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Original article

Fluctuations in dietary intake during treatment for childhood leukemia: A report from the DALLT cohort

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SUMMARY

Background: Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Nutritional morbidities are a persistent problem facing pediatric patients during and after treatment and age-gender groups that are at risk for nutritional conditions have not been clearly identified. Therapy is a contributing factor; however, the role of dietary intake remains largely unknown. Prior to conduct of interventional trials, an understanding of the effects of treatment on fluctuations in dietary intake is necessary.

Methods: We enrolled 794 children with ALL in a prospective clinical trial. Dietary intake was collected with a food frequency questionnaire at diagnosis and throughout the course of treatment for pediatric ALL. Reported values were compared to the Dietary Recommended Intake (DRI), and normative values (NHANES). Hierarchical linear models and multilevel mixed-effects ordered logistic regression models were used to evaluate longitudinal changes in dietary intake; independent samples *t-test* with Bonferroni correction was performed to compare to NHANES.

Results: Of the evaluable participants at each timepoint, dietary intake was obtained on 81% (n = 640), 74% (n = 580) and 74% (n = 558) at diagnosis, end of induction phase of treatment, and continuation, respectively. Despite exposure to corticosteroids, caloric intake decreased over therapy for most age-gender groups. Predictive models of excess intake found reduced odds of over-consuming calories (OR 0.738, $P < 0.05$); however, increased odds of over-consuming fat (OR 6.971, $P < 0.001$). When compared to NHANES, we consistently found that ≥1/3 of children were consuming calories in excess of normative

List of Abbreviations: ALL, Acute Lymphoblastic Leukemia; AMDR, acceptable macronutrient dietary ranges; BMI, body mass index; DALLT, The Diet and Acute Lymphoblastic Leukemia Treatment; DFCI, Dana-Farber Cancer Institute; DRI, Dietary References Intakes; FFQ, food frequency questionnaire; HLM, hierarchical linear models; HR, High-risk; HSFFQ, The Harvard Food Services Questionnaire; IQR, interquartile range; MCAR, Missing Completely at Random; NHANES, The National Health and Nutrition Examination Survey; RDA, Recommended Dietary Allowance; SR, Standard risk; TRT, treatment-related toxicity; YAFFQ, Youth and Adolescent Food Frequency Questionnaire; VHR, Very-high risk.

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values. For select micronutrients, a small proportion of participants were above or below the DRI at each time evaluated.
Conclusions: Our study suggests that dietary intake fluctuates during treatment for ALL as compared to age-gender recommended and normative values. Improving our understanding of nutrient fluctuations and dietary quality will facilitate subsequent analyses addressing relationships of dietary intake, toxicity, and survival.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy with survival rates exceeding 90% for children with favorable features. However, treatment-related toxicity (TRT) continues to be a significant complication of care alongside an increasing recognition of the long-term effects of treatment. There also continues to be subsets of children who are not cured of their ALL.

A number of epidemiologic studies have evaluated the effects of dietary intake on cancer risk or outcomes among adults; however there is a dearth of information in pediatric ALL [1]. The majority of the published literature has described the increased risk of obesity, cardiovascular disease, and metabolic syndrome among survivors of ALL; virtually no information is available on the role of diet during treatment for pediatric ALL [2–4]. It is abundantly evident that excess calorie intake, and poor adherence to recommended dietary patterns are associated with an increased risk for development and recurrence of several adult cancers [5–7]. Dietary patterns have been associated with epigenetic changes including DNA methylation, particular in the setting of an elevated body mass index (BMI) [8–10]. Independently, an elevated BMI has been linked to an increased risk of leukemia and poorer outcomes among adults and children with leukemia [11,12].

Less is known about fluctuations in body size and dietary intake during the two-year treatment for pediatric leukemia. The observation that up to 50% of children with ALL who are within a normal weight category at diagnosis develop obesity by the end of therapy has led to increased research efforts targeting weight management during and after cancer therapy [13,14]. Weight gain may be explained by the treatment itself [15], increased dietary intake, poor dietary quality [16–18], or unhealthy behaviors learned over the course of treatment. It is abundantly evident that more information on nutritional intake during treatment is needed.

To this end, we present the results from The Diet and Acute Lymphoblastic Leukemia Treatment (DALLT) cohort study that examined the effect of treatment for pediatric ALL on fluctuations in dietary intake over the two-year treatment. We describe the effect of treatment for pediatric ALL on fluctuations in dietary and compare dietary intake to the recommended dietary intakes and normative values. We then examined variables that may be predictive of excess or low dietary intake and the association witBMI.

