

## Elevated vitamin A intake and serum retinol in preadolescent children with cystic fibrosis<sup>1–3</sup>

Rose C Graham-Maar, Joan I Schall, Nicolas Stettler, Babette S Zemel, and Virginia A Stallings

### ABSTRACT

**Background:** Persons with cystic fibrosis (CF) and pancreatic insufficiency (PI) are at risk of vitamin A deficiency because of steatorrhea, despite pancreatic enzyme replacement. Long-standing vitamin A supplementation may increase the risk of vitamin A toxicity.

**Objective:** The aim was to describe the vitamin A intake and serum retinol concentrations of preadolescent children with CF, PI, and mild-to-moderate pulmonary disease, who were cared for under current practice recommendations.

**Design:** This cross-sectional study evaluated children aged 8.0–11.9 y with CF and PI from 13 US CF centers. Dietary and supplemental vitamin A intakes were compared with the Dietary Reference Intakes (DRIs) for healthy children, CF recommendations, and data from the National Health and Nutrition Examination Survey (NHANES), 1999–2000. Serum retinol concentrations were compared with NHANES data.

**Results:** The 73 subjects with CF had a dietary vitamin A intake of  $816 \pm 336 \mu\text{g}$  retinol activity equivalents ( $165 \pm 69\%$  of the recommended dietary allowance), which was similar to the NHANES value. The supplement intake provided  $2234 \pm 1574 \mu\text{g}$  retinol activity equivalents/d and exceeded recommendations in 21% of the subjects with CF. Total preformed retinol intake exceeded the DRI tolerable upper intake level in 78% of the subjects with CF. The serum retinol concentration was  $52 \pm 13 \mu\text{g/dL}$  (range: 26–98  $\mu\text{g/dL}$ ), which was significantly higher than the NHANES value ( $37 \pm 10 \mu\text{g/dL}$ ; range: 17–63  $\mu\text{g/dL}$ ;  $P < 0.001$ ).

**Conclusion:** Although supplementation helps to prevent vitamin A deficiency in children with CF and PI, their high vitamin A intakes and serum retinol concentrations suggest that usual care may result in excessive vitamin A intake and possible toxicity that would increase the risk of CF-associated liver and bone complications. *Am J Clin Nutr* 2006;84:174–82.

**KEY WORDS** Vitamin A, retinol, hypervitaminosis A, cystic fibrosis, children, National Health and Nutrition Examination Survey, NHANES

### INTRODUCTION

Cystic fibrosis (CF), the most common life-shortening autosomal recessive disease in whites, is characterized by pulmonary disease, exocrine pancreatic insufficiency (PI), malabsorption, malnutrition, and growth failure. The median survival of persons with CF has increased from 14 y in 1969 to 35 y in 2004, which is evidence that the prevention of nutritional sequelae is vital (1). Vitamin A, a family of fat-soluble compounds essential for normal vision, gene expression, epithelial integrity, growth, and

immune function, is composed of preformed retinoids and provitamin A carotenoids (2). Ingested retinoids are solubilized in micelles, transported into enterocytes, reesterified in chylomicra, released into the lymphatic system, and circulated to the liver (2–4). Hepatic retinyl esters (REs) bind retinol-binding protein (RBP) and form holo-RBP, which circulates systemically bound to prealbumin (2, 4). Unbound REs amass in the liver with increased intakes of vitamin A, whereas serum retinol is homeostatically maintained (2, 4). Serum retinol usually accurately predicts vitamin A deficiency because it only decreases below 20  $\mu\text{g/dL}$  when hepatic stores are depleted. In chronic inflammatory states such as CF, serum retinol can be depressed because of a decreased synthesis of RBP, a negative acute phase reactant (2, 5, 6), and increased cellular demands. In contrast, vitamin A toxicity is not reliably assessed by serum concentrations or other noninvasive methods. Thus, a serum retinol concentration of 30–50  $\mu\text{g/dL}$  can be associated with either normal or potentially toxic stores (2).

