RESEARCH
Original Research

# Inadequate Dietary Intake in Patients with Thalassemia

Ellen B. Fung, PhD, RD; Yan Xu, MS; Felicia Trachtenberg, PhD; Isaac Odame, MD; Janet L. Kwiatkowski, MD, MSCE; Ellis J. Neufeld, MD, PhD; Alexis A. Thompson, MD; Jeanne Boudreaux, MD; Charles T. Quinn, MD, MS; Elliott P. Vichinsky, MD; for the Thalassemia Clinical Research Network

**ARTICLE INFORMATION**

**Article history:**
Accepted 19 January 2012
Available online 30 April 2012

**Keywords:**
Thalassemia
Dietary intake
Iron
Vitamin D


2212-2672/$36.00
doi: 10.1016/j.jand.2012.01.017

**ABSTRACT**

**Background** Patients with thalassemia have low circulating levels of many nutrients, but the contribution of dietary intake has not been assessed.

**Objective** Our objective was to assess dietary intake in a large contemporary sample of subjects with thalassemia.

**Design** A prospective, longitudinal cohort study using a validated food frequency questionnaire was conducted.

**Participants/setting** Two hundred and twenty-one subjects (19.7±11.3 years, 106 were female) were categorized into the following age groups: young children (3 to 7.9 years), older children/adolescents (8 to 18.9 years), and adults (19 years or older); 78.8% had β-thalassemia and 90% were chronically transfused. This study took place at 10 hematology outpatient clinics in the United States and Canada.

**Main outcome measures** We conducted a comparison of intake with US Dietary Reference Intakes and correlated dietary intake of vitamin D with serum 25-OH vitamin D and dietary iron with total body iron stores.

**Statistical analyses performed** Intake was defined as inadequate if it was less than the estimated average requirement. $\chi^2$, Fisher's exact, and Student's $t$ test were used to compare intake between age categories and logistic regression analysis to test the relationship between intake and outcomes, controlling for age, sex, and race.

**Results** More than 30% of subjects consumed inadequate levels of vitamin A, D, E, K, folate, calcium, and magnesium. The only nutrients for which >90% of subjects consumed adequate amounts were riboflavin, vitamin B-12, and selenium. Dietary inadequacy increased with increasing age group ($P<0.01$) for vitamins A, C, E, B-6, folate, thiamin, calcium, magnesium, and zinc. More than half of the sample took additional supplements of calcium and vitamin D, although circulating levels of 25-OH vitamin D remained insufficient in 61% of subjects. Dietary iron intake was not related to total body iron stores.

**Conclusions** Subjects with thalassemia have reduced intake of many key nutrients. These preliminary findings of dietary inadequacy are concerning and support the need for nutritional monitoring to determine which subjects are at greatest risk for nutritional deficiency. Future research should focus on the effect of dietary quality and nutritional status on health outcomes in thalassemia.

J Acad Nutr Diet. 2012;112:980-990.

THALASSEMIA, A TERM THAT DEFINES A GROUP OF deficiencies in the production of the α- or β-globin chain of hemoglobin, is one of the most common single gene disorders in humans. Nearly 60% of the total population is affected in some regions of Thailand, Laos, and Cambodia,[1] and although a much smaller prevalence is found in North America (0.1%), its incidence is increasing.[1-3] More than 200 α- and β-globin gene mutations have been identified. In its most severe form, individuals with either α- (especially hemoglobin H–Constant Spring) or β-thalassemia require routine red blood cell transfusions soon after birth for survival.

The most common cause of death is cardiac failure resulting from transfusional iron overload.[4,5] However, as chelation therapies have improved, subjects are living longer and nutritional status is becoming increasingly important. Patients with thalassemia commonly exhibit inadequate growth, poor immune function, increased oxidative stress, and decreased bone mineralization, all morbidities with links to poor nutritional status.[6-8] Recently, it has been shown that subjects with thalassemia have reduced body fat and lean mass and that these alterations in body composition are related to both reduced growth and decreased bone density.[9] In addition, Claster and colleagues reported that more than half of a sam-

ple of regularly transfused subjects with thalassemia residing in Los Angeles had deficient circulating levels of vitamins A, C, D, and selenium.[10] However, there is a paucity of data on the contribution of dietary intake to these possible nutritional deficiencies in thalassemia.

The objective of this study was to assess the dietary intake of key nutrients in a large, contemporary sample of subjects with thalassemia, who were identified through the Thalassemia Clinical Research Network, and to compare their intake to US Dietary Reference Intakes. The specific hypotheses for this study were as follows: subjects with thalassemia have an inadequate dietary intake of key nutrients in comparison with age- and sex-specific recommendations; dietary intake of vitamin D is insufficient to maintain adequate vitamin D status; and dietary intake of iron is unrelated to total body iron stores, particularly in chronically transfused subjects.

## METHODS

This study was conducted as part of the Thalassemia Clinical Research Network's Thalassemia Longitudinal Cohort study. The Thalassemia Clinical Research Network is a National Heart, Lung, and Blood Institute–funded research network composed of six core centers in the United States, Canada, and the United Kingdom and their 10 associated satellite centers. Patients with thalassemia who were regularly cared for at one of these centers were invited to participate in the longitudinal cohort study between May 2007 and December 2009. The overall goal of the longitudinal cohort study was to describe the prevalence and incidence of complications related to thalassemia. The study is a prospective, longitudinal, cohort study with baseline and annual collection of routine clinical care data through chart review, patient questionnaires, and detailed genotyping characterization. Patient inclusion criteria were diagnosis of thalassemia regardless of genotype but, in general, more severe phenotypes who required a minimum of annual monitoring of comorbidities at their local clinic, both sexes, and all ages. Exclusion criteria included subjects with thalassemia trait, those with $\alpha$-thalassemias and hemoglobin >9 g/dL with no history of major complications, those who had received a bone marrow transplant, or those subjects unwilling to be followed on an annual basis. The protocol was approved by the Thalassemia Clinical Research Network Data and Safety Monitoring Board and by the ethical review boards of all participating Thalassemia Clinical Research Network institutions. Informed written consent, and assent in the case of a minor, was obtained from all participants.

