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Comparison of Childhood Cancer Survivors' Nutritional Intake with US Dietary Guidelines

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Abstract

Background—Despite improved survival, childhood cancer survivors experience significantly elevated risk of premature mortality and serious morbidity due to chronic health conditions. Poor diet quality can exacerbate chronic health conditions in the survivors but their nutritional intake has not been adequately studied.

Procedure—We assessed the Healthy Eating Index 2010 (HEI-2010) in 22 survivors of pediatric acute lymphoblastic leukemia and lymphoma (median age = 11.7 years) and compared survivors' dietary intake to the 2010 Dietary Guidelines for Americans. Dietary data were collected using repeated 24-hour dietary recalls over a one-year period, which were averaged to estimate habitual intake.

Results—The mean HEI-2010 in childhood cancer survivors was 52.7, about 50 percent of the maximum score. Long-term survivors (time from diagnosis ≥ 10 years) had a significantly lower HEI-2010 than recent survivors (time from diagnosis < 5 years) ($\beta = -11.5$, 95% CI: -22.1, -0.9, $p=0.047$). For individual food groups and nutrients, survivors had a particularly poor adherence to green vegetables and beans, total vegetables, and whole fruits. None of the survivors met the

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guidelines for dietary fiber and potassium intake. Only 4%, 19%, 24%, and 29% met the guidelines for vitamin D, sodium, calcium, and saturated fat intake. The average intake in relative to the recommended intake was 32% for vitamin D, 50% for potassium, 63% for fiber, and 85% for calcium, but was 115% for saturated fat and 143% for sodium.

Conclusions—Childhood cancer survivors, in particular long-term survivors, have a poor adherence to the US dietary guidelines.

Keywords

Nutrition; Survivors; Childhood Cancer

Introduction

Dramatic improvements in the diagnosis and treatment of cancer in childhood have led to a rapidly growing cohort of survivors, now estimated to exceed 420,000 in the US.(1, 2) However, this success has brought the recognition that childhood cancer survivors (CCS) have significantly elevated risk of premature mortality and serious morbidity.(3-6) Of note, CCS experience a significantly high risk of chronic health conditions such as cardiovascular disease (CVD)(7-9) and related factors including hypertension,(10, 11) dyslipidemia,(10, 11) insulin resistance or diabetes,(10-13) and obesity(14, 15) at a young age.

Nutrition plays an important role in the etiology of chronic health conditions, and is among the few modifiable behaviors that can prevent or delay its early onset. Nevertheless, the nutritional intake in CCS has not been adequately examined, in particular among young CCS (i.e., children, adolescents, and young adults) who experience a similar risk for chronic health conditions as their middle-age siblings.(5) Existing studies provide some evidence suggesting a poor adherence of survivors' diet to the current dietary guidelines.(16-20) Few studies, however, have assessed dietary intake of a broad category of micronutrients and minerals. Accurately assessing dietary intake is also hindered by measurement errors often associated with the use of food frequency questionnaires.(21, 22)

Using repeated 24-hour dietary recalls, we assessed nutritional intake in young survivors of childhood acute lymphoblastic leukemia (ALL) and lymphoma; both are common cancer types diagnosed in children and adolescents. We compared survivors' nutritional intake to the age- and sex-specific recommendations in the 2010 Dietary Guidelines for Americans (DGA). We also explored whether nutritional intake in CCS differed by patient and treatment characteristics.

Methods

Eligible participants were identified from the records of the Pediatric Hematology/Oncology Clinic of the Floating Hospital for Children at Tufts Medical Center, Boston, MA.(23) To be eligible, patients had to (1) be diagnosed with ALL or lymphoma at age younger than 21 years, (2) be between the ages of 3-25 years at study enrollment, and (3) have completed all cancer treatment within the past 15 years and be in remission, or on-treatment and receiving maintenance therapy. Patients were excluded if they had relapsed, had undergone allogeneic

bone marrow transplant, had conditions known to influence food intake or energy expenditure, or were pregnant or lactating.