Nearly 90% of persons with CF have PI, which increases the risk of vitamin A deficiency because of fat malabsorption. Vitamin A deficiency, which causes night blindness, xerophthalmia, and immune dysfunction, has been documented in CF despite vitamin A and pancreatic enzyme supplementation (7–11). In 1999, Feranchek et al (12) reported vitamin A deficiency in 4–11% of children with CF during a 10-y follow-up from newborn screening. The 2002 CF guidelines recommend vitamin A supplements for all children with CF and PI, specifically 3000  $\mu\text{g}$  retinol activity equivalents (RAEs) per day for children aged >8.0 y (13, 14). CF-specific water-soluble preparations are widely used, including vitamins A, D, E, and K (Axcan Pharma,

<sup>1</sup> From the Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA (RCG-M, JIS, BSZ, NS, and VAS), and the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA (NS).

<sup>2</sup> Supported by the National Heart, Lung, and Blood Institute (RO1HL57448); the General Clinical Research Center (M01RR00240); the Nutrition Center at The Children's Hospital of Philadelphia; and the University of California at Davis Clinical Nutrition Research Unit (NIH NIDDK 35747). RCG-M was supported by a T32 (HL 07433) training grant.

<sup>3</sup> Address reprint requests to RC Graham-Maar, Division of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399. E-mail: grahamr@email.chop.edu.

Received November 11, 2005.

Accepted for publication March 24, 2006.

Birmingham, AL; available in the US market since 1992); Vitamax (Shear/Kershman Labs, Chesterfield, MO; available in the US market since 1996); and SourceCF (SourceCF Inc, Huntsville, AL; available in the US market since 2003). When taking moderately high doses of vitamin A supplements for long periods, persons with CF and well-treated PI may be at risk of vitamin A excess. Chronic hypervitaminosis A can cause liver disease, osteoporosis, and anorexia, problems encountered in CF alone. The vitamin A status of children with CF receiving care since the 2002 CF recommendations were made has not been described. We hypothesized that, in comparison with a nationally representative sample of preadolescent children of the same age range, preadolescent children with CF and PI receiving care under current practice recommendations have higher vitamin A intakes from food and supplements and lower serum retinol concentrations.

## SUBJECTS AND METHODS

This cross-sectional study examined the vitamin A intake and serum retinol concentrations of 8.0–11.9-y-old children with CF and PI, from 13 CF centers in the United States, who participated in a 24-mo prospective cohort study that evaluated the effect of growth on pulmonary function. The diagnoses of CF and PI were made at the home CF center on the basis of clinical symptoms, duplicate quantitative pilocarpine iontophoresis sweat tests (chloride > 60 mEq/L), and 72-h fecal fat analysis (<93% fat absorption or stool trypsin <80  $\mu$ L/g). Subjects were excluded from the original study if they had poor lung function [percentage of predicted forced expiratory volume in 1 s (FEV<sub>1</sub>) <40%], liver disease, insulin-dependent diabetes mellitus, *Burkholderia cepacia* sputum colonization, other growth-impairing medical conditions, or used growth-altering medications. The protocol was approved by the Committee for the Protection of Human Subjects of the Institutional Review Board at The Children's Hospital of Philadelphia and at the subjects' respective home CF centers. Informed written consent and age-appropriate assent were obtained from the parent or legal guardian and each subject, respectively. The reference population included 8.0–11.9-y-old children from the National Health and Nutrition Examination Survey (NHANES) 1999–2000, a nationally representative sample of the US household population.

Subjects with CF and subjects from NHANES, with the assistance of a parent or guardian, provided demographic information, including age, sex, race, and family income, via an interview conducted in person by research personnel. The subjects with CF were interviewed in a research facility, whereas the subjects from NHANES were interviewed in their homes. The parents or guardians were asked to identify their family income within multiple possible dollar ranges. These ordinal values were then converted into a continuous variable by assigning the median dollar amount of a given income range.