At baseline and again 1 year later, subjects were asked to complete a validated, self-administered food frequency questionnaire. Adults (19+ years) completed the 110-food item, Block 2005 (Nutrition Quest) questionnaire,[11,12] older children and adolescents (ages 8 to 18 years) completed the 77-food item Block 2004, and caregivers of young children (younger than 8 years) completed the 90-food item Block 2004 for Kids.[13-15] All questionnaires were designed to estimate usual intake from a wide array of commonly consumed foods. The food lists were developed from National Health and Nutrition Examination Survey (1999-2002) dietary recall data; the nutrient database was developed from the US Department of Agriculture Food and Nutrient Database for Dietary Studies, version 1.0.[16,17] For most individuals the questionnaire takes 30 minutes to complete. Portion size was quantified for each food according to a series of pictures and, at the end of each questionnaire, a series of "adjustment" questions improved the accuracy in assessing fat and carbohydrate intake. On the adult and adolescent questionnaires, supplement use was also quantified. Questionnaires were sent to Nutrition Quest for analysis and then results forwarded to the Thalassemia Clinical Research Network data coordinating center (New England Research Institutes). Intake of individual nutrients were quantified and defined as inadequate if less than the estimated average requirement (EAR) for age and sex.[18-22] By definition, the EAR is the intake level at which the reference data indicate that the needs of 50% of a healthy population will be met. It is typically used to assess the diets of groups of individuals after corrections have been made for day-to-day variation.[23,24] For vitamin K, for which an EAR was not available, the adequate intake recommendation was used in its place. The tolerable upper intake level for a nutrient was defined as the level above which the habitual intake of a particular nutrient might result in adverse effects. In addition, individual food choices were quantified into MyPyramid food group servings within each food frequency questionnaire. These servings were then compared to the US Department of Agriculture's recommended servings for dairy, whole grains, fruits, vegetables, and meat (http://www.mypyramid.gov). Since the time when the analytical and statistical analyses were performed in this study, the US Department of Agriculture recommendations have been changed from MyPyramid food group servings to MyPlate. Unfortunately, data from the Block Food Frequency could not be reanalyzed to reflect this change.

Circulating 25-OH vitamin D (ng/mL [nmol/L]) and liver iron concentration, a proxy for total body iron stores, were assessed clinically and recorded if performed within the previous year. Height and weight were self-reported as part of the food frequency questionnaire. Other relevant medical history, such as thalassemia genotype, year that chronic transfusion was initiated, and serum ferritin and liver iron concentration values, were obtained by review of medical records. As medical history and laboratory data were obtained primarily through chart review, not all subjects have all data points, therefore, sample size is included in each table when the sample is less than the total.

### Statistical Analysis

**Calculated Variables and Definitions.** Age groups were defined as young children (3 to 7.9 years), older children and adolescents (8.0 to 18.9 year), and adults (≥19+ years). Subjects were categorized as transfused if they were currently receiving transfusion therapy on a routine basis of eight or more transfusions during the 12 months before entering the study. They were categorized as nontransfused if they were receiving fewer than eight transfusions per year or were not currently receiving transfusion therapy. Body mass index was calculated as kilograms of body weight per height in square meters. Estimated energy requirement (EER) was calculated for each individual using their age, sex, height, and weight according to the Institute of Medicine Dietary Reference Intake equations.[25] Given anecdotal evidence that suggests that the majority of subjects with thalassemia participate in limited physical activity outside the home,[26] EER was estimated

based on a sedentary lifestyle activity coefficient of 1.0. Percentage of EER was calculated as %EER=(kcal/EER)×100.

**Analyses.** Continuous variables were summarized as means with standard deviations and categorical variables were summarized as percentages. General linear models were used to model the effect of iron and vitamin D intake on total body iron stores and circulating vitamin D levels after controlling for age, sex, race, and transfusion status. When the influence of race was explored, racial categories were collapsed to compare white vs non-white races (ie, Asian, black, mixed, other). Subgroup analyses were also performed in the nontransfused thalassemia group alone. All inferences are based on two-tailed tests with a threshold of $\alpha$=.05 for declaring significance. All analyses were conducted using Statistical Analysis Software (version 9.1.3, 2006, SAS Institute).

## RESULTS

### Subject Characteristics

A total of 302 subjects with thalassemia from sites that submitted food frequency questionnaire surveys were originally recruited and consented to participate in the larger trial, of which 221 completed the baseline nutritional assessments (73.2%). There were no significant differences between those who completed or did not complete the food frequency questionnaire in terms of sex, ethnicity, or transfusion status. However, in the adult cohort, subjects who completed the food frequency questionnaire were younger compared with the noncompleters (29.4 vs 33.8 years; $P$=0.02); and in the child cohort, the subjects who completed the questionnaire were 2 years older (5.9 vs 3.7 years; $P$<0.001) compared with those who did not. Of the 221 subjects included in this study, 60 were from Canada (14 younger children, 32 older children/adolescents, and 14 adults).

The majority of subjects were receiving chronic transfusion therapy (Table 1), as this type of patient commonly received routine clinical monitoring and was therefore more likely to be included in the Thalassemia Longitudinal Cohort Study selection process. Iron overload, reflected in elevated serum ferritin and liver iron concentration, was significantly higher in the adult group of subjects who were on transfusion therapy for a longer duration (10.3 years vs 9.3 to 9.4 years in the younger subjects; $P$<0.001). There was a nonsignificant correlation between liver iron concentration and years of chronic transfusion therapy for the group as a whole ($r$=0.09; $P$=0.26). A slightly different distribution of thalassemia genotype and race were exhibited by age group (Table 1), with a larger percentage of Asians in the youngest cohort. There were, however, no differences in sex distribution by age category. Serum 25-OH vitamin D was insufficient (<30 ng/dL, <75 nmol/L) in 63% of the patient population (mean=27.2±13.1 ng/dL, 67.9±32.7 nmol/L).

When data were analyzed for the adult subgroup who completed the food frequency questionnaire at both time points (n=46), there were no differences between the average intakes at baseline and those at year 1 in any of the macro- or micronutrients assessed (data not shown), that is, the variability within the nutrient studied was greater than the change observed between the baseline and year 1 visits. Given the stability of the dietary intake data and for simplicity, only the baseline data are presented here.

The average servings of many of the major food groups were lower than those recommended for healthy adolescents and adults (Table 2[27]). In particular, servings of dairy products (eg, milk, yogurt, cheese) and whole grains (eg, cereals, grains, bread) were significantly lower for both the older children/adolescents and adult groups (all, $P$<0.01). Adult subjects with thalassemia consumed an adequate number of servings per day of vegetables, particularly dark green vegetables and meat (eg, meat, poultry, legumes).

### Macronutrient Intake

Body mass index was in the normal range (ie, 18-25) for 74% of adult thalassemia subjects studied, and weight ($\Delta$=1.2±4.6 kg) and body mass index ($\Delta$=0.4±2.1) did not change significantly between the baseline and year 1 assessment for the adults in this study. Estimated average kilocalorie intake was between 107% and 163% of estimated caloric requirement based on age, weight, height, and an assumed sedentary lifestyle. The difference between intake and expenditure was much greater in younger children compared with adults ($P$=0.021), but not different between the adolescents and adults (Table 3). Older children and adolescents with thalassemia met the acceptable macronutrient distribution range for fat intake (Table 3; 25% to 35% of kcal as fat), carbohydrate (45% to 65% of kcal), and protein (10% to 30% of kcal). However, adults were consuming more kilocalories as fat on average than is considered acceptable for healthy adult individuals (~38% vs acceptable range, 20% to 35%). Average dietary fiber intake was far less than recommendations (25 to 38 g), regardless of age group considered.