For all participants, demographic variables and medical history were extracted from medical records. Non-fasting weight was measured in light clothing, without shoes, on a standing scale to the nearest 0.1 kg. Height was measured using a wall-mounted stadiometer in conjunction with a head board to the nearest 0.1 cm. Body composition including fat-free mass (FFM) and percent of body fat (%BF) were assessed by whole body dual x-ray absorptiometry (Hologic Discovery A. software version 12.6, Hologic Inc., Bedford, MA) and analyzed with Hologic APEX software version 3.3. Total energy expenditure was measured using the doubly labelled water method following a 7-day study protocol.(23)

The study was approved by the institutional review board at Tufts Medical Center/Tufts University. For patients under 18 years of age, parent consent and child assent were obtained prior to enrollment. Patients who had reached the adult age provided consent for their own participation.

Nutritional Intake

Nutritional intake was assessed by repeated 24-hour dietary recalls over a one-year study period, at enrollment, 6-month, and 12-month visits, respectively. At each visit, three repeated recalls (two weekdays and one weekend) were conducted. The initial 24-hour diet recall was administered in person at the study visit and two additional unannounced recalls were conducted by phone within seven days of the first recall. Dietary recalls were conducted by trained staff of the Dietary Assessment Unit at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, using the standardized multiple pass method developed for national dietary surveillance.(24, 25) The recall data were analyzed using the Nutrition Data System for Research software (NDSR, version 2011), developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN. Parents were used as proxy reporters for participants 12 years of age because previous research has documented considerable errors in recalls of food intake and portion size by children 12 years old or under.(26) Repeated recalls at each visit were averaged to improve the validity of estimating habitual nutritional intake.(22)

Statistical Analysis

We first calculated the Healthy Eating Index (HEI)-2010 to evaluate the overall diet quality of CCS following the methodology developed by the US Department of Agriculture. (27) The HEI-2010 measures the adherence to the 2010 DGA and has 12 components.(28) For each component, intakes of foods and nutrients are represented on a density basis, counted as amount per 1,000 kcal. The 9 adequacy components include total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids. The 3 moderation components include refined grains, sodium, and empty calories. For adequacy components, a score of 0 is assigned for no intake, and the scores increase proportionately as intakes increase up to the recommended intake. For moderation components, levels of intakes at the recommended intake are assigned the

maximum score and the scores decrease as intakes increase. A higher HEI score indicates a better adherence to the dietary guidelines. The maximum total score is 100.

We then examined survivors' diet quality in association with patient and treatment characteristics using Analysis of Variance (ANOVA). For patients aged 3-20 years old, BMI z-score was calculated using the 2000 Center for Disease Control and Prevention (CDC) growth charts for children.(29) Obesity was defined as BMI z-score ≥ 1.645 (95th percentile), overweight as BMI z-score ≥ 1.036 -1.644 (85th-94.9th percentile), and healthy weight as BMI z-score ≤ -1.645 -1.035 (5th-84.9th percentile), based on the current recommendations of the US Center for Disease Control and Prevention (30) and in accordance with previous studies.(31) For patients >20 years, BMI z-score and percentile were calculated based on the reference data for age 20 in the 2000 CDC growth charts.(32) We also conducted linear regressions with stepwise selection to identify significant predictors for diet quality with an entry and exit alpha of 0.05.

Last, we compared the mean intake of nutrients in CCS to the Dietary Reference Intakes (DRIs) published by the Institute of Medicine (33) by calculating the percentage of the CCS who met the age- and sex-specific DRIs. For most nutrients, the age- and sex-specific DRIs are based on Recommended Daily Allowance (RDA). For Linoleic acid, α -linolenic acid, potassium, choline, and vitamin D, the DRIs are based on Adequate Intake (AI). For sodium, the DRI is based on Upper Limit (UL). When no quantitative DRI value is available, the Dietary Guidelines (DG) recommendations (27) are used. An individual was considered to meet recommended intake for a specific nutrient if the intake level is equal to or above the RDA or AI according to his/her age and sex. For sodium, % calories from saturated fat, and cholesterol, an individual was considered to meet the recommended intake if the intake level is below the UL or DG. For % calories from macronutrients, the recommended intake was based on Acceptable Macronutrient Distribution Range (AMDR). An individual was considered to meet the recommended intake if the percentage falls into the age- and sex-specific AMDR. We also calculated the ratio of survival's actual intake to the age- and sex-specific DRIs $\times 100$. A ratio >100 indicates that the survivors consume a higher level of the nutrients than the recommended intake whereas a ratio <100 indicates a lower level of nutrients intake in CCS than the recommended intake.

