

ABSTRACT

Title of Document:

GROWTH DEFICITS AND NUTRIENT INTAKE OF INFANTS AND TODDLERS WITH INFANTILE ANOREXIA AND SENSORY FOOD AVERSIONS AT CHILDREN'S NATIONAL MEDICAL CENTER IN WASHINGTON DC

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Objective/Design: To determine growth and nutrient intake of children with IA (1-3 y), at diagnosis, and after counseling sessions. **Results/Discussion:** Both diagnostic groups (IA and IA+SFA) met criteria for wasting and underweight on average, however the two diagnoses did not present with significantly different mean growth percentiles or z-scores. Girls (n=28) had poorer mean (\pm SE) weight-for-height z-scores, -2.3 (\pm 0.17), than boys (n=34), -1.8 (\pm 0.14), respectively ($P < 0.05$). Girls met the DRIs for nutrients investigated, while boys did not. After counseling, girls' intake remained stable, whereas boys increased intake of all nutrients ($P < 0.05$). Catch up weight gain was not adequate for boys or girls of either diagnosis to restore weight related growth percentiles and z-scores during the study period (mean of 7 mo.). **Conclusion:** These data establish the first IA growth rate benchmarks that may be improved upon with further clinical intervention, particularly for IA boys.

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WASHINGTON DC

By

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Dedication

To all the children who struggle with feeding and eating disorders, to their families, and to faculty and staff at Children's National Medical Center who are committed to their recovery.

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This project would not have been possible if it were not for the community of kind, caring, and generous individuals, deeply dedicated to their work and committed to developing the next generation of scientists and practitioners.

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Thank you.

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List of Abbreviations

IA – Infantile Anorexia

SFA – Sensory Food Aversions

IA+SFA – Infantile Anorexia and Sensory Food Aversions (children with both disorders)

FTT – Failure to Thrive

NOFT – Non-organic (non-medical) Failure to Thrive

CDC – Centers for Disease Control and Prevention

FITS – Feeding Infants and Toddlers Studies (A collection of studies on infant and toddler feeding habits and practices, beginning in 2002)

IOM – Institute of Medicine

DRI – Dietary Reference Intakes

RDA – Recommended Dietary Allowance

EER – Estimated Energy Requirement

EAR – Estimated Average Requirement

AI – Adequate Intake

UL – Tolerable Upper Intake levels

RAE – Retinol Activity Equivalent

Specific Aims

The goal of this study was to describe the growth deficits and nutrient intake of infants and toddler's diagnosed with Infantile Anorexia (IA), or the combination disorder of IA with Sensory Food Aversions (IA+SFA), at diagnosis (baseline) and at follow up visits after psychiatric and nutritional counseling at Children's National Medical Center (Children's) in Washington D.C. This is the first study to characterize the nutrition status of this population and it will contribute to the limited pool of information about the impact of IA and IA+SFA feeding disorders on young children.

The four main objectives of this study were as follows:

- 1) To determine the severity of growth deficits in IA and IA+SFA children at diagnosis (i.e. baseline), by examining mean growth percentiles and Z-scores based on the Centers for Disease Control and Prevention (CDC) growth charts.**
 - a. To determine if there were significant differences in growth between the different diagnoses, genders, and ages at baseline.
- 2) To establish whether nutrient deficiencies accompanied poor growth observed at baseline, by examining mean nutrient intake values of key nutrients.**
 - a. To provide a descriptive comparison of mean nutrient intake values of each group with the Institute of Medicine's (IOM) Dietary Reference Intake values (DRIs).

- b. To determine if there were significant differences in nutrient intake between different diagnoses, genders, and ages at baseline.
- c. To descriptively compare mean nutrient intake values of each group with mean intake values of a reference group of children (FITS data).

3) To examine the percentage of supplements and fluids consumed by each group at baseline, and to determine if significant changes in supplement and fluid consumption occurred after counseling.

- a. To determine if there were descriptive differences in supplement and fluid consumption between the different diagnoses and genders at baseline and after counseling.
- b. To descriptively compare supplement and fluid consumption of IA and IA+SFA children with the reference group of children (FITS data).

4) To understand the impact of counseling at Children's National Medical Center on growth rate and adequacy of nutrient intake in IA and IA+SFA Children.

Hypotheses

- 1) Children with IA and IA+SFA will exhibit severe anthropometric deficits at diagnosis (baseline) and there will be differences between the two diagnoses when gender and age are controlled;
- 2) Nutrient deficiencies (intake below the DRI) will accompany growth deficits observed at diagnosis and mean nutrient intake values will be descriptively lower in children with either IA or IA+SFA than the mean intake values of reference children the same age (FITS children);
- 3) Fluids and supplements will contribute to a large portion of the children's total daily intakes (of both diagnoses) at diagnosis;
- 4) Growth (weight and length/height) and diet (whole food and nutrient intake) will improve among all of the children during the follow-up sessions, post-counseling, at Children's National Medical Center. Children will rely less on fluids and supplements and more on whole foods to fulfill nutrient needs.

Introduction

Current knowledge regarding the growth patterns and nutrient intakes of children with Infantile Anorexia (IA) or the combination disorder of IA with Sensory Food Aversions (IA+SFA) is limited. Previous research on malnourished children has focused on those whose limited nutrient intake and growth faltering was due to underlying medical conditions or deprivation in developing countries. There is little research on children who have no underlying disease or obvious deprivation, yet have poor dietary intake and substantial growth faltering.

In the past, anorexic infants were all classified together as having “Non-Organic Failure to Thrive” (NOFTT), non-organic meaning no disease, regardless of the etiological nuances. The current literature on IA has focused on cognitive development and on mother-toddler interactions during feeding. Little or no research has simultaneously described the nutrient intake and growth of children who have been diagnosed with IA or IA+SFA, two specific feeding disorders grounded in unique etiologies, that fall under the outdated umbrella term of NOFTT.

This study will be the first to describe the growth and nutrient intake of children who have IA and IA+SFA feeding disorders. This study will be the first to establish growth and nutrient intake benchmarks that can be used to determine rates of catch-up growth that may be possible with clinical intervention. Although the underlying psychological and physiological causes of IA and IA+SIA are important, such an analysis is outside the scope of this project.

Literature Review

It is estimated that 25% -35% of children in the US are “picky” or “fussy” eaters (1), and in a recent large US cross-sectional survey, the percentage of caregivers who perceive their children to be “picky” eaters increased with the age of the infant from 19% at 4 months, to 50% by 19 months of age (2). Longitudinal research suggests that feeding problems and eating disorders that start early are stable over time (1,3). Rydell, Dahl, and Sundelin (1994) reported that 70% of infants with severe eating disorders continued to have serious feeding problems when re-assessed at 4 y and 6 y (1,3). It is also estimated that 1% to 2% of infants and toddlers have severe feeding disorders that are accompanied by poor weight gain and stunted height (1). Feeding disorders that manifest in extreme food refusal (i.e., excluding whole food groups from the diet) increase the risk for nutrient deficiencies critical to growth and development.

Infantile Anorexia (IA) and Sensory Food Aversions (SFA)

The onset of IA often begins during the transition to spoon- and self-feeding, sometime between 9 and 18 months, as children begin to gain more control of their actions, as they learn to walk and talk, and as they discover the world around them. They become so busy, that they seem to have no more time to sit in the high chair and eat (4). Typical behaviors of children with IA include: lack of appetite, disinterest in eating, enhanced interest in play or exploration during mealtimes, extreme food refusal when offered most foods, tantrums or climbing out of high chair and/or leaving the table to play

after only a few bites are eaten. All these factors contribute to poor overall intake on a daily basis (4).

Children with SFA have similar characteristics to children with IA, but differ in food refusal behavior. Children with SFA tend to restrict intake of certain foods but maintain intake of other foods, so unlike IA children, the total quantity of food consumed may not be an issue (1,4,5). Children with SFA typically have severe aversions to specific foods based on the tastes, textures, smells, and/or appearances that they find unappealing or are associated with unpleasant experiences (e.g., gagging, vomiting). Some reactions to these foods include grimacing, gagging, vomiting, or spitting out the food. This behavior can progress from refusing one food (e.g, green peas) to refusing whole food groups (e.g., all vegetables), which increases the risk for nutrient deficiencies (1,4,5). Some children exhibit a combination of both IA and SFA, referred to as IA+SFA in this paper. Children with the combination disorder can exhibit IA behavior (food refusal in general), with strong aversive reactions to certain foods, typical of SFA behavior.

Parent-child conflict occurs when parents struggle to coax their IA or IA+SFA children into eating more. Often, the parent establishes a pattern of force-feeding and tries to feed the child in between meals or provide the child with fluid formulas and supplements throughout the day. The result is a child who is satiated and whose hunger and food intake are externally regulated by the parent, rather than being internally regulated by the child (1,4,5). Infants and toddlers have the innate ability to adjust intake

to meet caloric needs if allowed to do so (6). Recognizing signs of hunger, and then feeding until satiated, is one of the main goals of therapy for children with IA.

Nutrition

Previous research from developing countries provides strong evidence that nutrient deficiencies in young children can lead to long-term health complications. A recent study has confirmed that the optimal window for growth and for preventing serious health complications is before 2 years of age (7a). Some of the long-term health consequences associated with stunted growth (weight and height) include: impaired cognitive development (inadequate iron), impaired immunity (inadequate zinc, vitamin D, vitamin C), compromised bone, muscle, and nerve health (inadequate calcium, vitamin D, phosphorus), and a higher risk of mortality (7).

Although all nutrients are essential, zinc deficiency has been shown to be particularly detrimental during infancy, leading to impaired immune function and growth deficits (7). Other growth limiting nutrients in infancy include: iron, phosphorus, and calcium (7). Iron is necessary for carrying oxygen to all cells of the body including the developing brain and deficiencies have been associated with developmental and cognitive disabilities (8). Calcium is vital for proper bone, muscle, and motor development, nerve functioning, blood clotting, and regulating the heartbeat. It is important that adequate calcium is obtained during childhood when maximal bone and mineral deposition occurs. Vitamin A is essential for proper eye development and deficiencies can cause blindness (9).

With respect to the macronutrients, protein (especially from a variety of animal products) provides a rich source of essential amino acids. Protein-rich foods also deliver the majority of bioavailable zinc, iron, vitamin A, and vitamin D in the diet (8). Adequate fat intake from breast milk and/or infant formula is critical in early infancy, providing concentrated energy and a source of essential omega-6 and omega-3 fatty acids. Fat intake decreases during weaning with the introduction of complementary foods, which typically occurs between 6-12 months of age (10,11), and other sources of fat need to be introduced and accepted by the child.

Whole foods confer benefits (i.e. fiber and phytochemicals) that dietary supplements and fortified fluids alone may not provide. It is important that children are introduced to a wide variety of foods at a young age when healthy eating habits are established (6). Adequate intake of a variety of whole foods should be a main goal of therapy for children with IA and IA+SFA as opposed to providing nutrients in the form of supplements and fluid formulas. Some studies have found that supplementation alone may not be enough to reverse stunting and the associated health consequences (8). Additionally, excessive supplementation can be toxic in young children (8). Moreover, if young children reject whole foods that require significant chewing, they can fall behind in oral/motor development (4).

Growth

Feeding disorders in young children lead to growth deficits that may be irreversible if not properly treated before 12-24 mo of age (7a,12,13). Studies on growth patterns indicate that an individual's growth trajectory is established between the ages of 12-36 mo, after which stunting has been shown to remain permanent without proper early nutritional support (10,14). Longitudinal studies in India, Guatemala, and Honduras show that children who remained stunted up until age 5, had little catch-up growth beyond age 7, and remained shorter than their peers as adults (12). Growth patterns of undernourished children from various developing regions around the world display height-for-age and weight-for-height growth curves that fall well below the 50th percentiles and are never fully restored as the children grow older. Children between 12-36 mo of age with feeding disorders, such as IA and IA+SFA characteristically exhibit growth curves that falter and plateau well below the 25th percentiles (4) resembling growth curves of malnourished children in developing countries.

Growth Criteria

There is no single standard method for determining when children are at increased risk for malnutrition based on their growth status; however, the World Health Organization (WHO) (15) and pediatric specialists (16,17,18,19) agree that the following criteria provide warning signs: 1) If a child's weight is at or below the 3rd or 5th percentile for their age or for their height, on the CDC or WHO growth charts; 2) If a child's z-scores is ≤ -2 standard deviations (SD) away from the mean on a standard normal curve for weight (for age or for height) and for height-for-age; 3) If a child's

percent ideal body weight (for age or for height) is < 90% (16,19).; and 4) If a child's growth declines two major percentile categories (i.e., 50th to the 10th or 25th to the 5th) in a 6 month period, below an already established growth rate (15,16,18,19). If a child meets one or more of the above criteria, malnutrition is likely and a specialist should be sought.

Z-scores are often used in addition to growth percentiles when children are <5th percentile or above the 95th percentile (15,17). The z-score is a measure based on the standard normal bell-shaped curve, denoting standard deviation units from the central mean, median, and mode (all identical) (17). Experts recommend using z-scores to assess and monitor the nutritional status of malnourished children rather than using the CDC growth percentile and "percent ideal body weight" for-age or for-height (or percent median). There are several benefits to using z-scores to assess the nutritional status of both individuals and populations. Z-scores are easier to use than the other growth criteria because they are independent of age and gender, can describe means in more precise increments, and can characterize growth at the extreme ends of the distribution that are not represented on the CDC growth charts (16,17).

When using z-scores to assess nutritional status, both weight-for-height and height-for-age z-scores are recommended to provide an indication of both wasting (acute malnutrition) and stunting (chronic malnutrition). Weight-for-age is considered a poor indication of wasting in children, especially in children older than 12 months. After 12 months more growth variation occurs in children and weight-for-age fails to distinguish

between tall, thin, undernourished children from those that are short with adequate muscle mass. However, weight-for-age can be a valuable indication of wasting when followed over time (15,16). Although the CDC growth charts are less useful than z-scores for determining a child's nutritional status, clinicians can use the CDC charts to help parents interpret their child's progress compared to that of healthy children and to ensure they continue growing steadily without faltering (15).