### Vitamins and Mineral Intake from Dietary Sources

More than 30% of subjects consumed less than the EAR of vitamin A, D, E, folate, calcium, and magnesium (Figure 1). The only nutrients for which >90% of subjects consumed at least the EAR were vitamin B-12, riboflavin, and selenium. No subjects consumed more than the upper limit for vitamin D or E. Two adult subjects consumed >2,500 mg/day calcium, the upper limit for adults, and 68% of young children consumed more than the upper limit of vitamin A (900 $\mu$g/day), although it is unclear what proportion of these are provitamin A sources. Adults were more likely than children to consume less than the EAR of most every nutrient studied (Figure 2). These differences by age group were statistically significant, with the exceptions of vitamin D, K, B-12, niacin, riboflavin, copper, and selenium.

### Supplementation

Many subjects (31% to 57%) took multivitamin/mineral supplements in addition to their usual diet. The most common supplements consumed were calcium and vitamin D (Table 4). Multivitamin/mineral supplements were also commonly consumed by nearly half of all adolescents and adults. Whether or not the multivitamin/mineral supplements most commonly chosen contained iron was unfortunately not available in the from the Block Food Frequency Questionnaire.

### Relationship of Intake to Body Iron or Circulating Vitamin D Levels

General linear models were used to explore the relationship between dietary iron intake and liver iron concentration, a

**Table 1.** Baseline characteristics of subjects with thalassemia, including anthropometrics, genotype, transfusion history, and total body iron stores

| | Total | Young children | Older children and adolescents | Adults | *P* value[a] |
|---|---|---|---|---|---|
| No. of subjects | 221 | 30 | 83 | 108 | — |
| Age (y), mean±SD[b] | 19.7±11.3 | 5.4±1.4 | 12.6±3.3 | 29.0±8.3 | — |
| Male sex (%) | 48.0 | 40.0 | 54.2 | 45.4 | 0.31 |
| Race (%) | | | | | <0.0001 |
| Asian | 51.6 | 80.0 | 53.0 | 42.6 | |
| White | 43.4 | 13.3 | 38.6 | 55.6 | |
| Other | 5.0 | 6.7 | 8.4 | 1.9 | |
| Body mass index,[c] mean±SD | 20.3±4.5 | 15.9±2.7 | 18.3±4.1 | 22.9±3.3 | — |
| Thalassemia genotype (% of sample) | | | | | 0.01 |
| β-thalassemia | 78.8 | 73.3 | 80.5 | 79.0 | |
| E-β Thal[d] | 13.8 | 10.0 | 8.5 | 19.0 | |
| HbH/CS[e] | 4.6 | 13.3 | 6.0 | 1.0 | |
| Other | 2.8 | 3.3 | 5.0 | 1.0 | |
| Chronically transfused (% of sample) | 90.0 | 96.0 | 94.5 | 85.4 | 0.09 |
| Years on chronic transfusion therapy, mean±SD | 16.5±11.0 | 3.8±1.7 | 10.5±4.0 | 24.7±9.6 | <0.0001 |
| Serum ferritin (ng/mL[f]), median (range)[gh] | 1,236 (85-14,835) {216} | 921 (89-3,218) {29} | 1,136 (85-9,480) {82} | 1,441 (129-14,835) {105} | 0.004 |
| Liver iron concentration (mg/kg), median (range)[ghi] | 9.6 (1.0-42.9) {195} | 9.4 (3.0-21.3) {23} | 9.3 (1.1-42.9) {75} | 10.0 (1.0-40.0) {97} | <0.0001 |

[a]For continuous variables, *P* values are from analysis of variance; for categorical variables, *P* values are from Fisher's exact test.
[b]SD=standard deviation.
[c]Calculated as kg/m$^2$.
[d]E-β Thal=E-β-thalassemia.
[e]HbH/CS=hemoglobin H-Constant Spring.
[f]To convert ng/mL ferritin to pmol/L, multiply ng/mL by 2.247. To convert pmol/L ferritin to ng/mL, multiply pmol/L by 0.445. Ferritin of 1,000 ng/mL=2,496 pmol/L.
[g]Where numbers of subjects are different than the group as a whole, sample size is included in braces {}.
[h]Because of skewness of the data, serum ferritin and liver iron concentration are presented as median (range) and all analyses are performed in log scale.
[i]Liver iron concentration was determined by magnetic resonance imaging, liver biopsy, or Ferritometer.

**Table 2.** Food group servings: Comparison between subjects with thalassemia and 2006 USDA[a] recommendations[b]

| | Older Children and Adolescents | | Adults | |
|---|---|---|---|---|
| Food group[c] | USDA recommendation,[d] range | Thalassemia (n=83), mean±SD[e] | USDA recommendation, range | Thalassemia (n=108), mean±SD |
| Whole grains (oz) | 3.0-3.5 | 0.9±1.1 | 3.0-4.0 | 0.8±0.7 |
| Fruits (cups) | 1.5-2.0 | 1.3±1.2 | 1.5-2.0 | 1.0±0.8 |
| Vegetables (cups) | 2.0-3.0 | 1.7±1.4 | 2.5-3.0 | 2.9±2.6 |
| Dark green vegetables (cups) | 0.29-0.43 | 0.3±0.3 | 0.43 | 0.4±0.5 |
| Orange vegetables (cups) | 0.21-0.29 | 0.1±0.1 | 0.29 | 0.1±0.2 |
| Dairy (cups) | 3.0 | 1.3±1.0 | 3.0 | 1.3±1.2 |
| Meat (oz) | 5.0-6.0 | 4.4±4.0 | 5.0-6.5 | 5.1±4.7 |

[a]USDA=US Department of Agriculture.
[b]The Food Guide Pyramid was designed to educate consumers about daily servings of each food group that comprise a healthy diet based on the 2005 Dietary Guidelines for Americans.[27]
[c]Collection of foods that share similar nutritional properties.
[d]MyPyramid food group recommendations are the minimum number of servings for an individual who participates in <30 minutes of activity per day (www.mypyramid.gov). Ranges are provided for sex differences. Food group servings were not calculated in the Block Kids Food Frequency Questionnaire and are not available for the "young child" group.
[e]SD=standard deviation.

proxy for total body iron. Liver iron concentration was assessed on average within 4.4±3.4 months of the food frequency evaluation by either magnetic resonance imaging (72.1% of subjects), liver biopsy (4.1%), or Ferritometer (23.8%). There was no significant relationship between dietary iron intake and liver iron concentration in the group as a whole ($P$=0.13) or after controlling for age, transfusion status, sex, and race ($P$=0.11). Similar results were observed when total body iron was estimated from serum ferritin; no relationship was observed between dietary iron intake and ferritin after controlling for age, sex, race, and transfusion status ($P$=0.3). There was also no significant relationship between iron intake and total body iron when the same analysis was limited to only transfused subjects (n=105) ($P$=0.09 for liver iron concentration and $P$=0.4 for ferritin). There was also no relationship between dietary vitamin D intake or supplemental vitamin D and serum levels of 25-OH vitamin D after controlling for age, transfusion status, sex, and race (both, $P$=not significant).

