts (baloney, ham, salami)									
Fried chicken, chicken nuggets									
Other chicken or turkey									
Pork or ham									
Roast beef or steak									
Liver, organ meats									
Peanut butter									
Bread (slice) toast, roll, or pita									
Butter (not margarine)									
Margarine									
	0	1	2	3	4	5	6	7	8

	last 4 weeks		each week			each day			
Number of times	0	1-3	1	2-4	5-6	1	2-3	4-5	6+
Vegetable soup									
Other soup									
Cornbread or tortilla									
Eggs									
Bacon									
Hot cereal, grits									
Cold cereal									
Donut									
Sweet roll or muffin									
Pancake, waffle, or french toast									
English muffin or bagel									
Biscuit									
	0	1	2	3	4	5	6	7	8

1. What type of bread does your child usually eat:
   ☐ 1 white bread ☐ 2 whole wheat or dark bread ☐ 3 about half and half ☐ 4 DON'T EAT BREAD

2. What type of margarine does your child usually use:
   ☐ 1 stick ☐ 2 tub ☐ 3 squeeze ☐ 4 DON'T USE MARGARINE
   Is this margarine:
   ☐ 1 corn oil ☐ 2 nonfat ☐ 3 other

3. If your child eats cold breakfast cereal, what type:
   ☐ 1 high fiber (eg. All Bran) ☐ 2 unsweetened (eg. Corn Flakes) ☐ 3 sweetened (eg. Cap'n Crunch)

4. Does your child take a multi-vitamin pill (Flintstones, TriViFlor):
   ☐ 0 no ☐ 1 yes
   If yes, how often:
   ☐ 1 Every day ☐ 2 4–6 times a week ☐ 3 1–3 times a week ☐ 4 Less than one time a week

5. Does your child take a separate iron pill (not in the multi-vitamin pill above):
   ☐ 0 no ☐ 1 yes

6. Does your child take a separate fluoride supplement (not in the multi-vitamin pill above):
   ☐ 0 no ☐ 1 yes

7. Does your child eat fried food at home:
   ☐ 0 no ☐ 1 yes
   If yes, how often:
   ☐ 1 Every day ☐ 2 4–6 times a week ☐ 3 1–3 times a week ☐ 4 Less than one time a week
   If yes, what type of fat do you use to fry at home:
   ☐ 1 butter ☐ 2 margarine ☐ 3 crisco ☐ 4 corn oil ☐ 5 canola oil ☐ 6 olive oil ☐ 7 other vegetable oil

8. Do you bake cookies, cake or pies at home:
   ☐ 0 no ☐ 1 yes
   If yes, how often does your child eat home-baked cookies, cake or pies?
   ☐ 1 Every day ☐ 2 4–6 times a week ☐ 3 1–3 times a week ☐ 4 Less than one time a week
   If yes, what type of fat do you use to bake at home:
   ☐ 1 butter ☐ 2 margarine ☐ 3 crisco ☐ 4 corn oil ☐ 5 canola oil ☐ 6 olive oil ☐ 7 other vegetable oil

C. Medical Nutrition Support Form

DFCI Dietary Intake Study
Nutrition Support Data Collection Form

Date_____

Patient ID#_____

Survey Timepoint (Circle One)

Diagnosis Day 32 Consolidation Continuation

Total Parenteral Nutrition* (Circle One) Y N

Enteral Nutrition (PO Supplements or Tube Feedings) (Circle One) Y N

Enteral Nutrition Prescription:
Formula (IE: Pediasure, Ensure, etc) _____

Number of cans per day taken by mouth_____

If patient being fed by tube feeding:
Volume of supplement provided by tube feeding (# of cc's x # of hours).

Patient Example: Nutren Junior, 50ccs x 12 hours

*Please note that the nutrition prescription is not required for patients on total parenteral nutrition (TPN). Please only indicate yes or no as to whether the patient has received TPN during the period of the dietary survey.

D. Summary Tables of DRI Tables

Age Group	Fat* (% of Calories)	Protein*	Carbohydrate* (% of Calories)
1-3 years	30-40%	5-20%	45-65%
4-8 years	25-35%	10-30%	45-65%
9-13 years	25-35%	10-30%	45-65%
14-18 years	25-35%	10-30%	45-65%

**Values reported are the Acceptable Macronutrient Distribution Range (AMDR.) The AMDR is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. If an individual consumed in excess of the AMDR, there is a potential of increasing the risk of chronic diseases and insufficient intakes of essential nutrients.*