Results

Clinic records identified 67 eligible patients. An informational letter about the study was sent to potential participants. The letter contained an opt-out card, which, if returned, would preclude further contact by study staff. Five patients returned the opt-up card, 12 declined to participate during follow-up contacts, 28 did not respond after multiple contacts by phone or mail, and 22 patients were enrolled into the study between October 2011 and June 2012. All 22 participants completed at least one recall. The average number of recalls completed by each participant was 6.4.

The median age of study participants at enrollment was 11.7 (range: 4.7-24.9) years, and the median interval from cancer diagnosis was 5.6 (range: 0.3-17.0) years. The majority of the survivors were males (68%) and non-Hispanic whites (77%). The mean BMI z-score was

0.8 (SD = 1.0), corresponding to the 79th BMI percentile. More than 40% of the survivors were overweight or obese (Table I).

The mean HEI-2010 total score was 52.7 (SD=10.6), about half of the maximum score (i.e. 100) (Table II). Among individual components, whole fruit, total vegetables, greens and beans, seafood and plant protein, fatty acids, and sodium achieved less than 50% of the maximum scores, suggesting a poor adherence by CCS to these components (Figure 1). HEI-2010 total score was not associated with survivors' demographic and treatment characteristics in the univariate analysis. Results from stepwise regression indicated that long-term survivors (time from diagnosis ≥ 10 years) had a significantly lower HEI-2010 compared to those recently diagnosed (time from diagnosis <5 years) ($\beta = -11.5$, 95% CI: -22.1, -0.9). Patients' age, sex, race/ethnicity and other clinical features such as age at diagnosis, years since diagnosis, treatment status (on- vs. off-treatment), and receipt of cranial radiation were not associated with diet quality in CCS. Diet quality did not differ significantly between overweight/obese CCS and those with healthy weight (Table III).

When macronutrients intake in CCS was compared to the age- and sex-specific recommended intake in the 2010 DGA, none of the survivors met the recommended intake for fiber, and only 29% met the recommendation of having <10 % energy from saturated fat (Table IV). The mean intake of fiber was 63% of the recommended intake whereas the mean % energy from saturated fat was 15% above the recommended level.

For minerals, none of the survivors met the recommended intake for potassium, and only 24% met the recommended intake for calcium. However, 81% of the survivors exceeded the upper limit for sodium intake. The mean intake of potassium and calcium was 50% and 85% of the recommended level, respectively, whereas the mean sodium intake was 43% above the recommended level.

For vitamins, only 5% of the survivors met the recommended intake for vitamin D, 19% of the survivors met the recommended intake for vitamin E and choline, and 29% of the survivors met the recommended intake for vitamin K. The mean intake of vitamin D, vitamin E, choline, and vitamin K was 32%, 78%, 71%, and 75% of the recommended intake.

Discussion

Our study is among the few that have assessed nutritional intake in young survivors of childhood cancer (median age=11.7 years), and evaluated whether survivors' diet quality was associated with patient and treatment characteristics. The results suggest poor adherence by childhood cancer survivors to the current dietary guidelines for Americans, and long-term survivors with time from diagnosis for more than 10 years may be at particular risk of poor nutritional status.

Although dietary guidelines have been developed for cancer survivors, such as those developed by the American Cancer Society (34) and the World Cancer Research Fund/the American Institute for Cancer Research (WCRF/AICR),(35) these guidelines focus on survivors with malignancies other than childhood cancer. The long-term follow-up

guidelines for CCS developed by the Children's Oncology Group (COG) do not have cancer- and treatment-specific guidelines on nutrition.(36) The lack of specific dietary guidelines for CCS is partly due to the fact that CCS' nutritional intake is still poorly understood. We found a mean HEI-2010 of 52.7 in 22 CCS, similar to the mean HEI-2005 score of 55.5 in a previous study of 91 CCS (mean age=19 years), which assessed adherence to the 2005 DGA.(16) Prior studies, although used different indices and assessment methods to capture nutritional intake, have consistently reported poor diet quality in CCS.(16-18, 37) The mean diet quality score was either less than half (17) or only slightly above half of the maximum score,(16, 18, 37) ranging from 33% to 56%.