This study will describe the growth and nutrient intake of infants and toddlers, who were referred by their pediatricians to Children's National Medical Center (Children's) in Washington DC and subsequently diagnosed with IA and IA+SFA. The intention of this paper is to provide more information about nutrient intake and growth of children who have feeding disorders that are not rooted in disease or caused by third-world deprivation. The benchmarks established herein can be used to determine rates of catch-up growth that may be possible and improved upon with clinical intervention.

Experimental Design and Methods

Data Source

This study is a secondary analysis of growth and nutrient intake data of children diagnosed with IA (including IA+SFA) who participated in a psychiatric study at Children's National Medical Center in Washington, D.C. The data were previously collected from children who were referred by their pediatricians to Children's because of growth deficits and poor eating behaviors. The dataset was compiled during a five-year study (1999- 2004) that was conducted in two phases. Phase I was designed to validate several diagnosed feeding disorders and Phase II was intended to treat a subset of those disorders (IA and IA+SFA). The Children's National Medical Center Institutional Review Board approved the study protocol (20) and parents provided written informed consent. This study is a retrospective, observational, cohort study that describes the growth status and nutrient intake of IA and IA+SFA children at the time of diagnosis and after nine weeks of behavioral and psychological counseling.

Study Design I: Subjects and Diagnosis

Enrollment

Children with feeding problems and growth deficits were referred by their pediatricians to participate in a study for a diagnostic evaluation made by Irene Chatoor, MD, a feeding disorder specialist and psychiatrist, and her team at Children's. Among 477 children who were referred, the parents of 444 (93%) children agreed to participate

and their children were included in the diagnostic study. Children were excluded if parent consent could not be obtained, or if children were younger than one year or over the age of six years.

Diagnostic Interview and Physical/Medical Examination

A pediatric nurse practitioner collected histories of the child's feeding behaviors, developmental health, and physical health. Clinicians recorded whether children had ever been tube fed in the past and whether children had chewing or swallowing difficulties. Additionally, the nurse and a pediatric gastroenterologist conducted a medical exam to identify non-psychiatric (or medical, organic) causes of food refusal, such as gastro-esophageal reflux, or infections. Children with organic causes of food refusal were excluded from the study and were referred for medical treatment.

Diagnostic Anthropometric Data Collection (Dataset #1)

Trained clinicians measured (in triplicate) the children's weight (kg), recumbent length or height (cm) (note that height and length will be used interchangeably in this study due to the age range of the study population), and head circumference (cm), to the nearest 0.1 kg for weight and 0.1 cm for length/height and head circumference. Mean values were plotted on CDC growth charts. Standing height was measured if children were 36 months and older, otherwise recumbent length was measured. Weight measurements were conducted while children were in diapers or light clothing with no shoes, placed in the center of a calibrated beam or an electronic scale. Length/height measures were conducted in the same way, but with a calibrated scale that had a fixed

headpiece and movable foot-piece (only for length). Head circumference was measured using a flexible, non-stretchable measuring tape, just above the ears, eyebrows, and around the back of the head to obtain the maximum circumference. Measurements were recorded as ‘baseline anthropometrics at diagnosis’ and were analyzed for this research study.

Diagnostic Nutrient Intake Data Collection (Dataset #1)

Registered dietitians collected food records from parents who were asked to record all foods, beverages, and supplements consumed by the child for three consecutive days prior to the first visit. Trained dietitians administered a 24-hour recall to the parents if 3-day food records were unavailable or incomplete. Food models and a multiple-pass method were used during the 24-hour recall to ensure that as many food items as possible were remembered. Mean daily intake of energy and nutrients was calculated using Nutritionist Pro Software, v 3.0-4.2 (Axxya System, Stafford, TX).

The following nutrient intake values were compared to the IOM’s DRIs to determine adequate intake: calories per kilogram (kcal/kg), protein (g/kg), calcium (mg/d), iron (mg/d), and vitamin A (RAE/d). The children’s nutrient intake from fluids was also recorded and expressed as a percentage of the daily total energy (kcal/d) consumption. Intake of vitamin or mineral supplements were calculated using the nutrition label on the supplement container or by locating the Nutrition Facts Label for the supplement on the company website. Nutrient intakes were recorded as ‘baseline nutrition at diagnosis’ and were analyzed for this study.

Diagnostic Criteria for IA and IA+SFA

The study psychiatrists classified children as IA (including IA+SFA) if they were $\leq 90\%$ of their ideal body weight-for-height (acute malnutrition, Waterlow 1977) and/or $\leq 95\%$ of their ideal height-for-age (chronic malnutrition, Waterlow 1977), using the 50th percentile on the CDC growth chart as the “ideal”. Children also met the IA (including IA+SFA) criteria if their growth rate slowed and crossed two major percentile categories or more (i.e., from the 50th to the 10th percentile or from the 20th to the 5th percentile) in weight over a six-month period in the context of unhealthy feeding behaviors (18).

Among 444 children who were enrolled in the diagnostic study, 164 met the criteria for IA based on their food refusal behaviors and anthropometric measurements. Of the 164 IA children, 70 (32 IA and 38 IA+SFA) were included in a treatment study. The remaining 94 IA children were excluded from the treatment study: 55 children were excluded because they were under one year old or over three years old; 19 children were excluded because they did not meet the criteria for growth deficits (sub-clinical: growth slowed, but not enough); 13 children were excluded because of co-morbid medical conditions or Posttraumatic Feeding Disorder; the parents of 4 children refused to participate; the parents of 3 children sought private treatment elsewhere.

Study Design II: Randomized Treatment of IA and IA+SFA, (Figure 1)

Within three weeks of the diagnostic visit, families returned to the clinic for 6 IRB-approved treatment sessions designed to test two different psychiatric approaches (a 'treatment' and a 'control' approach) regarding parent-child interactions and parental engagement in the treatment process. The 70 children and their families were randomized into two groups to receive either the parent-centered counseling approach ('treatment'; n=36) or the child behavior observational approach ('control'; n=34) during the first 2 treatment sessions, scheduled one week apart, of 6 total treatment sessions. The subsequent 4 treatment sessions, scheduled two and three weeks apart, were similar for all patient families (Figure 1). Of the 70 enrolled children, the first eight participants were considered training cases for clinician investigators, *a priori*, and were excluded from the final analysis (n=62; 34 males, 28 females; 35 IA, 27 IA+SFA, Table 1). Nutrient and growth data collected by the clinicians during the treatment sessions were not used for analysis, but were collected for the sole purpose of tracking the children's nutrition status throughout the treatment.

Group 1 Received Parent-Centered Counseling ('Treatment')

The two-hour parent-centered psychiatric counseling sessions ('treatment') at visits 1 and 2 (performed about one week apart within 3 weeks after the initial diagnosis, figure 1) were designed to: 1) Explore the methods used by parents/caregivers in feeding and disciplining the child; 2) Discuss the parents'/caregivers' own upbringings and the extent this may affect how they interact with and discipline their child during mealtime;

3) Help parents better understand how their child makes the transition to self-feeding and how conflicts over meals can negatively impact the child's internal regulation of hunger. Parents were videotaped feeding their children during lunch. After lunch, parents viewed the taped session with the psychiatrist who provided specific examples for improving behaviors; and 4) Reassure parents that they can learn to implement techniques that will be taught in subsequent sessions, which will make mealtimes more pleasant and result in their child eating and growing properly (21).

Group 2 Received Observational Sessions ('Control')

During the two-hour child behavior observational sessions ('control') at visits 1 and 2 (Figure 1), the parents were videotaped while playing with their child. The goal of these sessions was for the psychiatrist to identify the parents' and toddlers' interaction styles and the toddlers' development stage. Afterwards, a questionnaire assessing parenting styles was administered to the parents and a discussion with the psychiatrist followed. The discussion focused on whether the interactions and behaviors during the videotaped sessions were typical, and if there were behavioral differences when the child was with one parent versus the other, or when both parents were present. During the second 2-hour session the parents watched videotapes describing normal physical, cognitive, emotional, and social development in healthy infants and toddlers. Afterwards, parents discussed their own parenting styles and their child's development with the psychiatrist. The psychiatrist in the observational sessions ('control') listened to the parents but did not give parenting advice at these initial sessions, even when the parents

asked for advice. Rather, the psychiatrist invited the parents to provide their own thoughts about what to do (22).

Group 1 and Group 2 Received Four Behavioral and Diet Counseling Sessions

During visits 3-6 (study weeks 3-11, beginning 4-7 weeks post-diagnosis), psychiatric care was the same for both randomized groups. These visits included 4 sessions of behavioral and diet counseling for the family offered by a registered dietitian (Figure 1). The counseling sessions were designed to teach parents specific feeding guidelines that would help the children recognize hunger and eat until full. In addition, the parents were given instructions for limit setting, for how to help their children learn self-calming, and how to problem solve as they were implementing the feeding guidelines and limit setting. The sessions consisted of the following three components: 1) Advising parents/caregivers on how to structure regular mealtimes to facilitate the child's awareness of hunger; 2) Advising parents/caregivers on how to appropriately increase child's energy intake; and 3) Monitoring the child's growth, food intake, and nutrient intake, which was a joint effort between the parent/caregiver and the dietitian. Growth measures (height, weight, head-circumference, and percentiles on the CDC growth charts) were recorded by the dietitian at each visit. Nutrient intake information was collected using two 24-hour recalls at two of the four visits, administered by the dietitian, and one 3-day food record, recorded by a parent/caregiver and reviewed with the dietitian. The goal of these sessions was to help parents/caregivers understand the child's nutrient needs and the appropriate growth patterns the child should be tracking. Feeding goals were tailored to the individual needs of the child. All dietary and growth data collected by registered dietitians during the treatment sessions, visits 3-6, were used only

for tracking the children's nutrition status, and were not available for research purposes or to the therapists.

Study Design III: Follow-Up Sessions (Dataset #2)

Three follow-up visits were scheduled, one, six, and twelve months post-counseling to assess changes in growth and nutrient intake from the time since diagnosis, after completion of the 6 treatment sessions (Figure 1). Data collection and procedures at the 3 follow-up sessions were similar to the diagnostic assessments for anthropometric measures and nutrient intake values. Dietitians, however, noted changes in growth and nutrient intake since previous visits. Follow-up data were analyzed and used for this study.

Attrition rates throughout treatment and follow up were high and dropouts occurred immediately after the diagnostic (baseline) visit. There were many reasons families decided not to continue participating. Some families moved away, others felt it was difficult to fit treatment into their schedules, some of the parents/caregivers became dissatisfied with the treatment while others felt that a few visits sufficiently resolved their children's issues. Some parent/caregivers had psychiatric or medical issues of their own and could not continue bringing their children in for appointments.

At diagnosis, there were 62 children in the study. The numbers (and percent) of children remaining with available growth data post-counseling were as follows (Figure

1): At follow-up visit 1, 38 children remained (61%); At follow-up visit 2, 29 children remained (47%) and; At follow-up visit 3, 23 children remained (37%). The numbers (and percent) of children remaining with nutrient intake data available post-counseling were as follows: At follow-up visit 1, 18 records were available (29%); At follow-up visit 2, 15 records were available (24%) and; At follow-up visit 3, 25 records were available (40%). This study compensated for attrition by analyzing trends over time (6 months), beginning from the time of diagnosis (baseline) and continuing on through the follow up sessions, using the linear regression technique.

Data Compilation and Processing

This study used two sets of data for the analysis; the first set, called dataset #1, is the nutrient intake and growth information from the diagnostic (baseline) visit. The second set of data, called dataset #2, is the nutrient intake and growth data from the 3 follow-up visits, post-counseling. This study characterizes the nutrition status of IA and IA+SFA children before and after counseling. This study does not compare the two different psychiatric treatment approaches, ‘Treatment’ vs ‘Control’, that occurred in the first 2 clinical visits after diagnosis. The two approaches are both considered part of the counseling regimen as a whole.

Descriptive data (gender, age, diagnosis, ethnicity), anthropometric measures, and nutrient intake values were examined, including: weight (kg), weight-for-height percentiles and z-scores, weight-for-age percentiles and z-scores, height (cm) or

recumbent length (cm) (for children under age 3 y), height-for-age percentiles and z-scores, head circumference (cm), and head circumference percentiles and z-scores. The children's CDC growth percentiles and z-scores were initially collected from clinical records, but were not used in the final analysis since many percentiles were based on the outdated CDC growth charts (prior to the year 2000). To correct this, all percentiles and z-scores were recalculated using the "SAS Program for the CDC Growth Charts", provided by the CDC website (2009) [Accessed September/October, 2009] and were based on the most recent versions of the CDC growth charts created in 2000. Z-scores were used in addition to growth percentiles because they are recommended for use with, and sometimes in place of growth percentiles, when all children cluster below the 5th percentile or above the 95th percentile (15,17).

The following nutrient intake information was analyzed: Total calories (kcal/kg/d), total calories from fluids (kcal/kg/d), total protein (g/kg/d), total protein from fluids (g/kg/d), total iron (mg/d), total zinc from fluid formula (mg/d), total vitamin A (RAE/d), total calcium (mg/d), and the micronutrient intake from vitamin or mineral supplements (non-food items, formulas and/or vitamins tablets). Intake values from supplements were calculated by hand if food records were missing using the total intake for a nutrient provided by Nutritionist Pro and the supplement brand name and quantity of intake provided by the 3-day food record or 24-hour recall. The percent intake of calories and protein from fluids and the percent intake of micronutrients from supplements were calculated. Fluids included milk (usually cow's, but sometimes soy), infant formulas (such as Pediasure, Isomil, Similac, Enfamil, Boost, and Carnation

Instant Breakfast mixed with milk or water, used to boost macro- and micro-nutrient consumption), fruit juices, and water. The various fluids were grouped together for the analysis. Supplements, in this study, refer to formulas and vitamins used for the sole purpose of increasing specific nutrients to encourage growth and weight gain (i.e. Pediasure and Flintstone's Complete Multivitamins – not including regular milk (or soy milk) as a beverage).