RDA, EAR, UL for Antioxidant Nutrients						
	Vitamin C mg		Vitamin E mg		Zinc mg	
Age Group	RDA (EAR)	UL	RDA (EAR)	UL	RDA (EAR)	UL
1-3 years	15 (13)	400	6 (5)	200	3 (2.5)	7
4-8 years	25 (22)	650	7 (6)	300	5 (4)	12
9-13 years						
Male	15(39)	1200	11 (9)	600	8 (7)	23
Female	15 (39)	1200	11 (9)	600	8 (7)	23
14-18 years						
Male	75 (63)	1800	15 (12)	800	11 (8.5)	34
Female	65 (56)	1800	15 (12)	800	9 (7.3)	34

RDA, EAR, UL for B6, B12, Folate						
	Folate mcg		B6 mg		B12 mcg	
Age Group	RDA (EAR)	UL	RDA (EAR)	UL	RDA (EAR)	UL
1-3 years	150 (120)	300	.5 (.4)	30	150 (120)	ND
4-8 years	200 (160)	400	.6 (.5)	40	200 (160)	ND
9-13 years						
Male	300 (250)	600	1.0 (.8)	60	300 (250)	ND
Female	300 (250)	600	1.0 (.8)	60	300 (250)	
14-18 years						
Male	400 (330)	800	1.3 (1.0)	80	400 (330)	ND
Female	400 (330)	800	1.2 (1.1)	80	400 (330)	

**AI=Adequate Intake; ND = Not Determined*

RDA, EAR, UL for Pantothenic Acid, Riboflavin, Thiamin						
	Pantothenic Acid mg		Thiamin mg		Riboflavin mg	
Age Group	RDA (EAR)	UL	RDA (EAR)	UL	RDA (EAR)	UL
1-3 years	2*	ND	.5 (.4)	ND	.5 (.4)	ND
4-8 years	3*	ND	.6 (.5)	ND	.6 (.5)	ND
9-13 years						
Male	4*	ND	.9 (.7)	ND	.9 (.7)	ND
Female	4*		.9 (.7)		.9 (.7)	
14-18 years						
Male	5*	ND	1.2 (1.0)	ND	1.3 (1.0)	ND
Female	5*		1.0 (.9)		1.0 (.9)	

**AI=Adequate Intake; ND = Not Determined*

RDA, EAR, UL for Niacin mg		
Age Group	RDA (EAR)	UL
1-3 years	6 (5)	10
4-8 years	8 (6)	15
9-13 years		
Male	12 (9)	20
Female	16 (9)	20
14-18 years		
Male	12 (12)	30
Female	14 (11)	30

RDA, EAR, UL for Bone Metabolizing Nutrients						
	Calcium mg		Vitamin D IU		Vitamin K mcg	
Age Group	RDA (EAR)	UL	RDA (EAR)	UL	RDA	UL
1-3 years	700 (500)	2,500	600 (400)	2,520	30*	ND
4-8 years	1,000 (800)	2,500	600 (400)	3,000	55*	ND
9-13 years						
Male	1,300 (1,100)	3,000	600 (400)	4,000	60*	ND
Female	1,300 (1,100)	3,000	600 (400)	4,000	60*	
14-18 years						
Male	1,300 (1,100)	3,000	600 (400)	4,000	75*	ND
Female	1,300 (1,100)	3,000	600 (400)	4,000	75*	

**= Adequate Intake; ND= Not Determined*

E. Summary Tables of NHANES

Age Group	Total Calories	Fat (grams)	Protein (grams)	Carbohydrate (grams)	Fiber (grams)
2-5 years					
Male	1641	58.2	58.4	228	11
Female	1486	52.2	51.9	207	10
6-11 years					
Male	2092	79.4	70.9	280	13
Female	1879	71.6	63.4	251	12
12-19 years					
Male	2707	100.9	99.1	352	14
Female	1906	72.3	64.2	253	13

Age Group	Vitamin C mg	Vitamin E mg	Zinc mg
2-5 years			
Male	104	4.6	8
Female	86.7	4.4	7
6-11 years			
Male	87	6	11
Female	75.4	6	9
12-19 years			
Male	86.6	7.7	13
Female	73.8	6	9

Age Group	Calcium mg	Vitamin D IU	Vitamin K mcg
2-5 years			
Male	1009	260	54
Female	957	244	44
6-11 years			
Male	1034	220	52
Female	885	184	48
12-19 years			
Male	1173	236	76
Female	878	152	59

Age Group	Folate mcg	Thiamin mg	Riboflavin mg	Niacin mg	B6 mg	B12 mcg	Pantothenic Acid mg
2-5 years							
Male	427	1.27	1.93	15.8	1.46	4.5	NR
Female	401	1.19	1.8	14.2	1.31	4.1	
6-11 years							
Male	530	1.58	2.15	21.7	1.74	5.2	NR
Female	470	1.39	1.8	18.9	1.57	4.5	
12-19 years							
Male	610	1.88	2.58	28.9	2.29	6.7	NR
Female	509	1.45	1.8	20.8	1.63	4.1	