For individual food groups, our study and a few others observed poor adherence by CCS to whole fruit and total vegetables.(16, 18, 37, 38) In particular, survivors had a low adherence to green vegetables: the component score only reached 20-22% of the maximum score;(16) and the actual intake in relative to the recommended intake was less than 50%.(17, 18) In contrast, CCS had a better adherence to dairy or milk (65-77%) (16, 17) and total protein foods or meat and beans (73-86%) (16, 17) although the adherence to the seafood and plant protein recommendations remained poor (38% in our study).

When energy-contributing macronutrients were evaluated, our study and two previous studies found CCS consumed high calories from saturated fat, (16, 17) and our study also detected a low ratio of unsaturated fat to saturated fat. In addition, our study and two previous studies (17, 18) found CCS had a poor adherence to fiber intake, likely due to the low consumption of green vegetables. For micronutrients and minerals, we observed a high intake of sodium and a low intake of calcium and vitamin D in CCS. These findings were consistent with previous studies(16, 17, 37) that reported a mean sodium intake > 3,000 mg/day and a high percentage of the CCS not meeting the recommended intake for vitamin D (19) and/or calcium.(19, 38, 39) Our study along with a previous study (19) also found a very low adherence by CCS to recommended potassium intake, which may be explained by the low consumption of vegetables and fruits.

The overall diet quality in CCS appears to be similar to that in the general population. Based on one-day 24-hour diet recall, the mean HEI-2010 total score in children age 2-17 years in the 2007-2008 National Health and Nutrition Examination Survey (NHANES) was 49.8.(40) The individual components that had the lowest percentage of the maximum score in the general population also included greens and beans (18%), whole grains (18%), and fatty acids (30%). However, children in the 2007-2008 NHANES had a much better adherence to total fruit and whole fruit (80% and 95%, respectively). It has to be noted, however, CCS not only have significantly higher risk of chronic health conditions than the general population but also develop chronic health conditions at a much younger age.(5) Poor nutritional intake can significantly exacerbate treatment-related chronic health conditions experienced by CCS.

Cancer diagnosis may serve as a "teachable moment" and trigger positive dietary changes in the survivors but may also adversely affect nutritional intake through complex pathways. Several regimens for treating hematologic malignancies include corticosteroids, which are known to be critically involved in regulating energy intake, storage, and mobilization. Two

previous studies in pediatric patients of ALL reported a significant increase in energy intake during corticosteroid therapy.(41, 42) Anecdotal observations from clinicians also indicate children crave high energy-density foods or salty foods during treatment. These intake patterns were originally thought to be acute responses to cancer treatment. However, recent evidence indicates that children have difficulty reversing unhealthy eating habits after treatment completion,(43) and a high proportion of CCS report taste preferences that interfere with adherence to a healthy diet.(44) Cranial radiation therapy (CRT) is used in leukemia regimens to prevent central nervous system relapse and can directly damage the hypothalamic pituitary region, impairing signaling reception from hormones such as ghrelin and leptin that regulate hunger and appetite.(14, 45-47) These findings support the notion that cancer treatment may have long-lasting impact on survivors' diet. Our sample size was limited and we did not find diet quality in CCS was associated with survivors' age, sex, or race/ethnicity neither was survivors' age at diagnosis or receipt of CRT, although there were some suggestions that long-term survivors (time from diagnosis ≥ 10 years) had a lower diet quality than more recent survivors (time from diagnosis <5 years). Only one previous study (16) evaluated diet quality in association with treatment exposure and found CCS treated with CRT had a lower diet quality than those treated without CRT. However, both studies were based on small cohorts of survivors. Large-scale studies with systematic assessments on patient and treatment characteristics are required to further quantify the impact of cancer diagnosis and treatment on nutritional intake in CCS.

The limitations of our study include small sample size that limits small differences in diet quality to be detected by patient or treatment characteristics and the lack of age- and sex-matched healthy controls. Our study included only survivors of childhood ALL or lymphoma and excluded CCS with comorbid conditions that affect dietary intake and energy expenditure, so the results may not be applicable to CCS with other cancer types or comorbidities. However, our study is among the few studies that assessed nutritional intake in young CCS using repeated 24-hour dietary recalls. We have previously validated energy intake (EI) reported from repeated dietary recalls and from food frequency questionnaire (FFQ), both against total energy expenditure (TEE) measured using the doubly labeled water method. We found substantial underreporting of EI from FFQ but not from repeated recalls: $(EI-TEE)/TEE \times 100\% = 21.8\%$ from FFQ and -0.9% from repeated recalls. The use of repeated recalls allowed us to accurately assess survivors' nutritional intake and compare that to the US dietary guidelines.