The nutrient values that are required on the Nutrition Facts Label were considered to be the most reliable (accurate and complete) nutrient data for foods included in the Nutritionist Pro software (used for this analysis), and among these, the study clinicians chose to track energy, protein, calcium, vitamin A, and iron. Zinc intake was also examined, but dietitians who coded the food records did not indicate whether or not the coded foods had associated values for zinc in the software. Thus, reported zinc intake from food may be underreported, whereas, supplemental zinc intake is assumed to be an accurate reflection of the food recorded.

Reference Population for Dietary Intake Comparison – FITS Study

Data for the reference population was taken from the Feeding Infants and Toddlers Study (FITS) conducted in 2004 (11). This study collected nutrient intake data from a large national random sample (n=998) of toddlers, ages 12-24 mo, using 24-hour recalls and 2-day food records. Mean usual nutrient intake was determined with software that calculated usual intakes using percentiles to estimate nutrient distribution (rather than mean nutrient intake/day). The Institute of Medicine (IOM) (23) recommends reporting mean usual intakes to estimate prevalence of nutrient inadequacy, rather than mean

intakes/day, because the amount of food infants and toddlers eat varies from day to day. This method attempts to capture nutrient intakes that may be missed if mean daily nutrient intakes are calculated based on one- or two-day food records. Additionally, the mean usual intake method is believed to have lower variance than the one-, two-, or three-day mean intake method. The results of other studies suggest (6, 24), however, that children in this age group do not show substantial variations in food intake from day to day. Therefore, some recent studies have used FITS data to calculate mean intakes per day (not usual intakes) from one-, two-, or three-day food records (6, 24). This study aims to capture the same outcome that the mean usual intake data of the FITS study is able to capture by using mean intake per day. However, comparisons between mean nutrient intake in this study and the FITS study should be considered with caution since different methods were used to determine mean intakes and because these comparisons were made descriptively, not statistically.

Statistical Analysis

All statistical analyses were performed using SAS® Release 9.1 (SAS Institute Inc, Cary, NC) and statistical comparisons were made at the alpha level of 0.05. Proc Univariate was used to test if response variables (anthropometric measures and nutrient intake variables) had a normal distribution. Variables were considered non-normal if they had a $P < 0.05$ for the Shapiro-Wilk Test and/or the Kolmogorov-Smirnov Test. Non-normal variables were transformed using the base-10 logarithm. Non-normal variables included: weight (kg), weight-for-age percentile, weight-for-height percentile, height-for-

age percentile, head circumference-for-age percentile, head circumference z-score, total energy (kcal/kg/d), protein from fluids (g/d), total iron (mg/d), total zinc (mg/d), total vitamin A (RAE/d), total calcium (mg/d), supplemental iron (mg/d), supplemental zinc (mg/d), supplemental vitamin A (RAE/d), supplemental calcium (mg/d). Means, regression coefficients, and standard errors of transformed variables were back-transformed for reporting, but P-values are presented as obtained in the analysis (with the transformed data).

Means of all anthropometric and nutrient intake variables were calculated when children were diagnosed (at baseline), for each diagnosis within each gender using the Means Procedure. Note that statistical analyses were not used to generate significant differences between children's nutrient variable means and the DRIs or the FITS data. Variable mean comparisons to reference values are descriptive. Variable mean comparisons among the different groups of children, however, are statistical and can be stated with confidence. Pearson correlation coefficients were used to determine relationships between growth variables (weight, height, head circumference) and all nutrient intake variables, including nutrient intake from supplements. Correlation coefficients were considered significant at the alpha level of 0.05.

The GLM procedure was used to construct three statistical models. The first model was constructed to test hypotheses 1, 2, and 3. The second and third models were constructed to test hypothesis 4.

Hypotheses 1,2, and 3:

1. Children with IA and IA+SFA will exhibit severe anthropometric deficits at diagnosis (baseline) and there will be differences between the two diagnoses when gender and age are controlled;
2. Nutrient deficiencies will accompany growth deficits observed at diagnosis and mean nutrient intake values will be descriptively lower in children with either IA or IA+SFA than the mean intake values of reference children the same age;
 - Deficiencies are determined by mean nutrient intake values that fall descriptively below the IOM's DRIs (25-27);
 - The reference data are from a large, national random sample of US children, ages 1-2 y (FITS data) (11);
3. Fluids and supplements will contribute to a large portion of the children's total daily intakes (of both diagnoses) at baseline and compared to FITS (11,24) data.

Test:

The first model was used to test the effects of diagnosis, gender, and age at diagnosis on anthropometric and nutrient intake variables at diagnosis (baseline) only. Interactions were determined by including the term 'diagnosis' by 'gender' in the model. Diagnosis and gender were chosen because they were significant as main effects. An estimate statement was included to determine the linear relationship between age at diagnosis and response variables. Children's nutrient values at diagnosis were averaged and classified by diagnosis (IA and IA+SFA) within each gender for a descriptive (not statistic) comparison to the Institute of Medicine's (IOM) Dietary Reference Intake

values (DRIs) (25-27) and to the mean usual intake data of children from the 2004 Feeding Infants and Toddlers Study (FITS) (11). Mean percent fluid and supplement intake of the total mean intake was calculated using Excel.

Hypothesis 4:

4. Growth and nutrient intake will improve among all children during the follow-up sessions, post-counseling. Children will rely less on fluids and supplements and more on whole foods to fulfill nutrient intake needs.

Test:

The second model was used to test the effects of diagnosis, gender, age at diagnosis, and time since diagnosis on the entire dataset, including all anthropometric measures and nutrient intake variables from the time of diagnosis through the third follow-up visit. Interactions were determined by including the terms ‘diagnosis’ by ‘gender’ and ‘time since diagnosis’ by ‘gender’ in the model (chosen because they were significant as main effects). Estimate statements were included to determine the linear relationship between age at diagnosis and time since diagnosis on the response variables.

Rate of change was added to the dataset for weight (kg) and height (cm) by determining the difference in each measure between consecutive visits for each child. A third model was used to test the effects of diagnosis, gender, age at diagnosis, and time since diagnosis on the rate of weight and height gain. Interactions were determined by including the terms ‘diagnosis’ by ‘gender’ and ‘time since diagnosis’ by ‘gender’ in the

model (chosen because they were significant as main effects). Estimate statements were included to determine the linear relationship between age at diagnosis and time since diagnosis on the rate of weight and height gain for both genders and diagnoses.

Tables

Table 1 shows demographic characteristics grouped by diagnosis. Table 2a was constructed to demonstrate the similarities and differences between the two diagnoses, a key aim of the study. Anthropometric and nutrient intake means were compared to the IOM references of individual basis for recommendations. Table 3a shows the mean growth percentiles and z-scores of all groups (boys and girls of both diagnoses). For table 2a and 3a, nutrition status cut-offs for percentiles and z-scores are from the CDC and/or WHO. Table 3b shows the mean increases in weight and height per day, per 6 months, and over the entire study period for each group (boys and girls of both diagnoses). Each child remained in the study for a different length of time and had a different number of weight and height measures (see Table 3b, superscripts g, h, and i). Each gender and diagnostic group had a different mean participation period for weight and height measures (in days). This number of days was used to find the average total weight and height gains over the entire course of the study (in days), using the rates of growth per day generated from SAS (the estimates or the slopes). The rates of growth in a 6 month period were determined from multiplying the rates per day by 180 days. The reference growth rates were determined from The CDC Growth Tables for children 3-4 yrs old (35.6 – 47.5 months) and the growth increments are based on the 50th percentile.

Table 4 shows the mean nutrient intake (including the percent of that intake from fluids or supplements) of all groups (genders and diagnoses) at baseline in comparison to the IOM's recommendations and to the FITs mean usual nutrient intakes per day. Table 4 also shows the change in mean nutrient intake after counseling for boys and girls because the two genders had statistically different changes in intake after counseling. The changes in mean nutrient intake for the diagnostic groups were not statistically different from one and other and thus are not shown. For more details about IOM reference and FITS nutrient intake calculations, see superscript notes in table 4.

Results

Subject Characteristics

The 62 children measured at baseline between November 2000 and March 2005 were predominantly non-Hispanic White (68%) and male (55%); 35 (51% male) were diagnosed with IA and 27 (59% male) were diagnosed with IA+SFA (Table 1). The average age (mean \pm SD) at diagnosis was 1.9 (\pm 0.6) years (22.5 (\pm 7.4) months) and children were 3.3 (\pm 0.9) years (39.7 (\pm 10.6) months) at the last follow-up measure (n=23). Age did not differ significantly between types of IA (Table 1).

Baseline Anthropometric Data

Children showed predominantly mild malnutrition (\leq 90% of ideal body weight-for-height), but no moderate or severe malnutrition (i.e., cases of severe malnutrition were excluded from enrollment). At diagnosis, children averaged 87.2% and 88.6% of ideal body weight-for-height for IA and IA+SFA groups respectively, and IA but not IA+SFA children met the additional enrollment criterion of \leq 95% of ideal height-for-age, averaging 95% and 102%, respectively (Waterlow Criteria, Table 2b).

There was evidence of wasting using the z-scores for weight-for-height for both diagnostic groups but not when using the growth percentiles (Table 2a). Evidence of underweight, or poor weight-for-age, was evident for both diagnostic groups using either

the z-scores or the growth percentiles (Table 2a). Similarly, IA+SFA children fell short of the IOM's reference value for weight, while IA children fell short of the IOM's reference values (1-3 yrs old) for both weight and height (Table 2a). IA+SFA children were significantly heavier and taller than IA children at diagnosis [mean (\pm SE) 10.9 (\pm 0.31) kg and 88.0 (\pm 1.34) cm versus 9.6 (\pm 0.25) kg and 81.9 (\pm 1.07) cm, respectively, $P < 0.05$] (Table 2a). Height-for-age and head circumference-for-age were in the normal range using all references (z-scores, growth percentiles, IOM) for both diagnostic groups (Table 2a).

Table 3a describes the genders within each diagnosis and shows that boys were underweight-for-age while girls were underweight-for-height (evidence of wasting) and age, on average, according to the CDC and WHO (Table 3a). Girls (n=28) had significantly worse weight-for-height and weight-for-age disparities at diagnosis than boys (n=34) when age was controlled, with z-scores averaging -2.3 (\pm 0.17) versus -1.8 (\pm 0.14) and -2.7 (\pm 0.16) versus -2.2 (\pm 0.13), respectively ($P < 0.05$) (Table 3a). There was no significant difference in weight-related z-scores or growth percentiles when children were grouped only by diagnosis. Nor were there differences in height related measures between the genders or diagnoses - all were classified as normal, or not stunted (Table 3a).

Head circumference measures, percentiles, and z-scores were in the normal range for children of both genders within each diagnosis (not shown in Table 3a, but shown by diagnosis in table 2a). Boys had significantly larger mean head circumferences than girls,

47.7 (± 0.24) cm versus 46.8 (± 0.25) cm, with z-scores averaging -0.3 (± 0.20) versus -0.4 (± 0.31) respectively, $P < 0.05$, when age was controlled. This is consistent with CDC reference values for boys and girls (1-3 yrs), (data not shown). Additionally, older children of both genders and diagnoses had significantly larger head circumferences than younger children [Slope estimate (\pm SE) of $+1.03$ (± 0.31) cm for each year older, $P < 0.05$, data not shown]. This is consistent with CDC reference data for children ages 1-3 years old (40).

Follow-up Growth Data

The outcome data were determined from three follow-up visits, obtained during an average of 7 months after the children's initial visit at the time of diagnosis. The data are presented in the tables and text as per 6 months, as well as 7 months, because 6 months is a more widely used time period for tracking children's growth (6). The mean age (\pm SD) of the children post-counseling was 39.7 (± 10.62) mo, or about 3 y and 3 mo. The number of children who returned for anthropometric measures were as follows: 38 (61%) at the first follow up, 29 (47%) at the second follow up, and 23 (37%) at the third follow up visit (Figure 1).

Weight

Both diagnostic groups had evidence of muscle wasting at diagnosis based on the Waterlow criteria and were underweight at the time of diagnosis, with z-scores averaging -2 or lower for weight-for-height and weight-for-age. Boys ($n=34$) and girls ($n=28$) of

both diagnoses gained weight after counseling, however, mean gains were not adequate to achieve significant improvements in the weight related percentiles and z-scores post-counseling (not shown, percentile and z-score values post-counseling were not significantly different from pre-counseling values). Thus catch up weight gain was not achieved for either gender or diagnosis during the study period. Despite this, girls on average (\pm SE) were able to gain weight at a rate faster than reference values for healthy children, at 1.02 (\pm 0.06) kg/6 mo vs. 0.96 kg/ 6 mo (or 5.65(\pm 0.31) g/d vs. 5.33 g/d), while boys gained weight a little slower on average than their healthy peers at 0.94(\pm 0.04) kg/6 mo vs. 0.95 kg/ 6 mo (or 5.22(\pm 0.22) g/d vs. 5.25 g/d; Table 3b). Statistically, however, boys' and girls' weight gain velocities and mean total weight gains during the study period did not differ significantly from one and other (nor were there differences between the two diagnostic groups).