## DISCUSSION

This is the first study of dietary intake patterns in subjects with thalassemia, a population identified previously as having a multitude of risk factors for altered nutritional status.[6,7,10] What is clear from these data is that many subjects with thalassemia residing in the United States and Canada consume inadequate intakes of key food groups and essential nutrients, and that intake appears to worsen with increasing age. Nutrients of particular concern are vitamin A, D, E, calcium, and magnesium. The level of inadequacy is particularly relevant given previous reports of reduced circulating levels of essential nutrients,[7,10,28-30] which suggest that nutrient requirements for subjects with thalassemia might actually be higher than recommendations for the US population.

In this observational study, the dietary intake patterns might be linked to some major health concerns that occur frequently in thalassemia. Most convincingly, the limited intake of dairy products and the key nutrients found in these foods, vitamin D, calcium, and magnesium might play a role in the development of osteoporosis. Vogiatzi and colleagues have shown that nearly half of all transfused subjects with thalassemia have low bone mass and are at a substantially increased risk for fracture.[8] Low bone mass was strongly predicted by reduced serum vitamin D after controlling for age, weight, and hypogonadism. In the present study, more than half the sample consumed less than the EAR for calcium and magnesium, and nearly all subjects, regardless of age were consuming less than the EAR for vitamin D. In addition, serum vitamin D remained deficient in >60% of the sample, despite routine supplementation with both calcium and vitamin D. This is similar to what has been observed in other cross-sectional samples of subjects with thalassemia.[7,10] Recently, it has been found that supplementation with vitamin D must be at a much higher dose, >2,000 IU/day, in order to maintain sufficiency.[29] In addition, because many subjects revert back to deficient levels when supplementation is stopped, it is recommended that vitamin D levels be monitored every 6 months in this population.[29] Clearly, focus on improving intake of dairy foods and/or the adequacy of bone-forming nutrients through higher-dose supplementation is crucial and can have lasting effects on preventing one of the most common ailments in these subjects.

It must also be noted that osteoporosis is a multifactorial disease, particularly in subjects with thalassemia. Hypogonadism is common and also strongly linked to development of low bone mass at a young age.[8] In addition, given the nature of the bone deficits observed with reduced bone geometries and cortical bone deficits,[31] the role of limited physical activity and increased sedentary behaviors cannot be dismissed.

Cardiomyopathy due to transfusional iron overload is the most common cause of death in thalassemia.[4,5,32] Iron overload can be successfully managed with chelation; however,

**Table 3.** Average dietary intake of energy, macronutrients, and micronutrients in subjects with thalassemia separated by age group[a]

| | Total | Young children | Older children and adolescents | Adults |
|---|---|---|---|---|
| No. of subjects | 221 | 30 | 83 | 108 |
| Energy intake and requirements | ← mean±standard deviation → | | | |
| Total kilocalories | 1,813±908 | 1,852±853 | 1,752±813 | 1,850±996 |
| Estimated energy requirement (kcal/day) | 1,749±439 | 1,203±110 | 1,580±346 | 2,008±360 |
| %EER[b] | 116.9±91.7 | 163.4±79.1 | 114.8±52.9 | 106.9±111.9 |
| Macronutrients | | | | |
| Protein (g) | 70.7±38.6 | 66±30.3 | 66.7±33.6 | 75.2±43.8 |
| Protein (% of kcal) | 15.7±3.4 | 14.4±2.4 | 15.2±3.0 | 16.5±3.7 |
| Carbohydrate (% of kcal) | 49.1±8.4 | 52.9±5.2 | 51.9±6.7 | 45.8±9.1 |
| Dietary fiber (g) | 13.8±7.9 | 13.4±6.8 | 13.7±7.7 | 14±8.3 |
| Fat (% of kcal) | 35.9±6.3 | 34.4±4.7 | 34.0±5.4 | 37.8±6.8 |
| Saturated fat (g) | 23.6±13.1 | 25.3±11.7 | 22.1±11.0 | 24.3±14.8 |
| Cholesterol (mg) | 256.1±161.6 | 240.3±115.1 | 242.9±168.7 | 270.9±167.1 |
| Fat-soluble vitamins | | | | |
| Vitamin A (RAE[c]) | 724.6±554.3 | 1,250.1±766.9 | 539.3±306.1 | 720.9±544.3 |
| Vitamin D (IU) | 149.1±103.7 | 194.7±96.2 | 153.1±101 | 133±104.7 |
| Vitamin E (mg) | 6.9±3.9 | 7.2±3 | 6.0±3.7 | 7.5±4.1 |
| Vitamin K (ug) | 143.1±151.7 | 57.7±39.3 | 85.8±84.8 | 189.6±176.4 |
| Water-soluble vitamins | | | | |
| Vitamin C (mg) | 121.0±83.3 | 122.6±92.2 | 135.2±86.6 | 109.5±76.8 |
| Folate ($\mu$g) | 292.5±162.1 | 352±192.1 | 315.8±154.9 | 257.5±151.5 |
| Thiamin (mg) | 1.4±0.7 | 1.6±0.8 | 1.4±0.7 | 1.4±0.8 |
| Niacin (mg) | 19.0±10.7 | 18.0±9.1 | 17.5±9 | 20.5±12.1 |
| Riboflavin (mg) | 1.8±0.9 | 2±0.9 | 1.7±0.8 | 1.8±0.9 |
| Minerals | | | | |
| Calcium (mg) | 792.1±417 | 858.7±354.6 | 785.6±404.3 | 778.4±444.1 |
| Magnesium (mg) | 245.6±126 | 234.9±110.4 | 227.3±111.6 | 263±138.8 |
| Selenium ($\mu$g) | 93.9±52.5 | 89.1±41.1 | 87.0±45.0 | 100.7±59.8 |
| Phosphorus (mg) | 1,158.1±577.1 | 1,210.3±528.3 | 1,124.4±535.9 | 1,169.8±623.2 |
| Copper (mg) | 1.2±0.7 | 1.1±0.5 | 1.1±0.6 | 1.3±0.8 |
| Iron (mg) | 12.5±6.7 | 13.1±7.5 | 12.1±6.1 | 12.5±7 |
| Zinc (mg) | 10.2±6.3 | 8.6±4.2 | 9.7±5.0 | 11.0±7.6 |