2. Patients and methods

2.1. Participants

Children and adolescents between the ages of 1 and 18, with newly diagnosed ALL (n = 794) were recruited to the study. Eligible participants for the described study were children and adolescents registered on the ALL as per the Dana-Farber Cancer Institute (DFCI) ALL Consortium protocol 05-001 (Clinical Trials Registration: NCT00165087). Consent to the treatment study was obtained as per the Institutional Review Board of all participating centers and served as consent to the companion study. The details of this trial have been described elsewhere [19].

2.2. Study design and procedures

Details on study respondents and procedures have been previously published [20]. Briefly, this is a prospective cohort study that collected dietary intake over the course of a treatment for pediatric ALL from May 2005 thru December 2013. Dietary intake was measured at three timepoints in therapy: Diagnosis; End of Induction (approximately 32 days from diagnosis); and Continuation (approximately 15-months from diagnosis).

Height and weight was abstracted from the case report forms. In the treatment protocol, reporting of weight and height was only required at diagnosis and in continuation. Weight status by z-score and percentile was determined as per guidelines from the Center for Disease Control and Prevention [21] using body mass index (BMI) for children 2 through 20 years of age.

2.3. Assessment of dietary intake

Three dietary tools were administered during the study period, The Harvard Food Services Questionnaire (HSFFQ) for children ages 1–5 years and the Youth and Adolescent Food Frequency Questionnaire (YAFFQ) for children ages 6–18 years were administered to study participants (or their guardians, depending on participant age). The methodology employed for the collection of dietary data and validation and administration of these tools have been previously published [22–24]. A third dietary tool collected information on the provision of enteral nutrition during the observation period, as previously described [20].

2.4. Reference values for dietary intake

Dietary intake obtained from FFQs was compared to two values, the Dietary References Intakes (DRIs) [25–27] and normative data from The National Health and Nutrition Examination Survey (NHANES), 2009–2010 [28]. For the macronutrients, reported dietary intakes were compared to the acceptable macronutrient dietary ranges (AMDR) as a percentage of total calories [26]. For micronutrients, reported dietary intakes were classified as under (intake below the Recommended Dietary Allowance (RDA)), met (intakes within the RDA), and exceed (intakes exceeding the RDA). The NHANES dataset was used to serve as comparison to normative data. Data are reported as mean intakes by gender, and age group.

2.5. Statistical analysis

Summary statistics, such as the frequencies and proportion were used to describe the sample population. Patients were grouped based on their sex and their age. Fisher's exact test was used to compare the survey completers and the non-completers at study entry.

At each time point, dietary intake distributions across age group and gender were examined for outliers and non-normality. The distribution of patients was characterized by median and interquartile range (IQR) utilizing previously published methodology [29]. Cases that were more than 1.5 IQR below the first quartile or above the third quartile were excluded as outliers. Little's Missing Completely at Random (MCAR) test was also performed to evaluate the missing data pattern.

To determine whether patients showed differing dietary intake patterns over the course of their therapy, we estimated a series of hierarchical linear models (HLM). In the within-person (i.e., level-1) models, continuous outcomes were estimated as a function of time. HLM use all available data and can better account for missing data, thereby providing less biased estimations [30]. The time variable was recoded to diagnosis, end of induction, and continuation so that estimates reflected the change between time points rather than trends across time. Starting with an unconditional means model, we entered variables using a forward stepwise entry method as follows: (1) time points, (2) demographic characteristics (gender and risk group), and (3) BMI. All dietary variables were energy-adjusted using the residuals methods [29].

To describe the change in all dietary intakes against the DRIs, we categorized patients' intake into three groups as per DRI classification: *under*, *met*, or *exceed*. We first described changes in dietary intake using the three DRI categories. Next, we merged the *under* and *met* categories to create a dichotomous intake variable for each macronutrient, where 0 = *under/met* DRI and 1 = *over* DRI. Then, using the dichotomous variables as outcomes, we performed multilevel mixed-effects logistic regression models to predict excess dietary intake across time. Again, we followed the forward stepwise entry method as described above. We also performed a series of regression models to investigate if changes in dietary intake (diagnosis vs. end induction and diagnosis vs. continuation) predict BMI by continuation. These regression models were controlled for gender and age.

Lastly, patients were classified into tertiles (low, mid, high) according to the energy intake for their age group and gender [29]. We then examined the difference between the mean energy intake for each tertile and the normative values from the NHANES dataset for each corresponding age group (as defined by NHANES) and gender at each time point. Independent samples t-test was performed and Bonferroni correction was applied for multiple testing. Stata 14.0 software (Stata Corp, College Station, TX) was used for estimating the multilevel models. All other calculations were performed using SPSS version 21.0 (IBM, Armonk, NY).