Height

Unlike mean weight gains, mean gains in height were large enough to reflect increases in mean height-for-age growth percentiles and z-scores. On average, children gained 1.4 (\pm 2.07) percent on the CDC growth charts ($P=0.0125$) and increased 0.13 (\pm 0.05) SD on the normal curve in 6 months ($P=0.0190$) across genders and diagnoses (data not shown). Girls however, demonstrated significantly better linear growth after counseling than boys, 4.14 (\pm 0.18) vs. 3.47(\pm 0.18) cm/ 6 mo., respectively ($P=0.0016$) (Table 3b). Girls of both diagnoses exceeded reference height velocities, as did IA+SFA boys, while IA boys did not (Table 3b). The average growth velocities of the two diagnostic groups were similar per day (and per 6 months), however IA children accrued

significantly less height than IA+SFA children over the course of the entire study on average (IA boys with a mean gain of 3.82 (± 0.22) cm and IA girls with a mean gain of 4.49 (± 0.21) cm, which is an average gain of 4.15 cm in 7 months for the IA group; IA+SFA boys had a mean gain of 4.48 (± 0.22) cm and IA+SFA girls had a mean gain of 4.80 (± 0.25) cm, which is an average gain of 4.64 cm in 7 months for the IA+SFA group; $P=0.0326$; Table 3b). This difference in total mean height gain maintained the height differences observed at baseline between the two diagnoses (IA<IA+SFA, Table 2a). The IA boys' lagged noticeably behind the other groups in growth on average (although not statistically) and their mean total height gain was less, on average, than the other groups over the study period (Table 3b). Therefore IA boys may have brought down the linear growth average and mean total gain in height for the entire IA group (Table 3b).

Head Circumference

Mean head circumference (\pm SE) in boys and girls of both groups continued to increase significantly by 0.81 cm/6 mo (± 0.11) ($P<0.0001$), within the normal range of growth for children ages 3-4 y, and there were no significant differences in velocity between the diagnostic groups or genders when age was controlled (data not shown). Older children at diagnosis had larger mean head circumferences than younger children throughout the duration of the study by a measure of 0.63 (± 0.2) cm per year older ($P=0.0005$), data not shown). This is typical of healthy children in this age group.

Summary of Growth

Gains in weight, height, and head circumference were significant over the course of the study, but weight gain, for both genders in either diagnostic group, was not enough to achieve notable increases in weight related percentiles and z-scores. After an average of seven months post-counseling, girls of both diagnoses were still classified as underweight for height (nutritionally wasted) and for age, while boys of both diagnoses were still classified as underweight for age. Girls of both diagnoses exceeded the reference velocity for weight, on average, while boys of both diagnoses gained weight more slowly than the reference velocity on average (Table 3b). Catch up weight gain was not achieved during this study period, however, for either gender across the diagnostic groups because neither gender greatly exceeded the reference rates of weight gain long enough to show statistically significant improvements in weight related percentiles or z-scores during the follow-up visits. Despite this, both genders' weight velocities are encouraging and give a glimpse into the possibility for continuing improvements if the rates are sustained over a longer period of time, especially for girls.

Height-for-age and head circumference-for-age remained in the normal range for children in this study after counseling. Girls of both diagnoses, however, gained height faster than the boys of both diagnoses and faster than the reference values, on average (Table 3b). IA boys were not considered stunted, however, their growth velocity and mean total linear growth lagged noticeably behind the other groups of children in this study (although not statistically) and behind the CDC reference values after counseling (Table 3b).

Nutrient Intake Data

Overview

The number of children for whom food records were available after counseling were as follows: 18 (29%) at the first follow up, 15 (24%) at the second follow up, and 25 (40%) at the third follow up visit (Figure 1). At diagnosis, girls met DRI for all the nutrients investigated (energy, protein, calcium, iron, zinc, vitamin A) and intake did not change significantly after counseling for any nutrient or supplement (Table 4). (Supplements were defined as multivitamins and/or formulas, excluding pure milks, such as cow's or soy). Boys did not meet the DRI for some of the nutrients investigated (energy, iron, calcium) at diagnosis but increased intake of all nutrients after counseling ($P < 0.05$, Table 4). IA boys, however, continued to fall short of recommended energy intake after counseling (Table 4).

Calories

At diagnosis, there were no significant differences in mean total energy (\pm SE) intake (kcal/kg/d) between the different diagnostic groups, across both genders, when age was controlled (Table 4). Mean energy consumption from fluids was also similar among all groups and fluids provided about 40% - 45% of the total mean energy intake in all groups (Table 4). On average, children met the EER and the RDA for daily energy intake, except for IA boys, who consumed 9.2 and 12.0 kcal/kg below the EER and RDA respectively (Table 4). After counseling, boys significantly increased their energy intake by 5 (\pm 2.52) kcal/kg/d while they decreased their energy consumption from fluids by 4

(± 1.80) kcal/kg/d (Table 4). Despite this energy increase, IA boys continued to remain below the EER and the RDA on average, for energy intake after counseling (Table 4).

Protein

At diagnosis, there were no significant differences in mean total protein (\pm SE) intake (g/kg/d) between the different diagnostic groups, across both genders, when age was controlled (Table 4). Mean protein consumption from fluids was also similar among all groups and fluids provided approximately 40% and 50% to the total mean protein intakes in boys and girls, respectively (Table 4). Mean protein consumption exceeded the RDA of 1.1 g/kg/d by two-fold for all groups (Table 4). After counseling, boys increased their protein intake by 0.3 (± 11) g/kg/d and protein from fluid consumption remained the same (Table 4).

Iron

There were gender differences at diagnosis for mean (\pm SE) iron consumption; IA boys consumed significantly less iron than IA+SFA boys [5.3 (± 2.34) versus 12.3 (± 2.18) mg/d], less than that of IA+SFA girls [who consumed 9.7 (± 2.62) mg/d] and less than that of IA girls [who consumed 14.5 (± 2.44) mg/d, $P < 0.05$] when age was controlled (Table 4). There was also an interaction between gender and diagnosis for supplemental iron consumption when age was controlled, such that IA boys consumed significantly less supplemental iron than IA girls [2.3 (± 1.85) versus 9.6 (± 1.92) mg/d, $P < 0.01$, not shown]. IA boys on average consumed 43% of their mean total iron intake from supplements and were unable to meet the RDA for iron, while IA girls consumed 66%

from supplements and exceeded the RDA (Table 4). IA girls consumed similar amounts of supplemental iron compared to IA+SFA boys [7.2 (\pm 1.72) mg/d] and to IA+SFA girls [6.6 (\pm 2.01) mg/d, not shown], who consumed 58% and 68% of their total average iron intake from supplements, respectively, and who also exceeded the RDA for iron. After counseling, boys in both diagnostic groups increased their mean intake of iron by about 2.2 mg in 6 months, which enabled the IA boys to achieve the iron RDA of 7.0 mg/d (Table 4).

Zinc

Mean total zinc intake and supplement consumption was similar between both diagnostic groups across genders when age was controlled at diagnosis (Table 4). On average, zinc supplementation was high and contributed 48% - 71% of the total mean zinc consumption (Table 4). All groups, except IA boys, met or exceeded the UL for zinc of 7 mg/d. IA boys did not reach the UL, but exceeded the RDA. After counseling, boys further increased mean zinc intakes by 1.8 (\pm 0.54) mg/d (P <0.01, Table 4).

Calcium

At diagnosis, boys consumed significantly less calcium on average (\pm SE) than girls across diagnostic groups when age was controlled [451 (\pm 77.7) versus 666 (\pm 82.8) mg/d respectively, P <0.05]. Mean consumption of supplemental calcium did not differ among the gender and diagnostic groups after age was controlled. On average, children in the study consumed 27%-50% of their total daily calcium intake from supplements (multivitamins and/or formulas – non including pure milks, cow's or soy). Despite the

large calcium supplement consumption, IA boys did not meet the RDA for calcium of 500 mg/d (Table 4). After counseling, boys of both groups increased their mean calcium intake by 146 (± 32.2) mg in 6 months, which may have enabled the IA boys to meet RDA recommendations (Table 4). Interestingly, calcium supplements did not contribute to this increase in calcium intake; calcium supplement intake was reduced (not significantly), indicating that boys may have consumed more foods with calcium (Table 4).

Vitamin A

At diagnosis, there were no significant differences in mean total vitamin A consumption among the different groups of children when age, gender, and diagnosis were controlled (Table 4). There was an interaction between gender and diagnosis for supplemental vitamin A consumption when age was controlled, such that IA boys consumed significantly less supplement than IA girls on average [154 (± 134) versus 502 (± 140) RAE/d, $P < 0.05$, not shown; 34% and 72% of total consumption came from supplements, respectively, Table 4]. Mean supplemental vitamin A consumption was similar among IA girls, IA+SFA girls, and IA+SFA boys [454 (± 150) versus 526 (± 125) RAE/d respectively, not shown; 60% and 54% of total vitamin A consumption came from supplements, respectively, Table 4]. On average, supplements contributed 34% - 72% of total daily vitamin A consumption. Mean total vitamin A consumption was high for all groups who reached or exceeded the UL for vitamin A (600 RAE/d), except for IA boys, who greatly exceeded the RDA, but did not reach the UL (Table 4). After counseling, boys of both diagnostic groups further increased their supplemental vitamin A intake by

81 (± 39.6) RAE/d ($P < 0.05$), which contributed to the significant increase in total vitamin A consumption of boys in both groups by 105 (± 60.1) RAE/d ($P < 0.05$, Table 4), so that IA+SFA boys continued to exceed the UL and IA boys exceeded the RDA.

Summary of Nutrient Intake

At diagnosis, girls met the DRI for all the nutrients investigated and intake did not change significantly after counseling (Table 4). Boys did not meet the DRI for some of the nutrients investigated (energy, iron, calcium) at diagnosis but increased intake of all nutrients after counseling to meet recommendations, except for IA boys, who continued to fall short of recommended energy intake after counseling ($P < 0.05$, Table 4).

Significant increases in energy, protein, zinc, and calcium intake did not coincide with significant increases in supplement intake, thus whole foods and non-supplemental fluids (i.e. milks and juices) were likely to provide these nutrients. Before counseling, fluids provided almost half of the children's energy and protein needs across gender and diagnostic groups (Table 4). After counseling, boys in both groups significantly reduced their consumption of calories from fluids by 4.4 (± 1.80) kcal/kg/d (Table 4), while protein intake from fluids did not change significantly. Girls' energy and protein intake from fluids remained the same after counseling.

Before counseling, all groups exceeded the RDA for zinc and vitamin A intake, while some groups met or exceeded the UL. After counseling, boys in both diagnostic groups continued to significantly increase their intake of zinc and vitamin A. All groups met or exceeded the UL for both zinc and vitamin A after counseling, except for IA boys

who exceeded the RDA but did not reach the UL (Table 4). Vitamin A supplement intake significantly increased and contributed to the higher vitamin A consumption in boys after counseling.

Nutrient Intake and Growth

The weights and heights (absolute) from diagnosis through the follow-up visits were tested for correlation with nutritional intake. No significant correlations were found for any group. Absolute head circumference was, however, correlated with intake of protein ($r=0.23$, $p=0.03$), calcium ($r=0.32$, $p=0.004$) and zinc (total: $r=0.36$, $p=0.001$; supplement: $r=0.24$, $p=0.03$).

Discussion

Fluids and Supplements Verses Whole Foods

As mentioned earlier, whole foods, such as fruits, vegetables and whole grains provide benefits (i.e. phytochemicals, antioxidants, fibers) that dietary supplements and fortified fluids alone may not provide. Some studies have found that supplementation alone may not be enough to reverse stunting and the associated health consequences (6,8,12). Additionally, if young children reject whole foods that require significant chewing, they can fall behind in oral/motor development (4,6). On average, fluids provided 40% to 50% of the energy consumed at the time of diagnosis and little improvement was gained after counseling as boys, but not girls, decreased the fluid contribution to their energy intake by an average of only 4 kcal/kg/day (Table 4). Fluids also provided a substantial portion of daily protein, approximately 40% for boys and 50% for girls, which did not change significantly after counseling (Table 4). These findings are similar to findings from case studies on children with similar feeding disorders (“Non Organic Failure to Thrive”- NOFT, feeding disorders with no underlying medical conditions). Tolia (Tolia, 1995) found that 7 children with NOFT at Children’s Hospital in Michigan consumed 40%-100% of their calories from fluid supplements (28).

It is typical of healthy children between the ages of 1-3 years old to rely on fluids, particularly milk, for a third of their total energy intake as they begin to wean off fluids and transition to solid foods (6). Skinner and colleagues (29) found that beverages provided 36% of the total daily energy intake on average for healthy children, ages 19-24

months, who participated in the FITS studies. A similar study found that beverages provided 38% of the total daily energy intake of healthy FITS children, ages 12-24 months, with the following contributions: 23.6% cow's milk, 6.4% juice, 4.7% sweetened beverages, 1.9% infant formula, and 1.6% breast milk (24). Fluids are a relatively large part of healthy children's diets, however, healthy children still consumed less fluid on average than the amount consumed by IA and IA+SFA children.

Large volumes of caloric fluids and fluid supplements suppress hunger, satiate appetite, and result in less consumption of whole foods (6). Wright and colleagues found that children who were classified as "poor or very poor eaters" based on their feeding behaviors, drank significantly more milk than "good to very good eaters," and that excessive milk intake was associated with poor appetite (30). The American Academy of Pediatrics (2006) recommends no more than 2 cups of non-fat or low-fat milk servings daily for children 1-3 years old, based on the Dietary Guidelines of 2005 (6,31). Brown and colleagues (2008) suggest that children should not exceed 26%-40% of their daily energy from fluids and parents should limit children's milk intake to no more than 24 ounces (3 cups) per day in order to make room for solid foods (6).

It is difficult for parents of children with IA feeding disorders to ensure that their children are consuming enough calories and protein from solid foods alone. Many parents will give their children fluids in place of solid foods because it is an easy way to add extra calories to their children's diets and simultaneously prevents conflict over foods that the children may not like. Dietitians can assist parents in planning a healthy diet and

include recommendations for appropriate fluid intake (milk and formulas) and successive goals for reducing fluid intake. Dietitians should reassure parents that children have the ability to regulate their own hunger if allowed to do so and reducing energy dense fluid intake will initiate hunger so children will be more willing to eat solid foods (6).

Recommendations to parents should include non-fluid, energy and protein dense foods that may appeal to these children to help them gain weight and learn proper oral-motor skills, such as chewing and swallowing. The main goals of therapy for children with IA or IA+SFA should be to help children wean off fluids, recognize their hunger, and eat mostly whole foods to meet nutrient needs. Furthermore, it is important that children are introduced to a wide variety of foods at a young age when healthy eating habits are established (32).