[a]All data are total nutrient intakes from diet alone, supplementation not included.
[b]% EER=% estimated energy requirement: kilocalorie intake/EER, where EER is calculated from individual patient age, weight, height, and physical activity coefficient of 1.0=sedentary physical activity.
[c]RAE=retinol activity equivalents.

vitamin C deficiency diminishes its effectiveness.[33,34] Others have observed significantly reduced levels of ascorbate in transfused subjects.[10,30] In addition, iron overload leads to an increase in non-transferrin–bound iron and a sequential reduction in circulating antioxidants.[35,36] In this study, adolescent and adult subjects consumed few orange vegetables, foods known to be rich in antioxidants. In addition, the inadequacy of dietary intake of key antioxidants (eg, vitamin E, C, and zinc) increased with advancing age. Some subjects, perhaps recognizing their diets were inadequate or who were

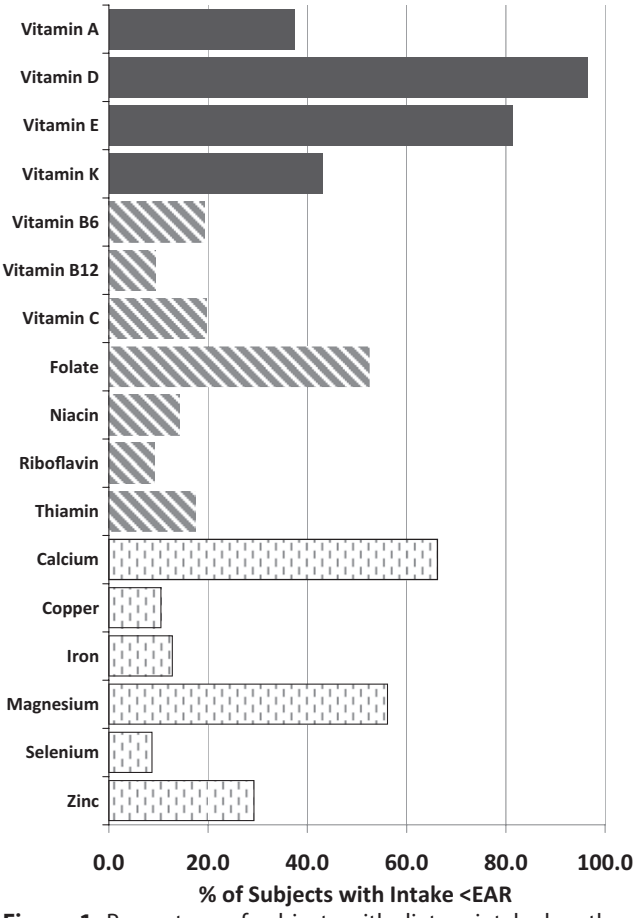


**Figure 1.** Percentage of subjects with dietary intake less than the estimated average intake (EAR) for specific nutrients (all subjects, n=221). Fat-soluble vitamins (black bars), water-soluble vitamins (striped bars), and minerals (light bars).

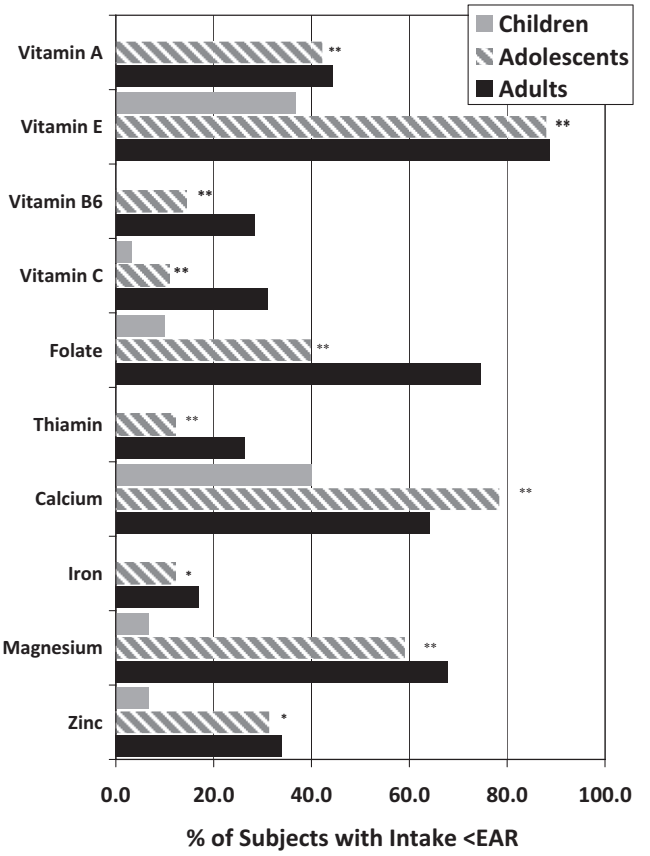


**Figure 2.** Dietary inadequacy increases with advancing age for some essential nutrients. Significance between age groups in individual nutrients by $^{**}P<0.001$ and $^{*}P<0.05$. Only nutrients for which there was a significant difference by age group are included here (omitted vitamins B-12, D, K, niacin, riboflavin, copper, and selenium). For some nutrients (ie, vitamins A and B-6, thiamin, and iron), none of the young children were consuming less than the estimated average intake (EAR); therefore, the percent in this figure is zero. Adult subjects are represented by the black bars, older children and adolescents by the striped bars, and younger children by the light gray bars.

prescribed them by their physicians, supplemented with either a multivitamin or vitamin C or E alone. However, the supplemental amount required to reduce oxidative stress in this iron-toxic population remains an unanswered question.

Dietary iron reduction has for decades been the focus of nutritional intervention in subjects with thalassemia because iron overload is a cause of substantial morbidity in both transfused and nontransfused subjects.[37] However, there is a paucity of data that link dietary iron intake with total body iron stores in thalassemia. In this study, there was not a significant relationship between dietary iron intake and total body iron stores estimated by either recent liver iron concentration or average serum ferritin measurement after correction for age, sex, race, and transfusion status. Clearly, for transfused subjects, the transfusional load of iron (200 mg iron/units×2 units every 3 weeks=19 mg/day) far outweighs the estimated absorption of iron from the diet (average iron intake in this study: 12.5 mg/day×10% absorption=1.25 mg/day). However, classic studies have shown that with very low hemoglobin levels (<9 g/dL), iron absorption increases dramatically and can approach 20%.[38] Therefore, the relationship between dietary iron intake and iron stores is likely to be quite different in the nontransfused patient with thalassemia, and could not be explored thoroughly in this study because of the limited number of nonchronically transfused subjects.