The subjects with CF completed 7-d, written, weighed food records after instruction at home using investigator-provided measuring cups, spoons, and a digital food scale. The records were analyzed for nutrients and total energy by research dietitians (Nutrition Data System, Minneapolis, MN). The NHANES subjects completed one 24-h dietary recall via structured interview conducted in person (80%) or by telephone (20%) 4–10 d

after the physical exam with the assistance of a parent or guardian. Dietary data were analyzed for nutrients and total energy (University of Texas Food Intake Analysis System version 3.99 and USDA 1994–98 Survey Nutrient Database). Total energy intake for both populations was expressed as kcal/d. For the subjects with CF, energy intake was also expressed as the percentage estimated energy requirement (%EER), a formula for predicting energy requirements based on age, height, weight, sex, and physical activity level (15). The physical activity of subjects with CF was calculated as the ratio of total energy expenditure measured by the doubly labeled water technique (16) to resting energy expenditure measured by indirect calorimetry (17) with the use of the protocol and methods described by Tomezsko et al (18). Retinol intake was reported as  $\mu$ g RAE, a percentage of the Recommended Dietary Allowance (RDA) for healthy children, a percentage of the Tolerable Upper Limit of intake (UL) for healthy children, and a percentage of CF-specific recommendations per day (2, 13).

During the in-person interview, the subjects with CF, assisted by a parent or guardian, provided the pediatric research staff with details of their intake of all vitamin supplements, including brand name and dose taken daily or weekly when the daily dose varied. An average daily dose of supplemental preformed and total vitamin A (in  $\mu$ g RAE) was calculated from manufacturer ingredient information (Table 1). When the brand name was missing, a dosage value was imputed by multiplying the daily number of tablets by 1292  $\mu$ g RAE per tablet (1204  $\mu$ g RAE as retinol, 88  $\mu$ g RAE as  $\beta$ -carotene), the average vitamin A content of the 4 most commonly used non-CF-specific multivitamin preparations in this cohort [Flinstones (Bayer, Morristown, NJ), Scooby-Doo (Bayer, Morristown, NJ), Centrum Kids (Wyeth, Madison, NJ), and Poly-Vi-Sol (Mead Johnson, Evansville, IN)]. The subjects from NHANES reported the product names and doses of all dietary supplements taken, and product containers, when available, were reviewed and matched to manufacturer ingredient data by NHANES research staff. All supplemental vitamin A doses were converted from international units (IU) into  $\mu$ g RAE of preformed and total vitamin A (Table 2) (2).

Serum was collected from the subjects with CF by research personnel at the CHOP General Clinical Research Center and shipped for retinol analysis by HPLC (Clinical Nutrition Research Unit Nutritional Assessment Laboratory, University of California, Davis). Serum from NHANES subjects was collected and processed by research staff in the Mobile Examination Center and shipped for retinol analysis by HPLC (Division of Environmental Health Laboratory Sciences, Centers for Disease Control and Prevention, Atlanta, GA).

The standing height and weight of the subjects with CF were measured and recorded in triplicate with the use of standard techniques (19) with a stadiometer accurate to 0.1 cm (Holtain, Crymych, United Kingdom) and a digital scale accurate to 0.1 kg (Scaletronix, White Plains, NY), and the mean values were used for analysis. The standing height and weight of the NHANES subjects were measured by using standardized techniques. For both groups of subjects, body mass index (BMI) was calculated ( $\text{kg}/\text{m}^2$ ), and z scores for height (HAZ), weight (WAZ), and BMI (BMIZ) were computed by using the 2000 National Center for Health Statistics reference data (20).

FEV<sub>1</sub> was measured in the CF subjects by using standard spirometry (21, 22) after administration of inhaled albuterol and

TABLE 1

Vitamin A content of multivitamin preparations and comparison with standard recommendations<sup>1</sup>