Excess Supplement Intake

Before counseling, boys and girls in both diagnostic groups exceeded the RDA for vitamin A and zinc intake on average, while some groups reached or exceeded the UL (Table 4). Approximately 50% or more of this intake was in the form of supplements (Table 4). After counseling, boys in both diagnostic groups continued to significantly increase their intake of vitamin A and zinc while the girls' consumption remained steady, but high. A significant increase in consumption of vitamin A supplements after counseling, contributed to the increase in total vitamin A consumption in boys (Table 4).

It is alarming that before counseling began, supplements provided approximately 65% of girls and 45% of boys' vitamin A and zinc consumption (combined) on average, especially in the context of inadequate energy intake in the case of the IA boys. It is also concerning that while the children were under clinical supervision, supplemental vitamin A intake continued to increase in boys to levels that greatly exceeded the RDA (for IA boys) and the UL (for IA+SFA boys).

Vitamin A

Clinicians should be cautious when prescribing supplements in the attempt to treat IA or IA+SFA. Over supplementation of fat-soluble vitamins, like vitamin A, can cause harm in large amounts (above the UL) and should be avoided. Fat-soluble vitamins, such as vitamin A, are stored in fat tissue and could accumulate to toxic levels, particularly in children (6,24). Clinicians should educate families about vitamin A toxicity, amounts recommended per day, and food sources of vitamin A. Additionally, clinicians may want to caution parents against using particular supplements that provide mega-doses of any vitamin or mineral and against those supplements that provide close to a full day's requirement of vitamin A. Many supplements contain a whole day's worth or more of vitamin A, and in combination with food and/or milk, can easily exceed the UL. Some food products also tend to be heavily fortified with both vitamin A and zinc. Clinicians can educate parents about which supplements to use, how much to use, and what food sources provide vitamin A and zinc in order to complement cautious supplementation. Consumption exceeding the UL is not advised. Additionally, there is no evidence to suggest that vitamin A, above the UL, would initiate growth benefits in malnourished

children. Vitamin A has been shown to have synergistic effects with iron and zinc (promoting iron and zinc uptake and utilization for development), but it has not been reported to directly promote weight or height gains in supplementation trials, alone or in combination with other micronutrients (33). As a general guideline for children with IA, vitamin A consumption exceeding the UL should be avoided.

Zinc

It remains controversial whether zinc supplementation in excess of the RDA results in accelerated weight gain or linear growth (34). Some studies have found increased weight gain and greater linear growth in children who were given extra zinc supplementation (above the UL) ranging between 10 mg-50 mg. Other studies found only modest increases in linear growth with zinc supplementation when children were already stunted, but not when children were of normal height and low weight (35). Similar studies have looked at the combination of iron and zinc supplementation and found that the double supplementation did not improve growth or development when compared to a placebo (18,33). A study on pregnant women who were supplemented with zinc found that the women who were supplemented gave birth to babies with larger head circumferences than those who had not been supplemented (36). More research must be done on the connection between zinc and head circumference before conclusions can be drawn. The association of zinc and other nutrients (protein and calcium) with head circumference in this study may be an indicator of generally better overall intake by those IA children with larger head circumferences. Research is inconclusive as to whether or not zinc in excess of the RDA promotes growth of any kind in mildly malnourished

children (35). Clinicians should monitor zinc intake in children with IA or IA+SFA to ensure children are meeting the RDA but not exceeding the UL.

It is important to note that in 2001, after the study was underway, the Institute of Medicine (IOM) reduced the RDA for zinc from the 1989 value of 10 mg/d for children 1-3 y to 3 mg/d and the UL was set at 7 mg/d. It is likely that some of the excessive zinc intake observed in the IA population was a result of the transition in manufacturing and formulas and supplements containing amounts of zinc that were designed to meet the older, higher RDA.

Considerations for Catch Up Growth

It is important for children with growth deficits to achieve catch-up growth, or a higher than average growth rate after a period of growth suppression due to deprivation or illness (9). At diagnosis, the low growth percentiles and mean z-scores (≤ -2 SD on the normal curve) in IA and IA+SFA children alerted clinicians to closely monitor the children's dietary intake, with the goal of reversing delays in growth. IA and IA+SFA children should have greatly *exceeded* typical growth rates for their gender and age group (CDC 2000, Table 3b) during the follow-up sessions in order to narrow the gap in weight and height with their healthy peers.

After counseling, boys of both diagnoses gained weight at approximately the same rate as the CDC reference velocity on average (Boys: 5.22g/d vs. Reference: 5.25

g/d; Table 3b). In contrast, girls' weight gain slightly *exceeded* reference velocity values (Girls: 5.65 g/d vs. Reference: 5.33 /d, Table 3b). However, despite this important gender difference, there was no statistical difference in total mean weight gain or mean weight gain velocity between the genders (or diagnoses, Table 2a) over the course of the study period. Nevertheless, the boys' lower weight gain and similar gain to what is typical of healthy boys indicates that catch up weight gain was not achieved for boys during the follow up period (7 months, on average) and perhaps the study period was not long enough to see boys catch up. Girls, it seems, were able to catch up in weight gain, exceeding the reference velocities, during the follow up period, however, as previously mentioned, these gains did not make significant improvements in the children's overall weight related growth percentiles or z-scores. The mean weight gain velocities may indicate, however, that girls had more potential to initiate catch up weight gain faster than the boys after counseling, especially if counseling had continued beyond the mean of about 7 months.

Previous research on catch up growth in mildly malnourished children suggest that 5 g/day is an acceptable targeted goal for catch up weight gain (37, 38, 39). Boys may have not exceeded typical weight gain rates during the study follow up period, but appeared to be on the right track according to Waterlow, Golden, and the WHO (37, 38, 39, 40). Clinicians should be aware that it might take longer than (an average of) 7 months for girls and boys with either IA or IA+SFA to catch up in weight related growth percentiles and z-scores, even after the children have reached the rate of weight gain similar to their healthy peers. More research is needed in this area to determine how long

this process should take. Family counseling should be continued until weight percentiles and z-scores are considered normal.

Linear growth was less of a concern than weight gain during the follow up period. Most children were not considered stunted at diagnosis, even though mean heights (for age) were well below the 25th percentiles (Table 2a, 3a). At diagnosis, IA+SFA girls were close to the cut-off for stunting at the 6th height-for-age percentile with a z-score of -1.7 SDs away from the mean, but caught up most significantly during the follow up visits, with statistically faster velocities than the boys' groups (Table 3a, 3b). IA children were only very mildly stunted on average according to the Waterlow Criteria (95% of ideal while 96% of ideal is considered normal, table 2b) (16) and it was only IA boys who fell descriptively significantly behind in mean height velocity after counseling compared with the other groups of children and with the CDC reference velocity (Table 3b). This may be associated with the IA boys' inadequate intake of total calories, iron, and calcium at diagnosis, however correlations between nutrient intakes and height velocity were not tested. Clinicians may want to pay special attention to IA boys to ensure they are meeting their nutritional needs to support linear growth.

It must be noted that despite improvements in growth for boys and girls of both diagnostic groups, boys were still classified as underweight-for-age and girls as underweight-for-height and age after counseling (40). On the other hand, statistically significant improvements in height percentiles and z-scores were observed in boys and girls after counseling, even though IA boys lagged behind reference growth velocities.

Improvement in height, within the context of little weight gain is encouraging, but not ideal. Gains in height are easier to achieve than gains in weight (39). Height requires less protein for tissue deposition and is an easier anabolic process than weight gain (all the more reason for clinicians to carefully monitor IA boys who lagged behind in height). As height increases, it is important that weight follow with enough energy consumption to maintain weight-for-height (39).

There is no definitive formula from authoritative sources that establishes the exact energy and protein requirements necessary for catch-up growth in mildly malnourished children, nor are there specific standardized targets for weight gain and height velocity. Waterlow (1996), Golden (2009), and the WHO/UNICEF (2009) (37,38,39) report different possible targets for weight gain and growth based on malnourished children in developing countries. Targets for catch up weight gain range from 5-20 g/d in a 6-month period (which is up to 4 times the typical weight gain), and targets for height gain range from 2 to 5 times the average height velocity for gender and age (up to 14.4 cm in 6 months for a stunted child). Studies have demonstrated that mildly malnourished children, 5 years old and younger, have achieved a growth rate within these target ranges by consuming 123-204 kcal/kg per day and approximately 3.0–3.5 g/kg of protein per day (37, 39).

In general, approximately 1.5-2 times the energy RDA (kcal/kg/d) and 2-3 times the protein RDA (g/kg/d) are adequate for children with mild malnutrition to achieve catch-up growth (37, 39, 41). Based on these estimates, growth, especially weight gain, in

IA and IA+SFA children may have been limited by inadequate calorie consumption, particularly in the case of IA boys. Protein consumption fell within the range approximated to initiate catch up growth in all groups, exceeding the RDA before and after counseling (Table 4).

It is not advisable for IA children to consume more than 15% of their diet in protein due to appetite suppression, even though excess protein may have a positive effect on linear growth (in theory but not necessarily in practice) (39). It is recommended that 10-15% of the diet come from protein, 35-45% from fat, and 45-65% from carbohydrates, similar to the macronutrient distribution recommended for a healthy adult population (39). Unfortunately, this study on IA children did not examine the macronutrient breakdown of the children's diets because data on fat intake were not collected. Future studies should address this. Dietitians should ensure that IA and IA+SFA children are consuming enough calories to initiate catch-up growth, while monitoring macronutrient distribution in the diet. Particular attention should be given to IA boys whose mean calorie consumption fell short of the RDA (while 50% came from energy dense fluids), but whose protein consumption was more than twice the RDA, and whose height velocity was slower than the other groups' and the reference velocity (Table 3b, 4).

As mentioned earlier, research is inconclusive as to whether or not excess supplementation of vitamins or minerals promotes catch-up growth in mildly malnourished children. Previous studies on malnourished children have shown that major

deficiencies in micronutrients, such as vitamin A, zinc, iron, and calcium, have detrimental effects on child growth and development, but it remains unclear whether supplementation beyond the RDA or the UL provides any additional growth benefits (9,12,33). Thus, clinicians treating IA and IA+SFA children should focus on helping them maintain their intake to meet the RDA and ensure they do not exceed the UL. Gradually increasing calorie consumption may be warranted as a main goal for these children while ensuring that adequate micronutrient intakes are maintained at the RDA.

Girls versus Boys

It is curious that girls of both diagnoses (IA and IA+SFA) had worse weight status than boys of both diagnoses, at the time of diagnosis (after age was controlled, Table 3a) and raises the question of whether there is a sex bias on the part of parents in when they seek treatment and/or whether primary care providers delay referral for girls, as it may be more socially acceptable for girls to be petite. More research is needed to determine why girls had more extreme weight deficits than boys when first diagnosed.

It is also unexpected that while girls had a worse weight status than boys at diagnosis, girls met the RDA for all nutrients investigated, while boys did not. The reason for this is unclear. Perhaps because the girls had alarmingly low weight for age/height percentiles and z-scores, their pediatricians (primary care providers) recommended that they immediately begin to consume supplements and/or formulas to boost growth. Thus, girls may have been more heavily supplemented *before* they were referred to Children's

by their pediatricians and *before* they were enrolled in the study, but it was too soon for their growth to catch up at the onset of the study. Moreover, 24-hour recalls and 3-day food records do not elucidate past nutritional intake in the same way growth does. Food records indicate present nutrient intake. It would have been interesting to include patient diet histories in this study to investigate whether the girls had lower nutrient intakes than the boys before the study began, to help explain the girls' lower weight status.

After counseling, boys improved their nutritional intake of all nutrients investigated, while they lagged behind the girls ($P < 0.05$) and the reference values in linear growth (Table 3b, 4). Girls' nutritional intake was steady throughout the study and they were able to maintain linear growth rates closer to the reference velocities than the boys. Perhaps the girls' adequate nutrition at baseline (meeting/exceeding the RDA) enabled the girls to meet reference linear growth velocities more quickly than the boys. Nutrient intake was not, however, correlated with absolute weight or height in any diagnostic or gender group. Weight gain and linear growth velocity were not tested for correlation. Another explanation for the girls' accelerated linear velocities may be because girls are expected to grow a little faster than boys between the ages of 2-3 years old, according to the CDC (40), and some of the children were still between the ages of 2-3 years during the follow-up sessions, even though the average age was 39.7 months.

It is encouraging that IA and IA+SFA boys increased their mean consumption of calories, protein, iron, and calcium over the duration of the study, enough to meet their calcium and iron needs (which were not met at baseline for some). Furthermore, while

boys total energy consumption increased, their energy intake from fluids decreased, indicating that more foods were consumed rather than fluids. This demonstrates the achievements that are possible over an average of 6 to 7 months post counseling. It is unclear why boys significantly improved their nutrient consumption over the follow up period while girls did not. Perhaps after the initial diet analysis, clinicians recognized that many of the boys were iron and/or calcium deficient at diagnosis while the girls met the RDA for all the nutrients investigated on average. Fortunately, the girls' intake did not significantly decrease, but remained steady during the follow up period.

IA versus IA+SFA

The ages of the two groups at the time of referral were similar (Table 1) and the reason why IA+SFA children were significantly heavier and taller (absolute measures) than IA children at diagnosis is unknown. Lesser magnitude of growth faltering, specifically absolute weight (kg), in the IA+SFA group (Table 2a) may be related to these children having identifiable distaste for specific foods, but also readily accepting certain foods they find appealing. This may enable parents to select and offer alternative foods not having distasteful characteristics to the IA+SFA children, which supply them with enough calories to slightly mask their feeding disorder and enable them to maintain more weight than the IA group (According to correspondence with Dr. Irene Chatoor, MD, [ichatoor@cnmc.org], email, October 8, 2010).