3. Results

3.1. Demographics

The demographics of the participants at study entry are presented in Table 1. At study entry, 794 children and adolescents were recruited to DFCI 05-001. Dietary intake was obtained on 81% (n = 640) at diagnosis, 74% (n = 580) at end of induction phase of treatment, and 74% (n = 558) during the continuation phase of evaluable participants. Relatively few participants on DFCI 05-001 declined participation in the dietary surveys (6% or less at each timepoint); the remaining uncollected surveys were due to either a clinical circumstance (e.g. death, removal from treatment, etc.) or administrative matters (Fig. 1). After removing outliers, 614, 562, and 539 surveys were available for analysis at each of the timepoints, respectively. We observed differences in ethnicity, race, and institution location between completers and non-completers (Table 1, Supplementary Tables 1 and 2). Little's MCAR test revealed that data was missing completely at random across all timepoints ($\chi^2 = 577.09$, df = 556, $p = 0.258$).

3.2. Patterns of change in mean caloric and macronutrient intake during treatment

Mean caloric and macronutrient intake by timepoint for each DRI age group, and gender are presented in Fig. 2a–d. We found a significant difference in total calorie and macronutrient (grams per day) intake over the course of therapy for several age-gender groups. Pattern of dietary change was not uniform for each age-gender group. Despite administration of high- and low-dose steroids over the study period, we observed a significant decline in caloric intake over the course of therapy for most age-gender groups. For macronutrients, we observed similar age-gender variations in fat and carbohydrate intake. Variations in fat intake equated up to 100 calories per day whereas variations in carbohydrate intake were up to 460 calories per day. Protein intake was moderate with fluctuations not considered clinically significant.

3.3. Mean intakes of calories, macro- and micro-nutrients, compared to DRIs

To describe how the reported intakes compared to the recommended dietary intake values for age and gender over the study period, we explored the proportion of dietary intakes that were below and above the DRI at each timepoint for calories, macronutrients, and select micronutrients. For calories, mean intakes for each age-gender group revealed that the majority of participants were above the DRI at each timepoint (Supplementary Table 3). Approximately 25% of participants were below the DRI at each timepoint. For fat, up to 50% of participants exceeded the DRI for fat; whereas for carbohydrate a small proportion (0–11%) exceeded recommendations.

For micronutrients, several age-gender groups were consuming below the DRI for vitamin C (Range 2%–43%), vitamin E (Range 53%–93%) and vitamin D (Range 78%–99%) across all timepoints (Supplementary Table 3). For folate, we observed participants above (Range 5%–58%) and below (4%–57%) the DRI across the three timepoints. We found up to 70% of participants exceeded the DRI for zinc; excess intakes were most notable among younger children.

3.4. Predictive models of excess dietary intakes (calories, carbohydrate, fat, and protein)

We applied multilevel logistic regression modeling to examine variables that may be predictive of intakes above or below the DRI. For calories, the odds for over consuming calories were 0.738 times lower at the end of induction ($P < 0.05$) and 0.424 times lower at continuation ($P < 0.001$), while controlling for all other variables (Supplementary Table 4 (Model 5)). Females had a 41% increase in the odds of reporting excess calorie intake compared with males of the same age group ($P < 0.05$), holding all variables constant. The odds for over consuming calories are 0.733 times lower for high risk (HR) and very high risk (VHR) patients relative to standard risk (SR) patients after controlling for all other factors ($P < 0.05$; Supplementary Table 4 (Model 5)). BMI classification at diagnosis was not predictive of fluctuations in caloric intake.

We found that the odds for reporting excess fat intake at the end of induction was 6.971 times higher ($P < 0.001$) (Supplementary Table 5 (Model 5)). The odds for over-consuming fat was 2.157

Table 1
Demographic characteristics at study entry[a].

Demographic characteristics	Total (N = 794)		Complete survey (N = 640)		Did not complete survey (N = 154)		*p-value*
	Frequency	%	Frequency	%	Frequency	%	
Gender							
Male	441	55%	356	56%	85	55%	0.93
Female	353	45%	284	44%	69	45%	
Age							
<3 years old	309	39%	249	39%	60	39%	0.47
4–8 years old	262	33%	213	33%	49	32%	
9–13 years old	136	17%	113	18%	23	15%	
14–18 years old	87	11%	65	10%	22	14%	
Race							
White	610	77%	516	81%	94	61%	<0.001
Black or African-American	39	5%	26	4%	13	8%	
Other	107	14%	71	11%	36	23%	
More than one race	14	2%	11	2%	3	2%	
Asian	24	3%	16	3%	8	5%	
Ethnicity							
Hispanic	150	19%	125	20%	25	16%	<0.001
Non-Hispanic	580	73%	475	74%	105	68%	
Ethnicity unknown	64	8%	40	6%	24	16%	
Initial Risk Group							
High Risk	332	42%	263	41%	69	45%	0.41
Low Risk	462	58%	377	59%	85	55%	
Final Risk Group[b]							
High Risk	344	46%	283	46%	61	45%	0.78
Low Risk	407	54%	331	54%	76	55%	
Institution Location							
Continental US	429	54%	322	50%	107	69%	<0.001
Canada	308	39%	264	41%	44	29%	
Puerto Rico	57	7%	54	9%	3	2%	
BMI % at Diagnosis[c]							
<5% (Underweight)	58	7%	44	7%	14	9%	0.38
6–84% (Normal)	507	65%	417	66%	90	60%	
85–94% (Overweight)	120	15%	92	14%	28	19%	
>95% (Obese)	102	13%	83	13%	19	13%	