F. Nutrient Mean Intakes for B Vitamins

Mean Intake of Vitamin B6 (milligrams) by Timepoint and Compared to NHANES*									
Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	1.8	0.03	1.7	0.02	2	0.04	p=.071	
Female	291	1.8	0.06	1.6	0.03	1.8	0.06	p=.067	
Male	376	1.8	0.04	1.7	0.03	1.9	0.05	p=.272	
1-1.99 years	50	1.4	0.05	1.6	0.07	1.4	0.09	p=.008	
Female	30	1.4	0.08	1.4	0.08	1.2	0.07	p=.000	* *
Male	20	1.4	0.07	1.9	0.12	1.9	0.09	p=.000	* *
2-5 years	352	1.4	0.02	1.4	0.02	1.5	0.04	p=.527	
Female	152	1.4	0.03	1.5	0.04	1.5	0.07	p=.752	1.31
Male	200	1.4	0.02	1.4	0.03	1.4	0.04	p=.078	1.46
6-11 years	157	2.5	0.09	2	0.04	2.3	0.09	p=.342	
Female	74	2.6	0.13	2	0	2.2	0.14	p=.038	1.57
Male	83	2.4	0.12	2	0	2.4	0.12	p=.126	1.74
12-19 years	108	2.3	0.1	2	0.05	2.5	0.14	p=.649	
Female	35	2.2	0.22	1.7	0.07	2.1	0.16	p=.098	1.63
Male	73	2.4	0.1	2.1	0.07	2.7	0.19	p=.778	2.29

*All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.

Mean Intake of Vitiamin B12 (micrograms) by Timepoint and Compared to NHANES*									
Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	6.2	0.15	5.9	0.15	6	0.16	*P* =.470	
Female	291	6	0.22	5.7	0.24	6.2	0.26	*P* =.540	
Male	376	6.5	0.2	6.1	0.18	6.5	0.21	*P* =.759	
1-1.99 years	50	4.1	0.25	5	0.38	4.4	0.26	*P* =.472	
Female	30	4.1	0.3	4.9	0.53	4.4	0.37	*P* =.297	* *
Male	20	4.1	0.413	4.8	0.381	4.9	0.28	*P* =.005	* *
2-5 years	352	4.5	0.1	4.7	0.19	5	0.19	*P* =.137	
Female	152	4.4	0.11	4.8	0.32	5	0.3	*P* =.353	4.1
Male	200	4.6	0.15	4.7	0.22	5	0.244	*P* =.184	4.5
6-11 years	157	9.1	0.39	7.4	0.29	8.3	0.42	*P* =.172	
Female	74	8.8	0.58	8	0.43	8.8	0.87	*P* =.347	4.5
Male	83	9.3	0.51	7	0	8.1	0.53	*P* =.099	5.2
12-19 years	108	8.8	0.54	8.1	0.47	0	0.55	*P* =.455	
Female	35	8.6	1.1	6.8	0.88	8.1	0.86	*P* =.017	4.1
Male	73	8.9	0.58	8.7	0.54	9.5	0.69	*P* =.721	6.7

*All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.

Mean Intake of Niacin (milligrams) by Timepoint and Compared to NHANES*									
Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	20	0.313	20	0.19	20	0.38	*P*=.383	
Female	291	19.5	0.48	19	0.33	19.6	0.61	*P* =.634	
Male	376	20.5	0.41	19.9	0.25	21.1	0.48	*P* =.387	
1-1.99 years	50	13.7	0.57	15.4	0.93	13.7	0.68	*P* =.195	
Female	30	12.8	0.89	15	1.4	13.1	0.78	*P* =.002	* *
Male	20	14.7	0.72	16.2	0.71	15.4	0.83	*P* =.050	* *
2-5 years	352	14.6	0.17	15.9	0.24	15.7	0.41	*P* =.000	
Female	152	14.6	0.24	16.1	0.4	16.1	0.78	*P* =.001	14.2
Male	200	14.6	0.24	15.7	0.28	15.3	0.38	*P* =.046	15.8
6-11 years	157	29.1	0.9	25.1	0.44	26.8	0.93	*P* =.105	
Female	74	30	1.3	25.5	0.6	25.8	1.4	*P* =.002	18.9
Male	83	28.4	1.2	24.7	0.6	28	1.1	*P* =.150	21.7
12-19 years	108	27.8	0.98	25	0.54	28.7	1.4	*P* =.509	
Female	35	26.1	2.3	21.9	0.96	23.7	1.7	*P* =.170	20.8
Male	73	28.9	1	26.5	0.64	30.6	1.8	=.849	28.9