Typically, children with pure IA (no SFA) will refuse to eat most foods and do not have a select few foods that they prefer over other foods. SFA children (without IA) on the other hand, are usually of normal weight and some are even overweight because they prefer to eat mostly “snack” food and are averse to many other foods (i.e. fruits, vegetables, meat). “Snack” foods are usually calorie dense with little nutrient value or satisfying fiber and protein to satiate appetite making them easy to overeat. Similar to SFA children, it seems that the limited selection of foods the IA+SFA children choose to eat, has provided enough calories to enable them to gain weight more quickly than the IA children (Table 2a, 3b) (According to correspondence with Dr. Irene Chatoor, MD, [ichatoor@cnmc.org], email, October 8, 2010).

This result was unexpected because IA+SFA children usually have more difficulties and conflict during feeding than IA children (perhaps because they only want snack foods). This highlights another explanation for why IA+SFA children may have been heavier than IA children at diagnosis; parents of these children may have sought help more quickly than parents of IA children due to severe distress about their child’s food selection. Clinicians should be aware of the potential for differences in food preferences between IA and IA+SFA children. Despite better absolute anthropometric measures at diagnosis than IA children, IA+SFA children are still at risk for nutrient deficiencies and growth deficits if not treated early. Interestingly, the IA+SFA group had a lower (although, not statistically lower) mean height-for-age percentiles and z-scores than the IA group (Slight differences in the mean ages of each group may account for

this) (Table 1, 2a). However, Table 2a shows that IA+SFA had accrued significantly more height on average than the IA group after counseling.

Of the IA and IA+SFA groups, IA boys gained the least height (descriptively, not statistically) over the course of the entire study period (3.82 (\pm 0.22); Table 3b), which is consistent with their poorer nutrient intake at baseline compared with the intake of the other groups. The IA boys may have been disadvantaged by mean intakes of energy, iron and calcium that were below recommended levels at baseline, perhaps indicating greater sub-clinical nutrient deficiencies than other study groups, that may have impeded their ability to catch up to the growth velocity of their healthy reference peers. Yet, height (absolute) during the follow-up period was not statistically correlated with nutritional intake for any diagnostic or gender group. Based on these findings, clinicians may consider more frequent monitoring of IA boys to provide additional opportunities for intervention to enhance healthy growth.

FITS Reference Children

Data for the reference population were taken from the Feeding Infants and Toddlers Study (FITS) conducted in 2002 (11, 24). In that study, data were collected from a large national random sample of toddlers, ages 12-24 mo (n=998), using 24-hour recalls and 2-day food records. Comparisons between mean nutrient intake of IA and IA+SFA children and children in the FITS study should be considered with caution

because different methods were used to determine mean intakes and because these comparisons were made descriptively, not statistically.

Mean intake of calories, protein, and calcium were lower in both the IA and IA+SFA children than in the FITS healthy toddlers, but fluid consumption was approximately 10% higher on average in IA and IA+SFA children (Table 4). The most notable difference in nutrient intake between the FITS healthy toddlers and the two groups was that of supplement consumption. Supplements provided IA and IA+SFA children with a much larger percentage of vitamin and mineral intakes at diagnosis than they provided for the children in the FITS study (Table 4). For instance, supplemental iron comprised 43%-68% of the IA and IA+SFA children's total iron intake on average, while FITS children consumed only 14% of their total iron intake from supplements. This pattern was the same with respect to zinc, vitamin A, and calcium intake (Table 4). The children with feeding disorders relied heavily on supplements to fulfill their nutrient needs, while healthy toddlers obtained the majority of their vitamins and minerals from food or non-supplemental fluids (i.e. milk and juice). The most striking discrepancy between the two groups of toddlers in this regard was the total and supplemental calcium intake; calcium supplements (formulas and vitamins) provided a mean of 2.4% of the healthy toddlers' total calcium intake, which was 939 mg/d; IA and IA+SFA children depended on calcium supplements for approximately 27%-50% of their total calcium intake (which ranged from 405 – 638 mg/d). This did not include calcium from milk in either group (healthy children or children with feeding disorders). IA and IA+SFA

children consumed less calcium than the healthy toddlers, and more of their consumption was in the form of supplements than from calcium rich foods and drinks.

Clinicians should help parents of IA and IA+SFA children strategize ways to include more calcium-rich foods in their children's diets and use supplements more sparingly to fill in the gaps. Interestingly, similar to the IA and IA+SFA children, healthy children in the FITS studies greatly exceeded the RDA for zinc and vitamin A. Studies have shown that FITS children who exceeded the RDA for zinc and vitamin A, had consumed more zinc and vitamin A in the form of supplements than those FITS children who did not exceed the RDA. On average, 68% of supplement users and 38% of non-users exceeded the UL for zinc. Similarly, 97% of users and 15% of nonusers on average had excessive vitamin A intakes above the UL (42). Approximately 43% of children in the US between 12-24 months old exceeded the UL for zinc, while 35% exceeded the UL for vitamin A (11, 42). This demonstrates that there is widespread over-consumption of zinc and vitamin A supplements in the general population of toddlers and it is not unique to the IA and IA+SFA population. This provides evidence that it is important for clinicians to carefully monitor the use of zinc and vitamin A supplements (as well as foods heavily fortified with these nutrients) in IA and IA+SFA children.

Study Limitations

This analysis is based on growth and nutrition data that were collected over a five-year time period by several clinicians and may be subject to inconsistencies between methods used to take anthropometric measures and administer the 24-hour recall. The sample from which the data were collected was a mostly Caucasian, non-Hispanic group of children from the US mid-Atlantic region, all middle-class and predominantly from the upper middle class. Thus, the data may not be representative of all children with IA or IA+SFA, affecting the ability to generalize the results.

Because the CDC growth curves were updated during the time the study was underway (in 2000), it is possible that the study sample would have included or excluded different children who were diagnosed with IA based on anthropometric criterion relative to growth curves in use at the time the study began. Additionally, the CDC recently recommended the use of the WHO growth charts, updated in 2006 after the study was concluded, for infants and children from birth to two years, which may also have an effect on the diagnostic categories (43). In particular, the WHO growth charts represent a lighter and taller sample than the CDC growth charts (except from birth to 6 months) (43). If the 2006 WHO growth charts would have been used for diagnosis, this would have resulted in classifying the IA and IA+SFA groups as heavier and shorter than they appeared to be using the CDC charts, perhaps resulting in a better nutrition status (growth percentiles and z-scores) with less growth deficits. The WHO growth charts are based on a large international sample of healthy breast-fed infants, and can be used as a standard

for child growth, while the CDC charts are based on a smaller random sample of mostly formula fed infants and are used as a reference for growth (43). (The CDC Z-scores were not used as one of the inclusion/ exclusion criteria, or as the basis for IA or IA+SFA diagnosis, but they were generated after the children were enrolled in the study to help analyze growth status. Instead, growth percentiles and the Waterlow Criteria cut-off points were used together).

The initial two of seven treatment sessions differed among subjects, some parents receiving one style of therapy ('treatment' or 'intervention'), and the remainder, a different style of therapy ('control'). The different therapy styles were not controlled for or factored into the analysis and therefore may have caused an unknown effect on the data. However, the purpose of this study is to provide a general description of the growth potential for children once behavioral treatment has begun and not to compare therapy styles, which most likely differ among clinicians. (Note that the diagnosis of IA and IA+SFA is somewhat of a subjective process and is therefore another limitation of this study).

Attrition rates throughout treatment and follow up were high and dropouts occurred immediately after the diagnostic (baseline) visit. There were several reasons families gave for not continuing. Some families moved away, others cancelled appointments because it was difficult to fit treatment into their schedules, some of the parents were dissatisfied with the treatment while others were of the opinion that a few

visits sufficiently resolved their children's issues. Some families had another baby and were unable to make the time and effort to follow through with the treatment.

High attrition rate (37%) over the course of the study did not allow for reporting mean growth and mean nutrient intakes after counseling for each child at the last follow-up in order to make comparisons to baseline means. Instead, significant mean trends, or changes over time, were reported with all of the children that continued on after the initial visit, even if a child had only two time points at which measures were taken. Means after study completion were calculated based on these trends. This may have caused an unknown bias in the data set and perhaps children who remained in the study were healthier or less healthy to begin with (this was not assessed or controlled for).

Additionally, the analysis did not control for differences in the children's background such as race, socio-economic status (household income level), number of parents in the primary residence, or parental stress levels, all of which may have provided a more thorough explanation of the differences in growth and nutrient intake seen between the girls and boys of both diagnoses. Also, parental height and birth weight were not included in the analysis to control for the genetic contributions of shorter stature or for the variation in weight measures and weight gain that may be associated with birth weight. Previous studies have shown that growth velocity is slower in children with higher birth weights (44), while a child's full growth (height) potential is greatly influenced by heredity (12). Future studies should assess weight in the context of birth weight and height, and in the context of parental height.

Furthermore, this study did not control for or identify which children were breast-fed versus formula-fed and for how long. Research shows that breast-fed infants grow slower than formula-fed infants and by 18 months of age breast-fed infants are leaner, longer and have lower weight-for-height z-scores than formula-fed infants, even after complimentary foods have been introduced (45). Additionally, from 2 months onward, healthy breast fed infants seem to track below the CDC weight-for-age mean z-score, while they track nicely along the mean z-score for weight-for-age on the WHO growth charts (43).

Nutrient intake data were based on either parent-reported 24-hour recalls or 3-day food records. The clinicians who recorded the data for this study used both methods to collect nutrient intake information. If the parent did not come to a visit with a 3-day food record, 24-hour recalls were used in its place. The analysis combined the two methods by averaging the 3-days and counting it as one day. This may have affected the accuracy of the intake data. These methods are also subject to over- or underreporting intake. It is believed that over-reporting is more common than under-reporting (24, 46). However, the excess mean intakes of vitamin A and zinc found in this study were consistent with data from the FITS studies. Moreover, 24-hour recalls and 3-day food records do not necessarily represent a child's "usual intake" because they are based on only a few days. Nonetheless, evidence suggests that there is less variation in the dietary intakes of young children from one day to the next than in older children and adults (24).

Energy assessments relied on general recommendations for healthy population based on age and sex. No individual physical activity expenditures were determined to consider whether IA children may have energy needs that are higher than typical amounts, which potentially could provide a partial explanation for the lack of catch up growth. Additionally, some children were started on fluid supplements by their pediatrician prior to referral to Children's, so nutrient intake at diagnosis does not necessarily reflect the intake corresponding to the growth deficits.

The study was limited by the reliability of the *NutritionisPro* software to accurately calculate nutrients in the diet that are not required to be on food Nutrition Facts Labels. The nutrient values that are required on the Nutrition Facts Label were considered to be the most reliable nutrient data for foods included in the Nutritionist Pro software, and among these, the study clinicians chose to track energy, protein, calcium, vitamin A, and iron. Zinc intake was also examined and included in the study due to the critical role zinc plays in the healthy development of infants, but dietitians who coded the food records did not indicate whether or not the coded foods had associated values for zinc in the software. Thus, reported zinc intake from food may be underreported (and therefore zinc intake from food may be higher than reported), whereas, supplemental zinc intake is assumed to be an accurate reflection of the food recorded.

This study would have been more interesting if additional nutrients critical to child growth and development would have been included in the analysis such as fat (including the omega-3 fatty acids DHA and EPA), vitamin E, vitamin D, vitamin C,

folate, and fiber. Vitamin D has been shown to be deficient in many pregnant women, infants, and toddlers and is related to calcium absorption and bone mineralization (47). Recent studies have shown a relationship between vitamin D and growth, such that a reduced concentration of 25 (OH)- vitamin D late in pregnancy is associated with reduced whole body and lumbar spine bone-mineral content in children at age 9 years (48). Similarly, after vitamin D deficient infants were supplemented, they increased their percent body fat significantly more than the control group who was not supplemented (47). It would have also been interesting to explore the amount of DHA consumed in IA and IA+SFA children. DHA (a long-chain omega-3 fatty acid, docosahexaenoic acid [22:6 n-3]) is very important in infant growth and development. It has been found to be low in pregnant women and infants, like vitamin D. Obstacles in obtaining adequate DHA include the overestimation of the amount of DHA found in regularly eaten food sources and warnings from the Environmental Protection agency (EPA) targeting pregnant women about mercury in fish, a very rich source of DHA (49).

It would have also been helpful to determine which beverages contributed to fluid consumption, particularly with respect to dietary intakes of calories and protein. Unfortunately, this study did not analyze the fluid supplements (or infant formulas, such as Pediasure) separately from the contributions made by other milk, juice and other beverages. Comparisons of mean infant formula, mean milk consumption, and mean juice consumption between the IA and IA+SFA groups and with children in the FITS study would have been insightful. Similarly, supplement intake from infant formulas and capsules were not analyzed separately and it would have been interesting to obtain the

percent contribution of each to get a better sense of which supplement type was being used more frequently than others (i.e., formulas versus capsules).

Additionally, biomarkers of nutritional status, (such as albumin, thyroxin-binding pre-albumin, retinol binding protein, transferrin (all for protein status), hemoglobin, hematocrit, transferrin saturation, erythrocyte protoporphyrin (all for iron), urine calcium, erythrocyte metallothionein with serum zinc, and serum vitamin A) were not collected for this study and may have provided a more thorough description of the children's nutrition status and perhaps would have given insight into specific nutrient deficits and their associations with growth failure. Other indices of nutritional status, such as dual-energy X-ray absorptiometry (DXA) scan, which measures bone mineral density and body composition, and arm muscle area (AMA), the preferred method for assessing lean tissue or muscle, were not collected and would have been beneficial. No one method, marker, or index is full proof. Thus it would have been preferable to use many relevant methods together, to better understand the relationship between the children's nutrition status and growth (50, 51).

Finally, comparisons of the data with FITS data, the DRIs, and the growth velocity references were descriptive, not statistical, and should be interpreted as a general characterization of this population in relation to other relevant findings and less a determination of which group in this study was statistically below or above any one reference point. Future studies on this population should address these limitations in order to confirm our results and explain the data more thoroughly.