[a] Fisher's exact test was performed to compare the survey completers and non-completers.
[b] 43 patients were missing final risk group data; Induction failures/deaths were not assigned final risk group. High risk group includes: high risk (N = 260), very high risk (N = 66), Philadelphia chromosome+ (N = 18).
[c] 7 patients were missing BMI % at diagnosis information due to height below 77 cm and missing height data.

($P < 0.001$) times higher for HR/VHR compared to SR. For males with HR/VHR, the odds of fat over-consumption increased by two fold, whereas a protective effect was observed for females. BMI classification at diagnosis was predictive of fat intake. For underweight and overweight patients, the odds of over-consuming at the end of induction, further reduced by a factor of 0.186 and 0.187, respectively ($P < 0.05$; $P < 0.01$, respectively). Similar odds ratios were observed for carbohydrates as were observed calories. Due to the majority of patients meeting the DRI for intake of protein, few significant associations were observed (data not shown). Finally, we investigated if change in dietary intake predicted BMI by continuation. An increase in adjusted carbohydrate intake from diagnosis to the end of induction predicted increased BMI at continuation ($P < 0.05$). No significant associations were observed with calories, fat, or protein.

3.5. Comparison of caloric intake to normative values

Comparison of reported intakes to NHANES (Fig. 3a–c) revealed that at least 33% of children in each age-gender groups at diagnosis and during treatment consume calories significantly above normative values reported by NHANES. At the same time, we observed that children within the lowest tertile were significantly below NHANES for most age-gender groups across each timepoint. Reported intakes from children falling in the middle tertile were not significantly different than those reported by NHANES for nearly all age-gender groups.

4. Discussion

To the authors' knowledge, DALLT is the first study to describe fluctuations in dietary intake among pediatric patients receiving treatment for ALL and treated on a single therapeutic protocol. Given the prolonged exposure to corticosteroids, and the previously reported increases in BMI over the course of treatment in children with ALL, we expected to observe a sharp rise in dietary intake over the course of treatment with significant differences in odds ratios for fat intake between SR and HR/VHR ALL. Contrary to these expectations, we found a significant reduction in total caloric intake with only select groups at higher odds for over-consumption. This was less evident among younger age children (<3 years of age) potentially due to more proactive use of medical nutritional therapy. Despite reductions in total intakes, we found that the majority of participants' reported caloric intakes were still above the DRI at diagnosis and throughout therapy and that a select group of patients reported intakes that also exceeded normative values (NHANES). Collectively this suggests that either treatment for pediatric ALL or the disease process itself may promote intake over and above what is routinely observed in the healthy pediatric population. Our study did not identify demographic factors that were consistently predictive of excess