**All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.*

Mean Intake of Pantothenic Acid (milligrams) by Timepoint *								
Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)
		Mean	Std Error	Mean	Std Error	Mean	Std Error	
Overall	667	6	0.13	6	0.08	6	0.18	*P=.077*
Female	291	5.9	0.21	5.5	0.11	6	0.26	*P*=.066
Male	376	6.1	0.18	5.7	0.1	6.4	0.23	*P*=.622
1-1.99 years	50	4.5	0.16	5.6	0.29	5.1	0.31	*P*=.022
Female	30	4.4	0.22	5.2	0.3	4.4	0.29	*P*=.000
Male	20	4.9	0.271	6.2	0.592	7	0.68	*P*=.048
2-5 years	352	4.5	0.05	4.8	0.09	5	0.17	*P*=.180
Female	152	4.4	0.07	4.7	0.13	5.2	0.32	*P*=.457
Male	200	4.6	0.08	4.8	0.12	4.8	0.16	*P*=.025
6-11 years	157	8.8	0.42	6.8	0.18	7.7	0.46	*P*=.068
Female	74	9.3	0.63	7	0.29	7.5	0.67	*P*=.007
Male	83	8.4	0.57	7	0.24	8	0.614	*P*=.571
12-19 years	108	7.8	0.48	6.6	0.2	8.6	0.7	*P*=.589
Female	35	7.7	1	5.7	0.29	7.1	0.76	*P*=.023
Male	73	8	0.53	7	0.24	9.1	0.94	*P*=.990

**All values are adjusted for calories. NHANES data not reported.*

Mean Intake of Riboflavin (milligrams) by Timepoint and Compared to NHANES*									
Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	2.4	0.03	2.3	0.02	2	0.04	p=.381	
Female	291	2.3	0.04	2.2	0.04	2.4	0.05	p=.382	
Male	376	2.4	0.04	2.3	0.03	2.5	0.05	p=.675	
1-1.99 years	50	1.8	0.08	2	0.07	1.9	0.07	p=.355	
Female	30	1.8	0.1	2	0.1	1.8	0.08	p=.167	* *
Male	20	1.9	0.14	2	0.11	2.1	0.11	p=.048	* *
2-5 years	352	2	0.02	1.9	0.03	2.1	0.04	p=.367	
Female	152	1.9	0.04	1.9	0.05	2.1	0.07	p=.474	1.8
Male	200	2	0.03	1.9	0.04	2	0.05	p=.049	1,93
6-11 years	157	3.2	0.08	2.8	0.05	3	0.09	p=.007	
Female	74	3.2	0.12	2.80	0.08	3	0.12	p=.002	1.8
Male	83	3.1	0.104	2.80	0.07	3	0.13	p=.237	2.15
12-19 years	108	2.9	0.1	2.8	0.06	3.1	0.13	p=.588	
Female	35	2.7	0.2	2.5	0.11	2.6	0.18	p=.257	1.8
Male	73	3	0.11	2.9	0.08	3.2	0.17	p=.705	2.58

*All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.

Mean Intake of Thiamin (milligrams) by Timepoint and Compared to NHANES*									
Age Group	N	Time 1		Time 2		Time 3		P Value (Adjusted Values)	NHANES (2005-2006)
		Mean	Std Error	Mean	Std Error	Mean	Std Error		
Overall	667	1.6	0.02	1.5	0.02	2	0.03	*P*=.351	
Female	291	1.6	0.03	1.5	0.02	1.6	0.04	*P* =.310	
Male	376	1.6	0.03	1.6	0.02	1.7	0.04	*P* =.841	
1-1.99 years	50	1.2	0.04	1.4	0.07	1.3	0.05	*P* =.011	
Female	30	1.2	0.06	1.3	0.08	1.2	0.04	*P* =.001	* *
Male	20	1.3	0.07	1.8	0.12	1.6	0.1	*P* =.002	* *
2-5 years	352	1.3	0.01	1.3	0.02	1.3	0.03	*P* =.128	
Female	152	1.3	0.02	1.3	0.03	1.3	0.06	*P* =.692	1.19
Male	200	1.3	0.02	1.3	0.03	1.3	0.03	*P* =.023	1.27
6-11 years	157	2.2	0.07	1.9	0.03	2	0.07	*P* =.063	
Female	74	2.2	0.1	2	0.05	1.9	0.11	*P* =.009	1.39
Male	83	2.1	0.09	2	0.04	2.1	0.09	*P* =.216	1.58
12-19 years	108	2	0.07	1.8	0.03	2.1	0.1	*P* =.727	
Female	35	1.9	0.15	1.6	0.06	1.8	0.12	*P* =.263	1.45
Male	73	2.1	0.08	1.9	0.042	2.3	0.14	*P* =.988	1.88

*All values are adjusted for calories. **For children 1-1.99, NHANES data not reported.