Clinical Applications – A Checklist for Clinicians:

- 1) Ensure calorie consumption meets the RDA, particularly for IA boys.
 - a. May gradually increase calories up to approximately 1.5 times the RDA to boost growth in children who fall behind reference velocities.
 - b. Monitor the macronutrient distribution to avoid excess fat deposition and/or over-consumption of protein that may suppress appetite.
- 2) Ensure adequate nutrient intake (below the UL), particularly of iron and calcium for boys.
 - a. Monitor supplement use, particularly vitamin A and zinc- avoid excess
 - b. Monitor intake of foods fortified with vitamin A and zinc
 - c. Ground practice in evidence based research considering the association between excess nutrient intake (above the UL) and growth.
- 3) Gradually reduce fluid intake while maintaining adequate calorie and nutrient intakes.
 - a. Replace fluids with a variety of whole foods that are energy and nutrient dense, particularly rich in iron and calcium, selected based on the child's preferences or goals developed during psychological counseling sessions.
 - i. Some examples of appealing foods may include: cheeses, yogurts, smooth peanut-butter - or other nut-based butters, bananas, high carbohydrate fruits, yams, potatoes, grains, breads, pastas, beans, eggs, chicken, and adding oil to foods, all depending on developmental ability and avoiding any potential choking hazards.

- b. Ensure milk (or other energy dense fluid) consumption does not exceed 2-3 cups per day to make room for solid foods. This will also help children develop proper chewing and swallowing skills.
- 4) Ensure weight gain is at least 5g/day. Monitor weight velocities using the WHO or the CDC references (Table 3b).
- 5) Ensure gains in height are at least 3.5 cm in 6 months or continue to progress along reference velocities specific to gender and age (Table 3b).
- 6) Head circumferences should continue to track between the 25th and 50th percentiles on the CDC growth charts, as the children get older.
- 7) Educate parents/care-givers in methods to monitor the child's growth, food intake, and nutrient intake, and provide practical solutions to achieve the diet-related goals developed and agreed upon by the psychologist and the family.
- 8) Continue to follow up with children for at least one year and up until they meet typical growth velocities and percentiles or z-scores for weight and height.
- 9) Communicate regularly with the other medical professional caring for the child, such as the psychiatrist, the speech pathologist, and the pediatrician, until the child reaches an acceptable growth pattern.

Nutritional goals must be tailored to the individual child, and each child's progress monitored to re-adjust goals as needed in order for underweight IA and IA+SFA children to reach their full genetic growth potential and catch up with their peers. Readers are encouraged to use data in this report as a benchmark, with the caveat that the observed intake and growth might be improved upon.

Conclusion

This study set out to test the following hypotheses:

- 1) Children with IA and IA+SFA would exhibit severe anthropometric deficits at diagnosis (baseline) and there would be differences between the two diagnoses;
- 2) Nutrient deficiencies (intake below RDA) would accompany growth deficits observed at diagnosis and mean nutrient intake values would be lower in children with either IA or IA+SFA than the mean intake values of FITS children (11);
- 3) Fluids and supplements would contribute to a large portion of the children's total daily intakes at diagnosis;
- 4) Growth (weight and length/height) and diet (whole food and nutrient intake) would improve among children with both IA and IA+SFA after counseling; and children would rely less on fluids and supplements and more on whole foods to fulfill nutrient needs after counseling.

Reference growth data for age and sex (CDC) confirmed the first hypothesis that children with IA and IA+SFA had mild to moderate anthropometric deficits at diagnosis (not severe), particularly for body weight (as expected, given the diagnostic criteria for each). On average, both diagnostic groups met criteria for wasting and underweight. The IA toddlers were significantly shorter and weighed less than the IA+SFA group, however the two diagnoses did not present with significantly different growth percentiles or z-scores. When the data were examined by gender, girls had significantly worse weight-for-height and weight-for-age than boys and were considered underweight for height and age, suggesting that parents and/or primary care physicians did not recognize the severity of

growth failure in girls or delayed the referral of girls to specialists for other reasons. Boys were considered underweight-for-age but not underweight-for-height.

Boys, but not girls, had nutrient deficits at diagnosis, partially confirming the second hypothesis. Perhaps the girls lower weight status prompted primary care physicians to start them on supplements earlier than boys (albeit a bit late), before study enrollment and diagnoses, and thus girls were able to meet nutrient needs, while boys did not. IA boys did not meet daily calorie or iron recommendations and boys of both diagnoses fell short on their daily calcium needs. It could be argued that boys of both diagnoses were deficient in calorie consumption necessary to initiate catch-up growth, particularly weight gain. Mean protein intakes descriptively met or exceeded the RDA among all groups. Mean intakes of calories, protein and calcium fell below the usual intake of healthy toddlers. Fluids and supplements provided one third to one half of the children's nutrient needs, more than the usual intake of their peers, confirming the third hypothesis. Supplement consumption of vitamin A and zinc exceeded the RDA by 150% - 325% and 150% - 246% respectively in all children, which was consistent with data on healthy children, especially those who consumed supplements with those nutrients.

After counseling, both diagnostic groups gained weight at a similar rate, however, boys fell slightly short of their healthy peers while girls exceeded weight velocities of their healthy peers. Despite significant weight gains, there were no statistically significant improvements in weight related percentiles and z-scores for boys or girls of either diagnosis post-counseling. Catch up weight gain was not achieved over the study period

for boys because they did not greatly exceed reference weight velocities. Girls exceeded weight gain reference velocities, however, study period may not have been long enough to see this increase translate to the weight related growth percentiles and z-scores. Thus, the time frame of the study (mean of 7 months) was not long enough to see significant weight gain. Significant linear/height gains were achieved among all groups, including height related percentiles and z-scores. Most groups also exceeded the reference velocities, except for IA boys who had descriptively slower rates of linear growth than the reference values and the other groups of children. This slow growth velocity in IA boys may be associated with their poor baseline intake of calories, iron, and calcium; however, the correlation of nutrient intake to height velocity (or weight velocity) was not examined and should be examined in future studies. Mean head circumference was within the normal range for both diagnostic groups and continued to track normally after counseling. Boys and older children had larger mean head circumferences than girls and younger children, which is consistent with reference data. Head circumference (absolute) in all groups was positively correlated with intake of protein (0.23, $p=0.03$), zinc (0.36, $p=0.001$), calcium (0.32, $p=0.004$), and supplemental zinc (0.24, $p=0.03$) with no differences in diagnosis or gender.

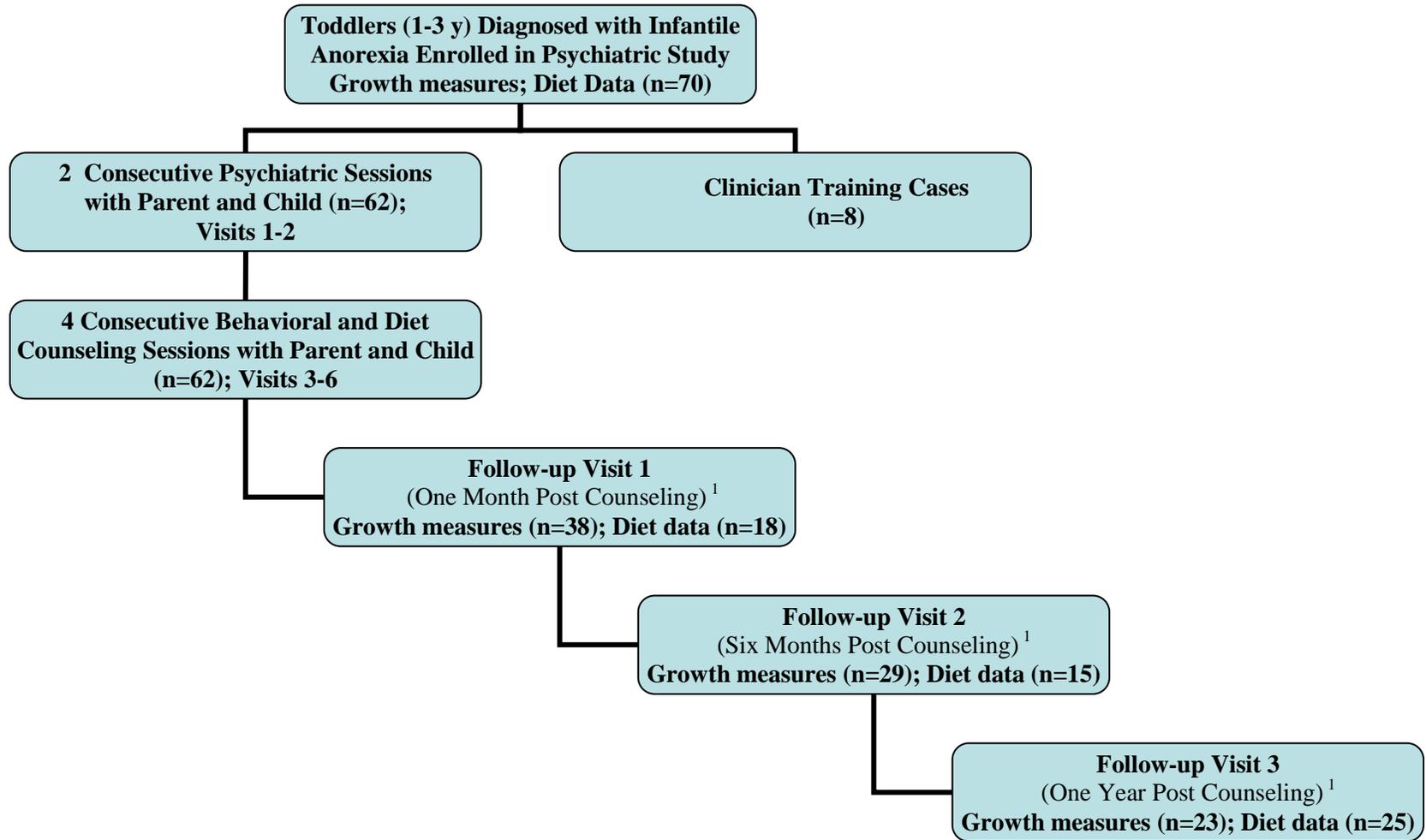
Clinical intervention achieved some of its best diet-related results by improving iron intake for IA boys and calcium intake for boys of both diagnoses, whose intake at diagnosis fell below the RDA/AI; the improved intake of iron and calcium decreased their risk of deficiency by meeting recommendations, an example of what can be achieved under clinical care over a mean period of 7 months. Boys but not girls made

significant improvements in transitioning off fluids to consume more caloric whole foods, but further improvements are needed. Boys also continued to increase their intake of supplemental vitamin A and zinc, and all groups greatly exceeded the RDA for vitamin A and for zinc. Perhaps clinicians and/or parents were too generous with supplements in the attempt to correct for growth and nutrient deficits. The child's medical team should focus on finding approaches that will lead to balanced catch-up growth, particularly weight gain, without over-supplementation (i.e. gradual increase in calorie intake). The fourth hypothesis was partially confirmed in that improvements were observed in growth, mainly in length/height, for all groups and dietary/nutrient intake for boys after counseling; however, mean improvements in weight gain and macronutrient intake (overall calories per kilogram of body weight) were inadequate to restore growth deficits observed at baseline for boys and girls of either diagnosis.

This was the first study to describe the growth and nutrient intake of children who have IA and IA+SFA feeding disorders. This study demonstrates the challenges that parents and clinicians face to ensure adequate growth, nutrient intake, and whole food consumption in children with IA and IA+SFA. These data establish benchmarks of growth rates that are possible and may be improved upon with further clinical intervention. Future studies are needed to determine dose-response curves for calorie and protein consumption that help target levels that correlate with healthy catch-up growth. Moreover, the finding of nutrient associations with head-circumference at baseline should be further explored by testing the relationship of growth velocity and nutrient intake while under clinical care. Additionally, future studies should investigate whether there is

gender bias on the part of parents and/or primary care physicians in delaying referral of girls, but not boys, due to their lower weight percentiles and z-scores, or whether criteria for risk of nutritional wasting observed in girls at the time of diagnosis is accurate, or whether criteria applied to boys is insensitive. Perhaps IA and IA+SFA diagnostic criteria should be gender specific based on these findings. A new study is currently underway to follow up with the children from this study, approximately five to ten years after the data for this study were collected. It too will be the first study of its kind.

Figure 1. Time course of study measures in relation to clinical care for toddlers diagnosed with IA or IA+SFA



¹ Mean time period post counseling

Table 1. Demographic characteristics by diagnosis.

	Total (n = 62)	Infantile Anorexia (n=35)	Infantile Anorexia + Sensory Food Aversions (n=27)
Gender (%)			
Male	34 (55%)	18 (51%)	16 (59%)
Female	28 (45%)	17 (49%)	11 (41%)
Race/ethnicity (%)			
Asian (non-Hispanic)	8 (13%)	6 (17%)	2 (7%)
Black (non-Hispanic)	3 (5%)	1 (3%)	2 (7%)
White (non-Hispanic)	42 (68%)	24 (69%)	18 (67%)
White (Hispanic)	4 (7%)	2 (6%)	2 (7%)
More than one race	5 (8%)	3 (9%)	2 (7%)
Age at diagnosis (months)^a	22.5 ±7.4	22.8±6.6	22.2± 8.5
Age post-counseling (months)^a	39.7 ±10.6	37.8 ±10.9	41.6 ±10.3

^a Mean±SD.

Table 2a. Growth parameters, macronutrient and fluid intake of toddlers (1-3 y) by diagnosis type (n=62) at baseline; and growth velocity after counseling^a (3-4 y).