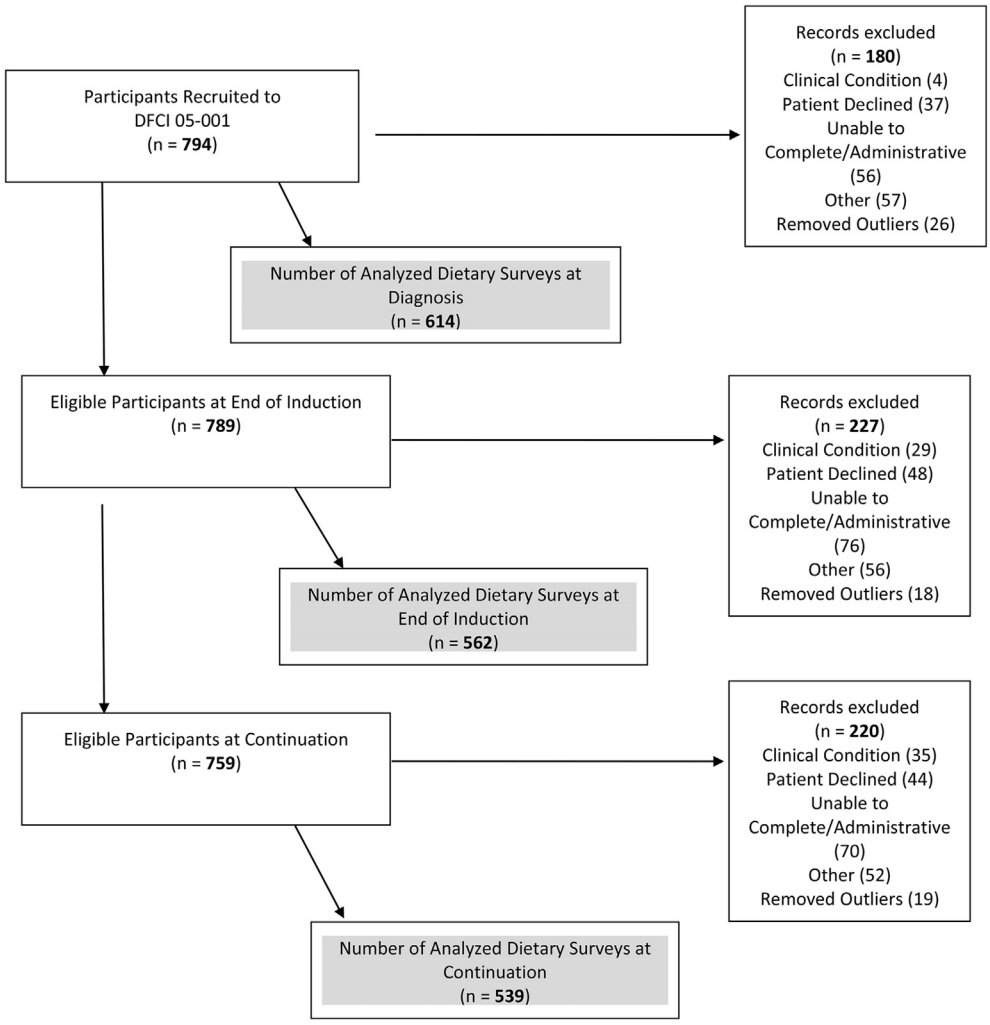

Fig. 1. DALLT flow diagram.

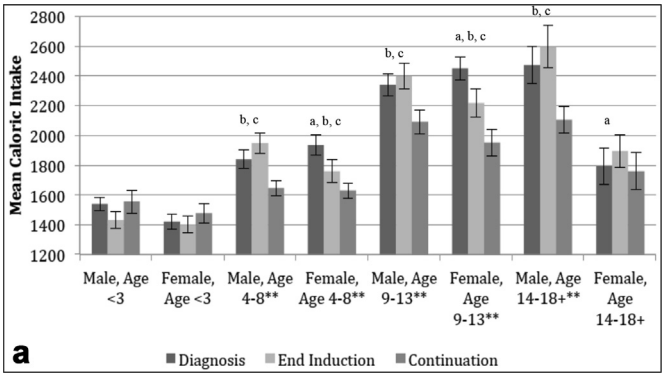

Fig. 2a. Caloric intake by age group by gender*. *Hierarchical linear models were estimated to compare the changes between all three time points; **P < 0.05. [a] Significant difference between Diagnosis and End Induction, P < 0.05. [b] Significant difference between Diagnosis and Continuation, P < 0.05. [c] Significant difference between End Induction and Continuation, P < 0.05.

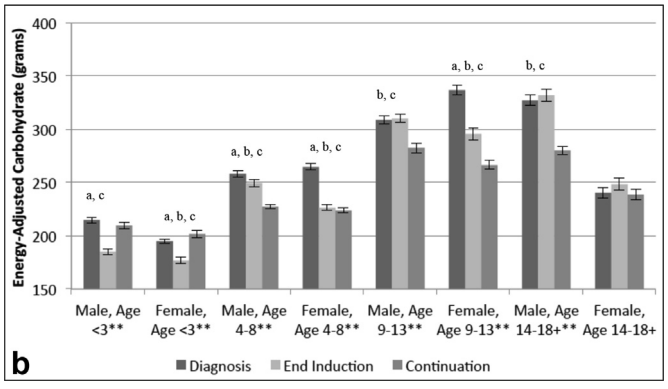

Fig. 2b. Energy-adjusted carbohydrate intake by age group by gender*. *Hierarchical linear models were estimated to compare the changes between all three time points; **P < 0.05. [a] Significant difference between Diagnosis and End Induction, P < 0.05. [b] Significant difference between Diagnosis and Continuation, P < 0.05. [c] Significant difference between End Induction and Continuation, P < 0.05.

intakes, which suggests that other variables may be responsible such as genetic predisposition, microbial environment, psychosocial variables, or learned behaviors. The observation that BMI at diagnosis was not predictive of dietary intake for most of the nutrients observed aligns with previously published data that change in BMI may be a more predictive indicator rather than BMI at diagnosis [31,32]; a finding that we also observed. Our study also highlights that attention is needed at both ends of the nutritional spectrum as participants reporting intake below the DRI were observed for several age-gender groups.