In summary, findings from our study suggest CCS, in particular long-term survivors, exhibit poor diet quality. Although this study may not directly inform changes in clinical management of this population, there is growing evidence suggesting that CCS experience unhealthy weight gain early in treatment and a large proportion of CCS become overweight or obese following treatment completion (~40%).(48) Conversations with parents need to be initiated early for healthy weight management through healthy eating and avoiding inactivity. For specific dietary recommendations, we need future large-scale studies to further understand dietary intake in CCS, how dietary intake in CCS are correlated with treatment and patient characteristics, and whether CCS's nutritional intake is associated with survival outcomes or quality of life measures. These findings will inform targeted dietary

interventions to improve the long-term health of the growing cohorts of childhood cancer survivors.

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Figure 1. HEI-2010 in Childhood Cancer Survivors. The dark dotted pattern indicates the mean HEI-2010 score (HEI Score), and the undotted pattern indicates the percentage of mean score to the maximum score (% HEI of Max. Score).

Table I
Characteristics of childhood cancer survivors, the Healthy Living Study, 2011-2012

Characteristics	N=22
Age at study enrollment, <i>years</i> , median (Q1, Q3)	11.7 (7.5, 19.5)
Gender, N (%)	
Male	15 (68.2)
Female	7 (31.8)
Race/ethnicity, N (%)	
Non-Hispanic white	17 (77.3)
Other	5 (22.7)
Diagnosis	
Acute lymphoblastic leukemia	17 (77.3)
Hodgkin's lymphoma	3 (13.6)
Non-Hodgkin's lymphoma	2 (9.1)
Treatment status, N (%)	
On-treatment	3 (13.6)
Off-treatment	19 (86.4)
Age at diagnosis, <i>years</i> , median (Q1, Q3)	4.5 (3.0, 7.0)
Years since diagnosis, median (Q1, Q3)	5.6 (2.8, 8.3)
BMI z-score, mean (SD)	0.8 (1.0)
Weight status, N (%)	
Healthy weight	13 (59.1)
Overweight/obese	9 (40.9)
Fat-free mass, <i>kg</i> , mean (SD)	34.2 (17.4)
Percentage of body fat, mean (SD)	29.2 (6.6)

Healthy Eating Index (HEI)-2010 and its components in childhood cancer survivors

Table II

HEI Components	Maximum Score	Standard for Maximum Score	Standard for Minimum Score of 0	Score in CCS Mean (SD)
Adequacy Components				
Total fruit	5	0.8 cup equiv. per 1,000 kcal	No fruit	2.6 (1.9)
Whole fruit	5	0.4 cup equiv. per 1,000 kcal	No whole fruit	2.3 (2.0)
Total vegetables	5	1.1 cup equiv. per 1,000 kcal	No vegetables	2.1 (1.3)
Greens and beans	5	0.2 cup equiv. per 1,000 kcal	No dark green vegetables or beans and peas	1.1 (1.7)
Whole grains	10	1.5 oz equiv. per 1,000 kcal	No whole grains	5.8 (3.1)
Dairy	10	1.3 cup equiv. per 1,000 kcal	No dairy	7.7 (2.3)
Total protein foods	5	2.5 cup equiv. per 1,000 kcal	No protein foods	4.3 (1.2)
Seafood and plant protein	5	0.8 cup equiv. per 1,000 kcal	No seafood or plant proteins	1.9 (1.8)
Fatty acids	10	(PUFAs+MUFAs)/SFAs 2.5	(PUFAs+MUFAs)/SFAs < 1.2	3.4 (2.9)
Moderation Components				
Refined grains	10	1.8 cup equiv. per 1,000 kcal	4.3 cup equiv. per 1,000 kcal	5.9 (2.6)
Sodium	10	1.1 gram per 1,000 kcal	2.0 gram per 1,000 kcal	3.5 (2.0)
Empty calories	20	19% of energy	50% of energy	12.1 (3.5)
Total HEI score	100			52.7 (10.6)