	IA (n=35)	IA + SFA (n=27)	Reference Group
Anthropometric measure			
Weight (kg)	9.6 (±0.25)	10.9 (±0.31) ^b	12 ^{cd}
Height (cm)	81.9 (±1.07)	88.0 (±1.34) ^b	86 ^{cd}
Head Circumference (cm)	47.4 (±0.23)	47.1 (±0.26)	47 ^{cd}
Growth percentile			
Weight-for-height	5 th (±1.27)	6 th (±1.60)	≤3rd is wasting ^d
Weight-for-age	3 rd (±1.02)	3 rd (±1.26)	≤3rd is underweight ^d
Height-for-age	20 th (±3.01)	10 th (±3.50)	≤5th is stunting ^d
Head Circumference-for-age	46 th (±5.07)	29 th (±8.61)	<5th associated with impaired development ^d >95th associated with impaired development ^d
Z-Score			
Weight-for-height	-2.1 (±0.14)	-2.0 (±0.17)	≤ -2 is wasting ^d
Weight-for-age	-2.5 (±0.13)	-2.4 (±0.16)	≤ -2 is underweight ^d
Height-for-age	-1.1 (±0.14)	-1.5 (±0.17)	≤ -2 is stunting ^d
Head Circumference-for-age	-0.1 (±0.19)	-0.7 (±0.32)	≤ -2 is below normal ^d
Nutrient Intake			
Calories (kcal/kg/d)	81 (±6.40)	91 (±6.35)	82 - 100 kcal/kg/d ^c
Calories (kcal/d)	778 (±61.4)	992 (±69.2)	1,000-1,300 kcal/d ^c
Fluid intake (% total kcal/d)	46%	43%	< 26-40% Recommended ^e
Protein (g/kg/d)	2.6 (±0.24)	2.8 (±0.23)	1.1 g/kg/d ^c
Protein (g/d)	25 (±2.3)	31 (±2.5)	13 g/d ^c
Fluid intake (% total protein g/d)	48%	45%	No reference
Growth velocity after counseling			
Weight gain (g/d)	5.38 (±0.27)	5.48 (±0.27)	5.25 – 5.33 ^f
Weight gain (kg/6 mo)	0.97 (±0.05)	0.99 (±0.05)	0.95 – 0.96 ^f
Height gain (cm/6 mo)	3.60 (±0.18)	4.05 (±0.18) ⁷⁴	3.42 – 3.60 ^f
Head circumference (cm/6 mo)	0.81 (±0.11)	0.81 (±0.11)	0.86 – 0.93 ^f

^aMean (±SE). IA: infantile anorexia; IA+SFA: infantile anorexia with sensory food aversion.

^bSignificant difference between diagnoses (P < 0.05).

^cInstitute of Medicine reference individual basis for recommendations, Girls and Boys, ages 1-3 y (23, 25).

^dCenter for Disease Control and Prevention and/or World Health Organization (15,39,40).

^eFluid intake recommendations (6,31).

^fCenter for disease Control and Prevention, Reference Growth Tables for children 3-4 yrs old (35.6 – 47.5 mo); Head circumference data is only available up to 36 mo; Growth increments based on the 50th percentile. Ranges indicate girls to boys or vice versa (40).

Table 2b. Baseline mean percent ideal body weight and height by diagnosis type, using the Gomez and Waterlow criteria.

Gomez Criteria¹	IA	IA+SFA	Gomez Criteria¹
Percent Ideal Body Weight-for-age	80%	91%	Malnutrition 90-110% = normal 75-89% = mild 60-74% = moderate < 60% = severe
Waterlow Criteria²			Waterlow Criteria²
Percent Ideal Body Weight-for-height	87.2%	88.6%	Acute Malnutrition (wasting): 91-110% = normal 80-90% = mild 70-79% = moderate < 70% = severe Chronic Malnutrition (stunting): 96-100% = normal 90-95% = mild 85-89% = moderate < 85% = severe
Percent Ideal Body Height-for-age	95%	102%	

¹ Gomez Criteria (19): Percent of reference **weight for age** = [(patient weight) / (weight of normal child of same age)] * 100

² Waterlow Criteria (16): Percent **weight for height** = [(patient weight) / (weight of a normal child of the same height)] * 100

Percent **height for age** = [(patient height) / (height of a normal child of the same age)] * 100

[WHO/CDC (15, 39, 40) growth percentiles and z-scores have replaced these criteria (in most cases) to define degree of malnutrition; however, Dr. Chatoor used the **weight-for-height Waterlow Criteria** as a cut-off point to determine enrollment into this study (<90% of Ideal)].

Table 3a. Baseline growth percentiles and z-scores^a (CDC) by diagnosis and gender (1-3 y); Nutrition status classification at diagnosis^b, (n=62).

Growth Category	Reference ^c	Boys			Girls		
		IA (n= 18)	IA+ SFA (n= 16)	All (n= 34)	IA (n= 17)	IA+ SFA (n = 11)	All (n = 28)
Weight-for-height	Wasted						
Percentile (SE)	≤ 3rd	5 th (±1.82)	9 th (±1.82)	7 th (±1.28) ^d	6 th (±1.77)	2 nd (±2.58)	4 th (±1.56) ^e
Z-score (SE)	≤ -2.0	-2.0 (±0.20)	-1.6 (±0.20)	-1.8 (±0.14) ^d	-2.1 (±0.19)	-2.4 (±0.28)	-2.3 (±0.17) ^e
Weight-for-age	Underweight						
Percentile (SE)	≤ 3rd	3 rd (±1.46)	6 th (±1.46)	4 th (±1.03) ^d	2 nd (±1.42)	1 st (±2.07)	2 nd (±1.25) ^e
Z-score (SE)	≤ -2.0	-2.4 (±0.18)	-1.9 (±0.18)	-2.2 (±0.13) ^d	-2.5 (±0.18)	-2.8 (±0.26)	-2.7 (±0.16) ^e
Height-for-age	Stunted						
Percentile (SE)	≤ 5 th	19 th (±4.03)	15 th (±4.02)	17 th (±2.84)	20 th (±3.91)	6 th (±5.70)	13 th (±3.44)
Z-score (SE)	≤ -2.0	-1.2 (±0.20)	-1.3 (±0.20)	-1.2 (±0.14)	-1.1 (±0.20)	-1.7 (±0.29)	-1.4 (±0.17)
Nutrition Status of each group ^c :		Wasted, Underweight	Normal	Underweight	Wasted, Underweight	Wasted, Underweight	Wasted, Underweight

^a Mean change in growth (±SE); ^b Nutrition Status Classification was determined by either the mean percentile or the mean z-score of each group. ^c Center for disease Control and Prevention (CDC) and World Health Organization (WHO) cut-offs for wasting, underweight, and stunting based on weight-for-height/age and height-for-age (15, 39, 40). ^{de} Significant difference in mean weight related percentiles and z-scores when children were grouped by gender (all boys vs. all girls, d vs. e), girls being worse off than boys, but no significant difference in growth percentiles/z-scores when children were grouped by diagnosis. Girls vs. boy p-values: weight-for-height percentile, p=0.02; weight-for-height z-score, p=0.04; weight-for-age percentile, p=0.02; weight-for-age z-score, p=0.01.

Table 3b. Growth velocity^a by gender and diagnosis after counseling¹ (3-4 y)², (n=62); Total mean gains during study period (mean of 195-218 days; approx. 7 months); Using 152 follow up measures.

Growth Category	Boys 201 ^h and 218 ⁱ days of follow up				Girls 195 ^h and 202 ⁱ days of follow up			
	IA (n=43) ^g	IA+ SFA (n= 37) ^g	All (n= 80) ^g	Reference ^f	IA (n= 46) ^g	IA+ SFA (n = 26) ^g	All (n = 72) ^g	Reference ^f
	Weight gain (g/ day) (±SE)	+5.22 (±0.22)	+5.27 (±0.22)	+5.22 (±0.22)	+5.25	+5.54 (±0.31)	+5.69 (±0.31)	+5.65 (±0.31)
Weight gain (kg/ 6 mo; 180 days) (±SE)	+0.94 (±0.04)	+0.95 (±0.04)	+0.94 (±0.04)	+0.95	+1.00 (±0.06)	+1.02 (±0.06)	+1.02 (±0.06)	+0.96
Total mean weight gain (cm) during length of study period (mean 7 months) ^h ; (±SE)	+1.05 (±0.07)	+1.06 (±0.07)	+1.05 (±0.05)	+1.06	+1.08 (±0.07)	+1.11 (±0.09)	+1.10 (±0.06)	+1.04
Height gain (cm/ day) (±SE)	+0.018 (±0.001)	+0.021 (±0.001)	+0.019 ^e (±0.001)	+0.020	+0.022 (±0.21)	+0.024 (±0.001)	+0.023 ^d (±0.001)	+0.019
Height gain (cm/ 6 mo; 180 days) (±SE)	+3.24 (±0.18)	+3.78 (±0.18)	+3.47 ^e (±0.18)	+3.60	+3.96 (±0.18)	+4.32 (±0.18)	+4.14 ^d (±0.18)	+3.42
Total mean height gain (cm) during length of study period (mean 7 months) ⁱ ; (±SE)	+3.82 ^b (±0.22)	+4.48 ^c (±0.22)	+4.15 (±0.15)	+4.36	+4.49 ^b (±0.21)	+4.80 ^c (±0.25)	+4.65 (±0.17)	+3.84

^a Mean change in growth (\pm SE);

¹ Change in growth, both mean weight gains and height gains were significant after counseling for boys and girls of both diagnoses (P<0.0001).

² Mean age after counseling for all children was 39.7 \pm 10.6 months, between ages 3-4 years.

^{bc} Significant difference in cumulative mean height gains between IA children and IA+SFA children, b versus c (P=0.0326).

^{de} Significant difference in mean height gain velocity between all girls and all boys, d vs. e (P=0.0016); No significant difference found in mean weight gains when children were grouped by diagnosis and/or gender.

^f Center for disease Control and Prevention, Reference Growth Tables for children 3-4 yrs old (35.6 – 47.5 mo); Growth increments based on the 50th percentile (40).

^g Indicates the total number of a group's measures throughout the duration of the entire study (repeated measures on the same child).

^h Mean length of study period was different for each group: 195 days for girls (weight) and 201 days for boys (weight); Mean of 7 months for all groups (or between 6 and 8 months).

ⁱ Mean length of study period was different for each group: 202 days for girls (height) and 218 days for boys (height); Mean of 7 months for all groups (or between 6 and 8 months).

Table 4. Mean energy and nutrient intake by gender and diagnosis for toddlers (1-3 y) with infantile anorexia (n=62), at diagnosis and after counseling.^a

	Boys			Girls			Dietary Reference Intake			FITS ^c (n=998; 1-2y)
	IA (n=18)	IA+ SFA (n=16)	All (n=34)	IA (n=17)	IA+ SFA (n=11)	All (n=28)	EER or EAR ^b (1-3 y)	RDA or AI (1-3 y)	UL (1-3 y)	
	At diagnosis		Change after counseling ^d	At diagnosis		Change after counseling ^d				
Calories (kcal/kg/d)	70 (±8.90)	95 (±8.29)	+5.0 (±2.52) ^e	93 (±9.29)	87(±9.94)	-2.9 (±2.88)	79.2	82 – 102	ND	96.0-113.5
% from fluids	49%	40%	-4.4 (±1.80) ^e	43%	46%	-3.4 (±1.80)				38.2%
Protein (g/kg/d)	2.4 (±0.33)	3.0 (±0.31)	+0.3 (±0.11) ^e	2.7 (±0.34)	2.6 (±0.37)	+0.1 (±0.12)	0.88	1.1	ND	3.6 - 4.3
% from fluids	44%	37%	+0.4 (±0.05)	51%	52%	+0.01 (±0.07)				38.0%
Iron (mg/d)	5.3 (±2.34)^g	12.3 (±2.18)^h	+2.2 (±0.72) ^f	14.5(±2.44)^h	9.7 (±2.62)^h	-1.2 (±0.79)	3.0	7	40	9.8
% from supplements	43%	58%	+1.4 (±0.60)	66%	68%	-1.5 (±0.68)				14.1%
Zinc (mg/d)	4.5 (±1.56)	7.4 (±1.45)	+1.8 (±0.54) ^f	6.9 (±1.63)	6.9 (±1.74)	+0.1 (±0.63)	2.5	3	7	6.9
% from supplements	48%	50%	+1.2 (±0.48)	67%	71%	-0.4 (±0.53)				7.9%
Vitamin A (RAE/d)	451(±201.1)	974 (±187.5)	+105 (±60.1) ^e	699(±209.9)	763(±224.8)	+28 (±67.3)	210	300	600	694
% from supplements	34%	54%	+81 (±39.6) ^e	72%	60%	-36 (±44.3)				18.2%
Calcium (mg/d)	405 (±78.6)^g	498 (±76.7)^g	+146 (±32.2) ^f	693 (±77.5)^h	638 (±88.1)^h	+38 (±35.4)	500	700	2500	939
% from supplements	36%	27%	-15 (±19.1)	50%	35%	-65 (±21.2)				2.4%

^aMean (±SE). AI: Adequate Intake; EAR: Estimated Average Requirement; EER: Estimated Energy Requirement; FITS: Feeding Infants and Toddlers Study; IA: infantile anorexia; IOM: Institute of Medicine; ND: not determined; RAE: retinol activity equivalent; RDA: Recommended Dietary Allowance; SFA: sensory food aversion; UL: Tolerable Upper Intake levels. Nutrient intake represents the total intake, including whole foods, dietary supplements, and infant formulas. Supplements include vitamins, minerals, infant formulas, and nutritional supplement drinks. Fluids include milk (cow's/soy), infant formulas, fruit juices, and water.

^bFor Dietary Reference Intakes (25,26,27), EER (kcal/kg/d) was calculated using 950 kcal/d for 1-2 year olds divided by the weight-for-age (kg) for 1-2 year olds. IOM recommends EER or EAR as a lowest threshold cut-off point to determine nutrient deficiency within a group. RDA for energy was calculated using the RDA for total kcal/d for 1-3 year olds, divided by average weight-for-age (kg) for boys and girls, 1-3 y.

^cFITS (11) total mean energy (1249 kcal/d) and protein (47 g/d) intakes were converted relative to unit weight using 11–13 kg weight-for-age. (FITS =50th percentiles). ^d“After counseling” refers to 6 mo after diagnosis or baseline; No significant changes in nutrient intake occurred after counseling when grouped by diagnosis or for girls of either diagnosis. For boys, significant change over the course of the study: ^eP<0.05; ^fP<0.01.

^gSignificant difference in means for the same nutrient at baseline (diagnosis), g versus h (P<0.05).

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