Given these preliminary dietary data in adequately transfused subjects with thalassemia, it is suggested that registered dietitians shift the focus of the nutritional message away from avoiding iron-rich diets toward concentrating on a more well-balanced diet rich in antioxidants and minerals.[6] When iron is avoided in the diet, zinc intake is frequently reduced; an essential nutrient that has been shown to be particularly beneficial to immune status, bone health, and growth in thalassemia.[39,40] As noted, intake of dairy foods is also low, which might, in part, be related to lactose intolerance. Therefore, strategies for increasing dietary calcium and magnesium should emphasize nondairy foods. Finally, shifting the focus toward more fruits, vegetables, and whole grains will not only enhance antioxidant intake, but also fiber and folate, critically important to red cell metabolism.

Whole-grain and dairy intake was surprisingly low in this group of subjects. However, when compared with the general

**Table 4.** Percentage of subjects with thalassemia taking micronutrient supplements separated by age group[a]

| | All (n=191) | | Adolescents (n=83) | | Adults (n=108) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Multivitamin/mineral supplements[b] | 76 | 44.0 | 32 | 44.0 | 44 | 44.0 |
| Single-nutrient supplements | | | | | | |
| Fat-soluble vitamins | | | | | | |
| Vitamin A | 74 | 39.2 | 31 | 37.3 | 43 | 40.6 |
| Vitamin D | 107 | 56.6 | 34 | 41.0 | 73 | 68.9 |
| Vitamin E | 79 | 41.8 | 31 | 37.3 | 48 | 45.3 |
| Water-soluble vitamins | | | | | | |
| Vitamin C | 94 | 49.7 | 32 | 38.6 | 62 | 58.5 |
| Folate | 92 | 48.7 | 32 | 38.6 | 60 | 56.6 |
| Thiamin | 75 | 39.7 | 31 | 37.3 | 44 | 41.5 |
| Riboflavin | 75 | 39.7 | 31 | 37.3 | 44 | 41.5 |
| Niacin | 75 | 39.7 | 31 | 37.3 | 44 | 41.5 |
| Vitamin B-6 | 75 | 39.7 | 31 | 37.3 | 44 | 41.5 |
| Vitamin B-12 | 75 | 39.7 | 31 | 37.3 | 44 | 41.5 |
| Minerals | | | | | | |
| Calcium | 100 | 52.9 | 32 | 38.6 | 68 | 64.2 |
| Copper | 59 | 31.2 | 31 | 37.3 | 28 | 26.4 |
| Magnesium | 71 | 37.6 | 31 | 37.3 | 40 | 37.7 |
| Selenium | 60 | 31.7 | 31 | 37.3 | 29 | 27.4 |
| Zinc | 65 | 34.4 | 31 | 37.3 | 34 | 32.1 |

[a]Supplementation usage information only obtained within the food frequency questionnaire for adolescent and adult subjects who answered this section of the questionnaire (n=191 of total sample, n=221).
[b]Multivitamin/mineral supplementation usage assumed to be without iron for most subjects because of their iron overload comorbidity. However, multivitamins with or without iron were not options on the Block Food Frequency Questionnaire and, therefore, the actual number of subjects taking multivitamin supplements without iron was not obtained.

population, intake of many of these food groups was not that different. In a recent publication from the National Cancer Institute, >90% of adult females from the National Health and Nutrition Examination Survey database do not meet the minimum recommendations for whole grains, dairy, fruit, or orange and dark green leafy vegetables.[41] The majority of adult males and adolescents also did not meet the dietary guidelines for many nutrient-rich food groups; although an overconsumption of fats and added sugars was ubiquitous. The US Department of Agriculture recently shifted its recommendations away from the "pyramid" structure to the "my plate" approach (http://www.choosemyplate.gov/). Perhaps this approach will provide all Americans, including subjects with thalassemia, a simpler way to plan their meals and meet their overall dietary guidelines.

In the present study, many subjects with thalassemia reported taking additional dietary supplements. The most common single nutrient supplements were calcium and vitamin D, presumably because so many subjects are known to have low bone mass. Nearly half of all subjects also reported taking multivitamin/mineral supplements, presumably without iron. Supplemental intake is much higher than what is typically observed in another prevalent hemoglobinopathy, sickle cell disease.[42] Dietary and supplemental intakes are presented separately in this article; however, if multivitamins are adhered to in this population, they might serve to augment considerably the daily dietary intake of many subjects with thalassemia.

Capturing the true dietary intake of groups of individuals is challenging, and every assessment technique has its flaws. Although the tools used in this study have been extensively validated and compared with other tools,[11-15,43] food frequency questionnaires in general have been shown to both underestimate[44] and overestimate intake in individuals.[45] The benefit to use of food frequency questionnaires is that they tend to capture intake patterns over time compared with 24-hour recalls or records that can alter intake and are less representative of overall intake patterns. In addition, the food frequency tool has been shown recently to be suitable for testing many diet–disease associations.[46] The aim of this

study was to compare the usual intake of a population (thalassemia) with current US dietary recommendations, which, by definition, are not intended for daily consideration. If subjects in this study tended to overestimate intake, then a very conservative estimate of the prevalence of deficiency would have been made in subjects with thalassemia. One way to estimate validity of intake data is to compare them to energy expenditure estimates. Adults in this cohort were relatively weight stable during the period of observation, baseline to year 1. Given this information, the adults estimated kilocalorie intake should be similar to their EER. For these adult subjects, %EER was close to 100% (Table 3); therefore, the assumption was made that these subjects lived a relatively sedentary lifestyle. In other words, the actual caloric intake and the percentage of estimated intake required for sedentary individuals was rather similar.

This study was limited with respect to the size of the cohort of nontransfused subjects. The majority of subjects (90%) were chronically transfused, therefore, the generalizability of these results to nontransfused subjects with thalassemia is limited. In addition, because of the current study design, circulating levels of many nutrients were not measured and therefore the relationship between dietary intake and other comorbidities in thalassemia could not be explored further. This was beyond the scope of this study; however, it is the obvious next step in understanding the full effects of nutritional status on overall health in subjects with thalassemia.

## CONCLUSIONS

Patients with thalassemia have reduced intake of many key nutrients (ie, vitamin A, D, E, K, folate, calcium, and magnesium). In addition, intake of some essential nutrients appears to worsen with age. The level of dietary inadequacy is concerning, particularly when these data are combined with previous reports of decreased circulating essential nutrients and the prevalence of many comorbidities with nutritional linkages. These preliminary findings support the need for nutritional monitoring to determine which subjects are at greatest risk for nutritional deficiency. Optimizing dietary intake through nutrient-dense foods and appropriate use of supplementation where necessary can improve overall health in these subjects. Given the limitations of this study, future research should focus more directly on the effect of dietary quality and nutritional status on health outcomes in thalassemia.