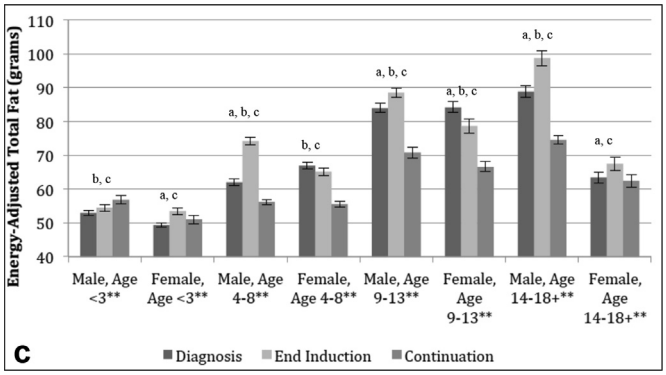

Fig. 2c. Energy-adjusted fat intake by age group by gender*. *Hierarchical linear models were estimated to compare the changes between all three time points; **P < 0.05. [a] Significant difference between diagnosis and end induction, P < 0.05. [b] Significant difference between diagnosis and continuation, P < 0.05. [c] Significant difference between end induction and continuation, P < 0.05.

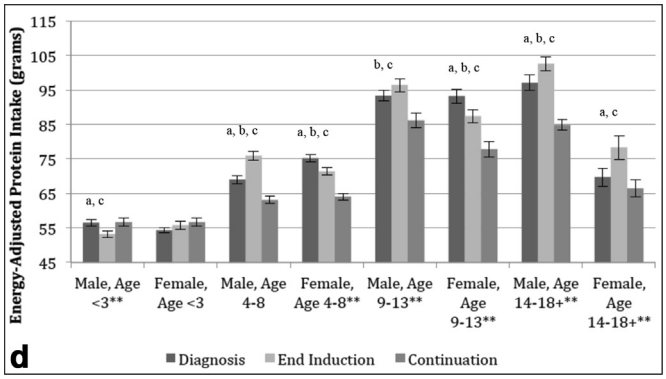

Fig. 2d. Energy-adjusted protein intake by age group by gender*. *Hierarchical linear models were estimated to compare the changes between all three time points; **P < 0.05. [a] Significant difference between diagnosis and end induction, P < 0.05. [b] Significant difference between diagnosis and continuation, P < 0.05. [c] Significant difference between end induction and continuation, P < 0.05.

Efforts to improve dietary intake may be more effectively directed towards monitoring of dietary intake of fat and carbohydrate, particularly during high-dose corticosteroid treatment. First, we found that participants had an increased odds of exceeding dietary fat intake during the early phases of therapy. Counseling patients on reducing fat intake may potentially improve outcomes as has been observed in pre-clinical models of pediatric ALL [33,34]. However, our finding that increased intake in carbohydrates was associated with a higher BMI by continuation aligns with data from healthy children describing the efficacy of targeting intake of carbohydrates for weight management [35–37]. An ongoing pilot study is evaluating the feasibility of this diet in preventing weight gain in pediatric ALL (Clinical Trials Identifier: NCT03157323).

In comparison to the general pediatric population, the proportion of participants below the DRI for vitamins D and E, and calcium were consistently higher than reported in the literature [38]. This may be due to clinicians advocating discontinuing vitamin and mineral supplements during treatment. Reductions in vitamin C may reflect avoidance of fruits during severe neutropenia. Recognizing the role of anti-folates in cancer treatment, the wide variation in intakes below and above the DRI will be the subject of further query. Finally, recognizing zinc's role in immune suppression, neuropathy and wound repair [39], the clinical relevance should be evaluated within the context of pediatric ALL.

Our findings lead to several hypothesis-generating questions. Examination of diet-outcome relationships in pediatric ALL needs to encompass assessments of multiple nutrients and assess variability across diverse age and gender groups [40,41]. The association of excess macronutrient intake in the pathogenesis of ALL and response to therapy is an understudied area. Excess dietary intakes of fat (particularly animal fat), simple carbohydrates, energy-dense foods, and reduced micronutrient intakes are pro-oxidative and inflammatory [42,43]. Excess dietary fat has a pro-obesogenic effect on the microbiome [44] and elucidate a mechanism contributing to obesity during ALL. Other factors may be attributable including reduced energy expenditure, genetics, or insults to the microbiome thereby affecting nutrient uptake and further promoting the inflammatory process [44–46].