Brand name (unit) <sup>2</sup>	Vitamin A content <sup>2</sup>	Vitamin A form <sup>3</sup>	Vitamin A		Vitamin A: total dose	Percentage of RDA		Percentage of UL as preformed retinol		Percentage of recommendation for CF patients aged $\geq 8$ y
			Preformed retinol	Carotenoid		Age 8–8.9 y	Age 9–11.9 y	Age 8–8.9 y	Age 9–11.9 y	
	<i>IU</i>		$\mu\text{g RAE}$		$\mu\text{g RAE}$	%		%		%
ADEK, 1 tablet	9000	40% Palmitate	1980	—	2520	630	420	220	116	84
		60% $\beta$ -Carotene	—	540						
ADEK, 1 mL	3170	50% Palmitate	872	—	1030	258	172	97	51	34
		50% $\beta$ -Carotene	—	158						
Vitamax, 1 tablet	5000	50% Acetate	860	—	1110	278	185	96	51	37
		50% $\beta$ -Carotene	—	250						
Vitamax, 1 mL	3170	100% Palmitate	1744	—	1744	436	291	194	103	58
SourceCF, 1 tablet or softgel	9000	40% Palmitate	1980	—	2520	630	420	220	116	84
		60% $\beta$ -Carotene	—	540						
SourceCF, 1 mL	3170	47% Palmitate	819	—	987	247	165	91	48	33
		53% $\beta$ -Carotene	—	168						
One-A-Day, 1 tablet (Bayer)	2500	80% Acetate	688	—	738	185	123	76	40	25
		20% $\beta$ -Carotene	—	50						
Flinstones, 1 tablet	5000	95% Acetate	1640	—	1665	416	278	182	96	56
		5% $\beta$ -Carotene	—	25						
Flinstones Complete (pre-2003)	3000	83% Acetate	857	—	908	227	151	95	50	30
		17% $\beta$ -Carotene	—	51						
Flinstones Complete (post-2003), with iron or calcium	2500	80% Acetate	688	—	738	436	291	76	40	25
		20% $\beta$ -Carotene	—	50						
Centrum Adult, 1 tablet	3500	71% Acetate	855	—	956	239	159	95	50	32
		29% $\beta$ -Carotene	—	101						
Centrum Kids, 1 tablet	5000	80% Acetate	1376	—	1476	369	246	153	81	49
		20% $\beta$ -Carotene	—	100						
Poly-Vi-Sol, 1 tablet	2500	100% Acetate	860	—	860	215	143	96	51	29
Mega-Teen (GNC), 1 tablet	5000	100% $\beta$ -Carotene	—	500	500	125	83	0	0	17
Daily One, 1 tablet (Twinlab)	10 000	100% $\beta$ -Carotene	—	1000	1000	250	167	0	0	50
Vit A Soft-Gel, 1 softgel	8000	100% Retinol	2400	—	2400	600	400	267	141	80

<sup>1</sup> See references 2, 14, and 37.<sup>2</sup> See Subjects and Methods for manufacturer's names.<sup>3</sup> Information was obtained from author's personal review of product package labels or via personal communication with the manufacturer when labels were unavailable or unclear.

chest physiotherapy, compared with reference values, and expressed as a percentage of the predicted value (23). The coefficient of fat absorption (%COA) was calculated by using a 72-h stool collection and a 7-d weighed food record.

Descriptive statistics were calculated for the total group and stratified by sex and age groups (8.0–8.9 and 9.0–11.9 y) to allow for appropriate comparisons with the DRI-defined age groups. The average daily dietary vitamin A intake from 7-d diet records for subjects with CF were compared with the DRI, as RDA and UL for healthy children (2), and with CF-specific recommendations (3000  $\mu\text{g RAE/d}$ ) (13). A randomly sampled 1-d dietary vitamin A intake for the CF subjects was identified and used for comparison NHANES intake data. The mean daily supplemental vitamin A intake for the subjects with CF was compared with the RDA and UL for healthy children, with the CF recommendations, and with intakes of subjects from NHANES. Serum retinol concentrations of the subjects with CF were compared with those of subjects from NHANES. All variables were tested for

normality and skewness. All comparisons of descriptive variables between the CF and NHANES groups were performed by using appropriate statistical weights to account for the NHANES complex sampling strategy. For continuous variables, the adjusted Wald test was used. For binary or categorical variables, Pearson's chi-square test was used. All comparisons of vitamin A intake and serum retinol concentrations between the CF and NHANES groups were performed with linear regression with the use of appropriate statistical weights and adjustment for age, race, and family income. Statistical significance was defined as a *P* value  $< 0.05$ . All analyses were performed with STATA release 8.2 (STATA Corporation, College Station, TX).