### References


1. Vichinsky EP. Changing patterns of thalassemia worldwide. *Ann NY Acad Sci*. 2005;1054:18-24.
2. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Complications of B-thalassemia major in North America. *Blood*. 2004;104(1):34-39.
3. Vichinsky EP, Macklin EA, Waye JS, Lorey F, Olivieri NF. Changes in the epidemiology of thalassemia in North America: A new minority disease. *Pediatrics*. 2005;116(6):e818-e825.
4. Zurlo MG, De Stefano P, Borgna-Pignatti C, et al. Survival and causes of death in thalassaemia major. *Lancet*. 1989;2(8653):27-30.
5. Fung EB, Harmatz P, Milet M, et al. Morbidity and mortality in chronically transfused subjects with thalassemia or sickle cell disease: A report from the multicenter study of iron overload. *Am J Hematol*. 2007;82(4):255-265.
6. Fung EB. Nutritional deficiencies in patients with thalassemia. *Ann NY Acad Sci*. 2010;1202:188-196.
7. Vogiatzi MG, Macklin EA, Trachtenberg FL, et al. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassemia syndromes in North America. *Br J Haematol*. 2009;146(5):546-556.
8. Vogiatzi M, Macklin EA, Fung EB, et al. Bone disease in thalassemia: A frequent and still unresolved problem. *J Bone Miner Res*. 2009;24(3):543-557.
9. Fung, EB, Xu Y, Kwiatkowski J, et al. Relationship between chronic transfusion therapy and body composition in subjects with thalassemia. *J Pediatr*. 2010;157(4):641-647.
10. Claster S, Wood JC, Noetzli L, et al. Nutritional deficiencies in iron overloaded patients with hemoglobinopathies. *Am J Hematol*. 2009;84(6):344-348.
11. Mares-Perlman JA, Klein BEK, Klein R, Ritter LL, Fisher MR, Freudenheim JL. A diet history questionnaire ranks nutrient intakes in middle-aged and older men and women similarly to multiple food records. *J Nutr*. 1993;123(3):489-501.
12. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol*. 1990;43(12):1327-1335.
13. Cullen KW, Watson K, Azkievi I. Relative reliability and validity of the Block kids questionnaire among youth aged 10 to 17 years. *J Am Diet Assoc*. 2008;108(5):862-866.
14. Smith C, Fila S. Comparison of the kid's Block food frequency questionnaire to the 24-hour recall in urban Native American youth. *Am J Hum Biol*. 2006;18(5):706-709.
15. Marshall TA, Eichenberger Gilmore JM, Broffitt B, Stumbo PJ, Levy SM. Relative validity of the Iowa fluoride study targeted nutrient semiquantitative questionnaire and the Block kids' food questionnaire for estimating beverage, calcium, and vitamin D intakes by children. *J Am Diet Assoc*. 2008;108(3):465-472.
16. US Department of Agriculture, Human Nutrition Information Service. *Composition of Foods: Raw, Processed, Prepared (Revised Handbooks # 8-1, Dairy and Egg Products-1976 to #8-21, Fast Foods-1988). Nutrition Monitoring Division*. Washington, DC: US Government Printing Office; 1976-1988.
17. Centers for Disease Control and Prevention, National Center for Health Statistics. *National Health and Nutrition Examination Survey III*. Hyattsville, MD: National Center for Health Statistics; 1999-2002.
18. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin and Choline*. Washington, DC: National Academies Press; 1998:1-16.
19. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*. Washington, DC: National Academies Press; 2000:1-20.
20. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin D, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc*. Washington, DC: National Academies Press; 2001:1-28.
21. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academies Press; 1997:1-20.
22. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011:S1-S12.
23. Otten JJ, Hellwig JD, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements, Institute of Medicine*. Washington, DC: National Academies Press; 2006:19-68.
24. American Dietetic Association. Practice paper of the ADA: Using the dietary reference intakes. *J Am Diet Assoc*. 2011;111(5):762-770.
25. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids*. Washington, DC: National Academies Press; 2002:5-114.
26. Gariépy C, Lal A, Fung EB. Reduced physical activity in adult and pediatric patients with thalassemia. *Blood*. 2010; abstract online only.
27. US Department of Health and Human Services and US Department of Agriculture. *2005 Dietary Guidelines for Americans,* 2005. 6th ed. Washington, DC: US Government Printing Office; January 2005.
28. Livrea MA, Tesoriere L, Pintaudi AM, et al. Oxidative stress and antioxidant status in beta-thalassemia major: Iron overload and depletion of lipid-soluble antioxidants. *Blood*. 1996;88(9):3608-3614.

29. Fung EB, Aguilar C, Micaily I, Foote D, Lal A. Treatment of vitamin D deficiency in transfusion-dependent thalassemia. *Am J Hematol*. 2011;86(10):871-873.
30. Dissayabutra T, Tosukhowong P, Seksan P. The benefits of vitamin C and vitamin E in children with beta-thalassemia with high oxidative stress. *J Med Assoc Thai*. 2005;88(suppl 4):S317-S321.
31. Fung EB, Vichinsky EP, Kwiatkowski JK, et al. Characterization of low bone mass in young patients with thalassemia by DXA, pQCT and markers of bone turnover. *Bone*. 2011;48(6):1305-1312.
32. Aessopos A, Kati M, Farmakis D. Heart disease in thalassemia intermedia: A review of the underlying pathophysiology. *Haematologica*. 2007;92(5):658-665.
33. O'Brien RT. Ascorbic acid enhancement of desferrioxamine induced urinary excretion in thalassemia major. *Ann NY Acad Sci*. 1974;232: 221-225.
34. Nienhuis AW. Vitamin C and iron. *N Engl J Med*. 1981;304(3):170-171.
35. Walter PB, Fung EB, Killilea DW, et al. Oxidative stress and inflammation in iron-overloaded patients with $\beta$-thalassaemia or sickle cell disease. *Br J Haematol*. 2006;135(2):254-263.
36. Reller K, Dresow B, Collell M, et al. Iron overload and antioxidant status in patients with thalassemia major. *Ann NY Acad Sci*. 1998;850: 463-465.
37. Mariani R, Trombini P, Pozzi M, Piperno A. Iron metabolism in thalassemia and sickle cell disease. *Mediterr J Hematol Infect Dis*. 2009;1(1): e2009006.
38. De Alarcon PA, Donovan ME, Forbes GB, Landaw SA, Stockman JA. Iron absorption in the thalassemia syndromes and its inhibition by tea. *N Engl J Med*. 1979;300(1):5-8.
39. Shamshirsaz AA, Bekheirnia MR, Kamgar M, et al. Bone mineral density in Iranian adolescents and young adults with beta-thalassemia major. *Pediatr Hematol Oncol*. 2007;24(7):469-479.
40. Fikry SI, Saleh SA, Sarkis NN, Mangoud H. Study of serum zinc in relation to nutritional status among thalassemia patients in Damanhour Medical National Institute. *J Egypt Public Health Assoc*. 2003; 78(1-2):73-93.
41. Krebs-Smith SM, Guenther PM, Subar AF, Kirkpatrick SI, Dodd KW. Americans do not meet federal dietary recommendations. *J Nutr*. 2010;140(10):1832-1838.
42. Kawchak DA, Schall JI, Zemel BS, Ohene-Frempong K, Stallings VA. Adequacy of dietary intake declines with age in children with sickle cell disease. *J Am Diet Assoc*. 2007;107(5):843-848.
43. Boucher B, Cotterchio M, Krieger N, Nadalin V, Block T, Block G. Validity and reliability of the Block 98 Food frequency in a sample of Canadian women. *Public Health Nutr*. 2006;9(1):84-93.
44. Subar AF, Kipnis V, Troiano RP, et al. Using intake biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: The OPEN study. *Am J Epidemiol*. 2003;158(1):1-13.
45. Jackson MD, Walker SP, Younger NM, Bennett FI. Use of a food frequency questionnaire to assess diets of Jamaican adults: Validation and correlation with biomarkers. *Nutr J*. 2011;10(28): 1-11.
46. Midthune D, Schatzkin A, Subar AF, et al. Validating an FFQ for intake of episodically consumed foods: Application to the National Institutes of Health-AARP diet and health study. *Public Health Nutr*. 2011; Apr 13:1-10.