Table III
Healthy Eating Index (HEI)-2010 by characteristics of childhood cancer survivors

	N	HEI-2010	P ¹	β (95% CI) ²	β (95% CI) ³
Age at study, years		Mean (SD)			
<12	11	56.8 (10.0)		ref.	
12	11	48.6 (9.9)	0.07	-0.4 (-1.2, 0.3)	
Sex					
Male	15	51.8 (12.1)		ref.	
Female	7	54.6 (6.6)	0.58	2.7 (-7.5, 13.0)	
Race/ethnicity					
Non-Hispanic white	17	52.9 (9.8)		ref.	
Other	5	52.1 (14.2)	0.89	-0.8 (-12.3, 10.7)	
Age at diagnosis, years					
<5	11	53.6 (11.1)		ref.	
5	11	51.9 (10.5)	0.72	-1.7 (-11.3, 7.9)	
Years since diagnosis, years					
<5	9	52.6 (12.7)		ref.	
5-9	9	57.0 (5.4)		4.5 (-5.2, 14.1)	
10	4	43.3 (9.9)	0.09	-9.3 (-21.6, 3.0)	-11.5 (-22.1, -0.9)
Treatment status					
Off-treatment	19	51.8 (10.6)		ref.	
On-treatment	3	58.6 (10.5)	0.31	6.9 (-6.8, 20.5)	
Cranial radiation					
No	20	54.3 (10.9)		ref.	
Yes	2	46.7 (4.8)	0.41	-6.6 (-23.1, 9.8)	
Weight status					
Healthy weight	13	51.4 (9.4)		ref.	
Overweight/obese	9	54.6 (12.4)	0.51	3.1 (-6.5, 12.8)	

¹ANOVA;

²Univariate linear regression;

Stepwise linear regression

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Table IV
Comparison of dietary intake in childhood cancer survivors to the 2010 Dietary
Guidelines for Americans (DGA)¹

Nutrients	Intake		Percentage of meeting DGA (%)	$\frac{\text{Intake}}{\text{DGA}} \times 100$
	Mean	SD		
Macronutrients				
Protein (g)	72	19	---	230
(% calories)	15	4	95	---
Carbohydrate (g)	255	74	---	196
(% calories)	52	8	76	---
Total fiber (g)	15	4	0	63
Total fat (% calories)	33	6	62	112
Saturated fat (% calories)	11	2	29	115
Linoleic acid (g)	13	6	---	112
(% calories)	6	2	71	---
α -linolenic acid (g)	1.6	0.8	---	141
(% calories)	0.7	0.3	48	---
Cholesterol (mg)	213	99	81	71
Minerals				
Calcium (mcg)	931	337	24	85
Iron (mg)	16	6.6	62	165
Magnesium (mg)	233	58	52	112
Phosphorus (mg)	1157	326	71	157
Potassium (mg)	2141	696	0	50
Sodium (mg)	3057	814	19	143
Zinc (mg)	11	4.5	76	159
Copper (mcg)	1	0.3	86	169
Selenium (mcg)	100	20	100	246
Micronutrients				
Vitamin A (mcg RAE)	660	491	43	124
Vitamin D (mcg)	4.9	3.6	5	32
Vitamin E (mg AT)	7.6	3.3	19	78
Vitamin C (mg)	66	44	62	166
Thiamin (mg)	1.7	0.5	100	202
Riboflavin (mg)	2.1	0.8	100	248
Niacin (mg)	22	7	95	192
Folate (mcg)	421	224	67	145
Vitamin B ₆ (mg)	1.7	0.8	90	191
Vitamin B ₁₂ (mcg)	5.0	2.7	90	301
Choline (mg)	251	91	19	71
Vitamin K (mcg)	75	84	29	75

¹For most nutrients, the age- and gender- specific recommendations were based on Recommended Daily Allowance (RDA) published in the 2010 Dietary Guidelines for Americans. % calories for macronutrients were based on Acceptable Macronutrient Distribution Range (AMDR); linoleic acid, alpha-linolenic acid, potassium, choline and vitamin D recommendations were based on Adequate Intake (AI); and sodium recommendation was based on Upper Limit (UL).

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