## RESULTS

By design, the 73 children with CF and PI (age:  $9.4 \pm 1.0$  y ( $\bar{x} \pm \text{SD}$ ); 51% male; 96% white) had mild-to-moderate pulmonary disease (Table 3). As part of the supplement assessment,

**TABLE 2**  
Conversion factors for vitamin A expressed in different units<sup>1</sup>

Vitamin A source	Vitamin A form		Unit		
			IU	μg RE	μg RAE
Supplement	Preformed retinol	Retinol acetate	1	—	0.34
	Preformed retinol	Retinyl palmitate	1	—	0.55
	Carotenoid	β-Carotene	1	—	0.10
Diet	Preformed retinol	Retinol	1	—	0.30
	Preformed retinol	Retinol	—	1	1
	Carotenoid	β-Carotene	1	—	0.05
	Carotenoid	β-Carotene	—	1	0.08

<sup>1</sup> See references 2 and 3. IU, international units; RE, retinol equivalents; RAE, retinol activity equivalents.

82% of the subjects with CF provided specific brand names, 8% reported use of a general multivitamin, and 10% took no supplements. Among the 742 children from NHANES 1999–2000 within the age range corresponding to the inclusion criteria of the CF sample (age:  $10.0 \pm 1.8$  y ( $\bar{x} \pm$  SD); 50% male; 59% white), 89% completed a dietary intake assessment, 23% took vitamin A supplements, and 80% had serum retinol concentrations measured.

Based on the 7-d diet record, the mean daily dietary vitamin A intake of the subjects with CF was  $816 \pm 336$  μg RAE, providing  $165 \pm 69\%$  of RDA (Table 4). A randomly sampled, 1-d dietary vitamin A intake from subjects with CF was not significantly different from the 1-d dietary intake of subjects from NHANES

when analyzed with all ages combined and by DRI-defined age groups (Figure 1). The mean ( $\pm$ SD) daily supplemental vitamin A intake of subjects with CF was  $2234 \pm 1574$  μg RAE,  $83 \pm 17\%$  of which was preformed retinol. This intake was significantly higher ( $P < 0.001$ ) than the supplement intake of the NHANES subjects ( $1116 \pm 827$  μg RAE,  $89 \pm 17\%$  as preformed retinol). This difference remained significant when analyzed by DRI-defined age groups (Figure 2). Seventy-eight percent of the subjects with CF had total dietary and supplemental preformed retinol intakes exceeding the UL for healthy subjects without CF. Twenty-one percent had supplemental vitamin A intakes exceeding CF recommendations, and 49% had total dietary and supplemental vitamin A intakes exceeding supplement recommendations for CF patients.

The mean serum retinol concentration of the CF subjects ( $52 \pm 13$  μg/dL; range: 26 to 98) was significantly higher ( $P < 0.001$ ) than that of the NHANES subjects ( $37 \pm 10$  μg/dL; range: 17–63 μg/dL; Figure 3). Of the subjects with CF, only one had a serum retinol concentration below the NHANES 5th percentile (26.7 μg/dL), whereas 47% had a serum retinol concentration above the NHANES 95th percentile (51.3 μg/dL). By definition, 5% of the NHANES subjects had serum concentrations below the 5th percentile and 5% above the 95th percentile.

To explore the effect of the lower BMI seen in the CF subjects than in the NHANES subjects, secondary analyses were performed with the additional adjustment for BMI z score, and the results were unchanged.

**TABLE 3**  
Characteristics of subjects with cystic fibrosis (CF) and subjects from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) between the ages of 8.0 and 11.9 y

Characteristic	CF (n = 73)	NHANES (n = 742)	P
Age (y)	$9.4 \pm 1.0^1$	$10.0 \pm 1.8$	$<0.001^2$
Sex (% male)	51	50	NS <sup>3</sup>
Race (%)			$<0.001^3$
White	96	59	—
Black	1	18	—
Hispanic	0	3	—
Other	3	20	—
Annual family income ( $\times 10^3$ )	$59 \pm 22^4$	$40 \pm 52^5$	$<0.001^2$
Weight-for-age z score	$-0.36 \pm 1.17$	$0.48 \pm 1.61$	$<0.001^2$
Height-for-age z score	$-0.50 \pm 1.13$	$0.30 \pm 1.74$	$<0.001^2$
BMI for age z score	$-0.07 \pm 1.06$	$0.48 \pm 1.81$	$<0.001^2$
Energy intake (kcal/d) <sup>6</sup>	$2293 \pm 464$	—	—
Percentage estimated energy requirement (%) <sup>7</sup>	$135 \pm 32$	—	—
Energy intake (kcal/d) <sup>8</sup>	$2383 \pm 719$	$2076 \pm 1327$	$<0.001^{2,9}$
Forced expiratory volume in 1 s (% of predicted) <sup>10</sup>	$91 \pm 13$	—	—
Coefficient of fat absorption (%) <sup>11</sup>	$85 \pm 13$	—	—