## AUTHOR INFORMATION

E. B. Fung is an associate research scientist, Department of Hematology, Children's Hospital and Research Center Oakland and HEDCO Health Sciences Center, Oakland, CA. Y. Xu is an associate research scientist and F. Trachtenberg is a senior research scientist, New England Research Institutes, Inc, Watertown, MA. I. Odame is co-director, Haemoglobinopathy Program, Department of Hematology, Hospital for Sick Children, Toronto, Ontario, Canada. J. L. Kwiatkowski is director, Thalassemia Program, Division of Hematology, Children's Hospital of Philadelphia and Department of Pediatrics, Children's Seashore House, Philadelphia, PA. E. J. Neufeld is associate chief, Division of Hematology/Oncology, Children's Hospital Boston, Boston, MA. A. A. Thompson is director, Hematology Services, Department of Hematology, Children's Memorial Hospital, Chicago, Chicago, IL. J. Boudreaux is an assistant professor, Pediatrics, Department of Hematology, Children's Healthcare of Atlanta, Atlanta, GA. C. T. Quinn is director and hematology clinical and translational research associate, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX. E. Vichinsky is director, Hematology/Oncology, Department of Hematology/Oncology, Children's Hospital and Research Center Oakland, Oakland, CA.

Address correspondence to: Ellen B. Fung, PhD, RD, CCD, Department of Hematology, Children's Hospital and Research Center Oakland, HEDCO Health Sciences Center, 5700 Martin Luther King Jr Way, Oakland, CA 94609. E-mail: efung@mail.cho.org

### STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

### FUNDING/SUPPORT

This work was supported by the following National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute cooperative agreements: U01-HL65232 and NIH/National Center for Research Resources UL1-RR024134 to the Children's Hospital of Philadelphia, Philadelphia, PA; U01-HL72291 and by Harvard Catalyst CTSC U-01RR025758 to Children's Hospital, Boston, MA; U01-HL65233 to University Health Network Toronto General Hospital, Toronto, Ontario Canada; U01-HL65239 and CTSI UL1-RR024131 to Children's Hospital and Research Center Oakland, Oakland, CA; U01-HL65244 and CTSC UL1-RR024996 to Weill Medical College of Cornell University, New York, NY; and U01-HL65238 to New England Research Institutes, Watertown, MA. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute. The study sponsor (National Institutes of Health) did not participate directly in the study design, collection, analysis, or interpretation of the data or writing of this manuscript. The first draft of the manuscript was written by E. Fung, who did not receive any remuneration for its production.

### ACKNOWLEDGEMENTS

The following institutions and researchers contributed to the Thalassemia Clinical Research Network Thalassemia Longitudinal Cohort. Children's Hospital, Boston: Ellis Neufeld, MD, PhD, principal investigator, Jennifer Braunstein, NP, research nurse, Amber Smith, study coordinator, Latoya Lashley, study coordinator; Satellite: University of Texas Southwestern Medical Center at Dallas, Charles Quinn, MD, MS, principal investigator, Deborah Boger, RN, MSN, PNP, study coordinator, Leah Adix, study coordinator, Sandra Richardson, study coordinator; Children's Healthcare of Atlanta, Jeanne Boudreaux, MD, principal investigator, Leann Hassen, study coordinator; Baylor College of Medicine, Brigitta Mueller, MD, principal investigator, Bogden Dino, study coordinator. Weill Medical College of Cornell University: Patricia Giardina, MD, principal investigator, Dorothy Kleinert, RN, research nurse; Satellite: Winthrop University Hospital, Mark Weinblatt, MD, principal investigator, Linda Skelly, study coordinator. The Children's Hospital of Philadelphia: Janet Kwiatkowski, MD, principal investigator, Marie Martin, RN, research nurse, Sage Green, study coordinator; Satellite: Children's Memorial Hospital, Chicago, IL, Alexis Thompson, MD, principal investigator, Janice Beatty, RN, research nurse, Diane Calamaras, RN, CPNP, research nurse, Pauline Hess, study coordinator. Children's Hospital and Research Center, Oakland: Elliott Vichinsky, MD, principal investigator, Dru Foote, NP, research nurse, Nancy Sweeters, study coordinator, Olivia Vega, study coordinator; Satellites: Children's Hospital of Los Angeles, Thomas Coates, MD, principal investigator, Susan Carson, RN, research nurse, Eun Ha Pang, study coordinator, Rachna Khanna, study coordinator; Stanford Hospital, Michael Jeng, MD, principal investigator, Kokil Bakshi, clinical research associate; Children's and Women's Health Center of British Columbia, John Wu, principal investigator, Heather McCartney, RN, research nurse, Colleen Fitzgerald, study coordinator, Stephanie Badour, study coordinator. Toronto General Hospital, Toronto, Ontario, Canada: Nancy F. Olivieri, MD, principal investigator, Vivek Thayalasuthan, study coordinator; Satellite: Hospital for Sick Children, Isaac Odame, MD, principal investigator, Manuela Merelles-Pulcini, RN, study coordinator. University College London, John Porter, MD, principal investigator, Cindy Bhagwandin, study coordinator; Satellite: Whittington Hospital, Farrukh Shah, MD, principal investigator. NHLBI oversight, Kathryn Hassell, MD. Data Coordinating Center: New England Research Institutes, Sonja McKinlay, PhD, principal investigator, Lisa Virzi, RN, MS, MBA, project director, Felicia Trachtenberg, PhD, senior statistician.