Our study has several strengths. Dietary intake was collected prospectively in a large group of children treated on a single therapeutic protocol. The similarity of drugs used for the treatment for ALL suggests that our findings are likely generalizable to other treatment protocols for ALL and may serve as support for development of evidence-based nutritional guidelines for pediatric ALL. Missing data was limited in our study and was below that previously reported in dietary studies thus decreasing the likelihood of introduction of bias.

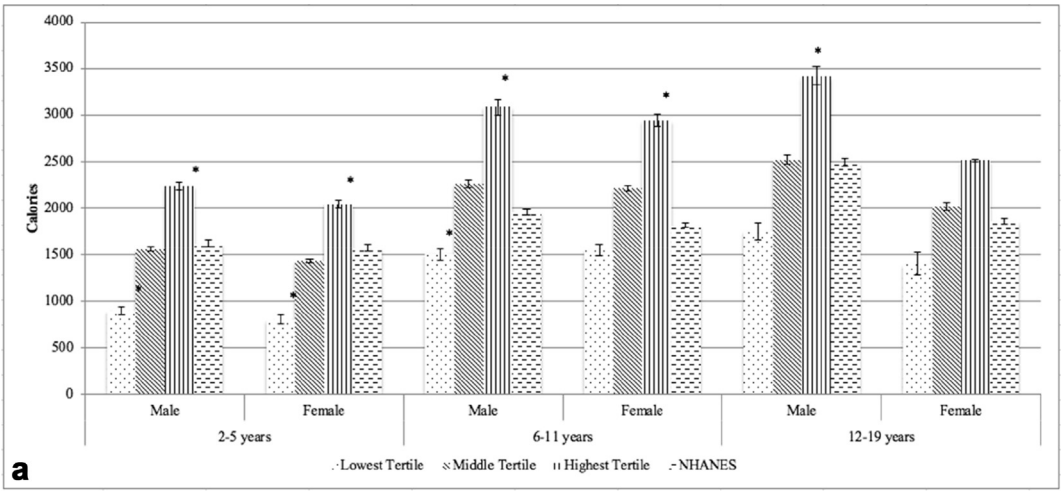

Fig. 3a. Comparison of diagnosis energy intakes to nhanes normative values[§]. [§]Independent samples t-test were performed to compare the mean energy intake for each tertile and the normative values from the NHANES dataset for each corresponding age group and gender. Bonferroni correction was applied for multiple testing; *P < 0.001; **P = 0.002.

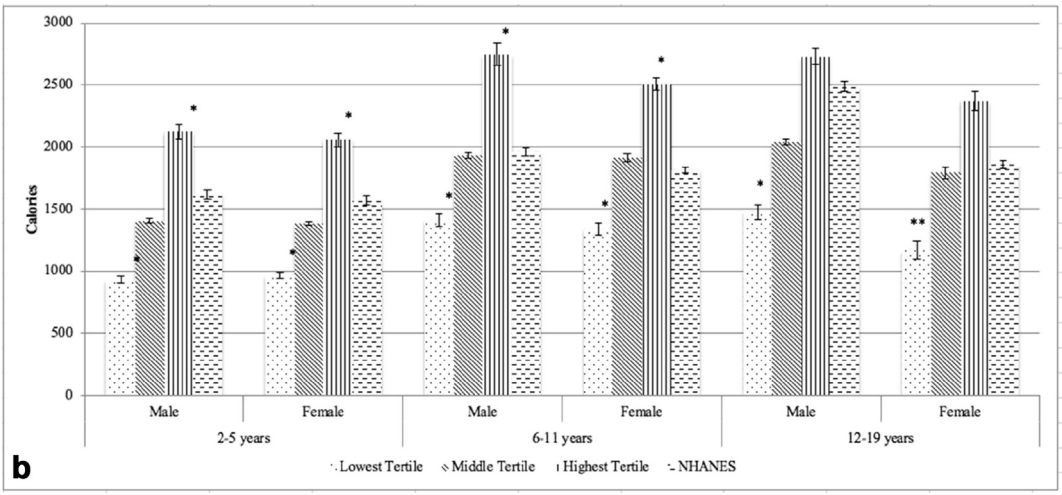

Fig. 3b. Comparison of end of induction energy intakes to NHANES normative values[§]. [§]Independent samples t-test were performed to compare the mean energy intake for each tertile and the normative values from the NHANES dataset for each corresponding age group and gender. Bonferroni correction was applied for multiple testing; *P < 0.001.

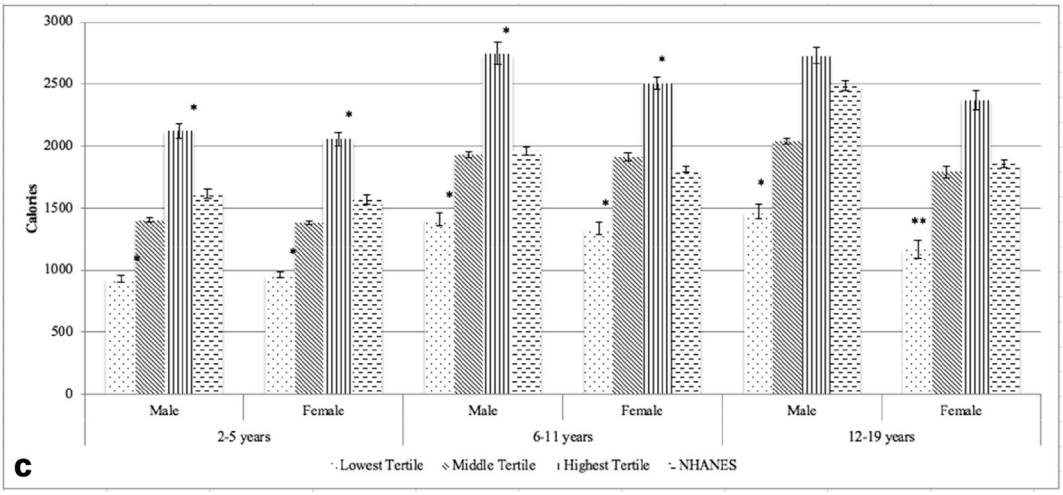

Fig. 3c. Comparison of continuation energy intakes to NHANES normative values[§]. [§]Independent samples t-test were performed to compare the mean energy intake for each tertile and the normative values from the NHANES dataset for each corresponding age group and gender. Bonferroni correction was applied for multiple testing; *P < 0.001; **P = 0.002.

Our study is not without limitations. The clinical data, including nutritional anthropometrics, was limited to those data that were required to be reported as part of the DFCI 05-001 treatment protocol. In this study, height and weight was only required to be reported at diagnosis due to the association of BMI at diagnosis predicting outcomes in pediatric ALL [12] and in continuation. Thus, our findings are limited to how the treatment itself impacts dietary intake over the course of treatment, and the predictive value of fluctuations in treatment and BMI at diagnosis are associated with BMI at continuation. Our decision to set the RDA as the reference value may lead to an overestimation of children and adolescents below the RDA. However, there remains controversy as to which reference value is best suited for the evaluation of populations with a chronic disease [47–49]. Moreover, neither reference value considers the risk factors associated with childhood ALL. To serve as normative data, we relied upon data collected by NHANES. As such, it is plausible that over-reporting rather than true excess consumption may attribute to excess intake, particularly since our data was collected with a FFQ. However, over-reporting appears to be limited, given that reported nutrient intakes in this study were similar to a previous report utilizing the same methodology [50]. Additional limitations of the use of FFQ including misreporting, recall bias and survey fatigue are possibilities that may impact the observed outcomes. However, we believe fatigue was limited in this dataset as all patients completed the entire survey and did not routinely indicate “never” for multiple food items. We also think this may be limited due to parents reporting for children or completed with the child. Our short time frame for dietary recall (one month versus previous year) reduced the risk of recall bias. Finally, we believe that misreporting may be limited as nutrition is an aspect of patients' care that parents are often overly attentive to nutritional intake throughout treatment for cancer. Our study did not account for other lifestyle factors affecting dietary intake such as physical activity, but error related to physical activity was minimized by the categorization of dietary intake by age and gender, which inherently controls for confounding variables related to energy intake [51]. Moreover, our conservative assumption that physical activity was low during the study period is further supported by the fact that participants were undergoing treatment for a chronic disease where hospitalizations are indicated during certain time points in therapy. We cannot eliminate misclassification, which is inherent to self-administered dietary questionnaires.

However, our systematic approach to the removal of outliers, implementation of a standardized approach for dietary collection may have minimized this limitation. Finally, dietary intake prior to diagnosis was referred to as 'normal intake'. It is plausible that the disease process itself altered dietary intake prior to diagnosis.

We found significant fluctuations in dietary intake over the course of treatment for pediatric ALL and have identified several areas within the diet that may be the target of future clinical interventions. Additionally, the outcome of this research may serve as a foundation for the development of evidence-based nutritional guidelines and has the potential to further improve clinical outcomes and reduce toxicities faced by survivors of pediatric ALL.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.12.021.

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