<sup>1</sup>  $\bar{x} \pm$  SD (all such values).

<sup>2</sup> Adjusted Wald test from survey weighted analysis to account for NHANES sampling weights.

<sup>3</sup> Pearson's chi-square test.

<sup>4</sup> n = 63.

<sup>5</sup> n = 665.

<sup>6</sup> Calculated as a daily average from the 7-d dietary record for the CF sample.

<sup>7</sup> n = 62.

<sup>8</sup> Represents a randomly sampled, 1-d dietary intake for CF subjects.

<sup>9</sup> Represents the comparison between a 1-d intake for subjects with CF and a 1-d intake for NHANES subjects.

<sup>10</sup> n = 71.

<sup>11</sup> n = 70.

**TABLE 4**  
Vitamin A intake of subjects with cystic fibrosis (CF) compared with that of subjects from the National Health and Nutrition Examination Survey (NHANES)

Vitamin A source and form	CF (n = 73)			NHANES (n = 663)			P <sup>d</sup>
	Vitamin A intake (95% CI)	Percentage of RDA <sup>f</sup> (95% CI)	Percentage of subjects with intake >UL <sup>2</sup>	Vitamin A intake (95% CI)	Percentage of RDA <sup>f</sup> (95% CI)	Percentage of subjects with intake >UL <sup>2</sup>	
	$\mu\text{g RAE}$	%	%	$\mu\text{g RAE}$	%	%	
<b>Diet</b>							
Performed retinol	716 ± 314 <sup>5</sup> (643, 789)	144 ± 62 (129, 158)	5	NA <sup>6</sup>	—	—	—
Total	816 ± 336 (738, 895)	165 ± 69 (149, 180)	16	843 ± 957 (764, 923)	157 ± 196 (141, 173)	13	NS
<b>Supplement</b>							
Performed retinol	1837 ± 1293 (1536, 2139)	380 ± 291 (312, 448)	70	1019 ± 819 (885, 1153) <sup>7</sup>	200 ± 187 (169, 230) <sup>7</sup>	25	<0.001
Total	2234 ± 1574 (1867, 2601)	460 ± 344 (380, 540)	73	1116 ± 827 (980, 1251) <sup>7</sup>	218 ± 188 (187, 249) <sup>7</sup>	26	<0.001
<b>Diet + supplement</b>							
Performed retinol	2553 ± 1369 (2234, 2873)	524 ± 311 (451, 596)	78	NA <sup>6</sup>	—	—	—
Total	3050 ± 1660 (2663, 3438)	624 ± 369 (538, 710)	88	2136 ± 1221 (1924, 2349) <sup>8</sup>	413 ± 287 (363, 463) <sup>8</sup>	75	0.002

<sup>1</sup> Recommended dietary allowance (RDA) = 400  $\mu\text{g}$  retinol activity equivalents (RAE) for 8.0–8.9-y-olds; and 600  $\mu\text{g}$  RAE for 9.0–11.9-y-olds.

<sup>2</sup> Tolerable upper intake level (UL) = 900  $\mu\text{g}$  RAE for 8.0–8.9-y-olds and 1700  $\mu\text{g}$  RAE for 9.0–11.9-y-olds. The UL assessment was developed to evaluate preformed retinol intake; however, all intakes were compared with the UL.

<sup>3</sup> Recommendation for patients with CF = 3000  $\mu\text{g}$  RAE; doses of supplemental vitamin A are specifically suggested; however, all intakes were compared with CF recommendations.

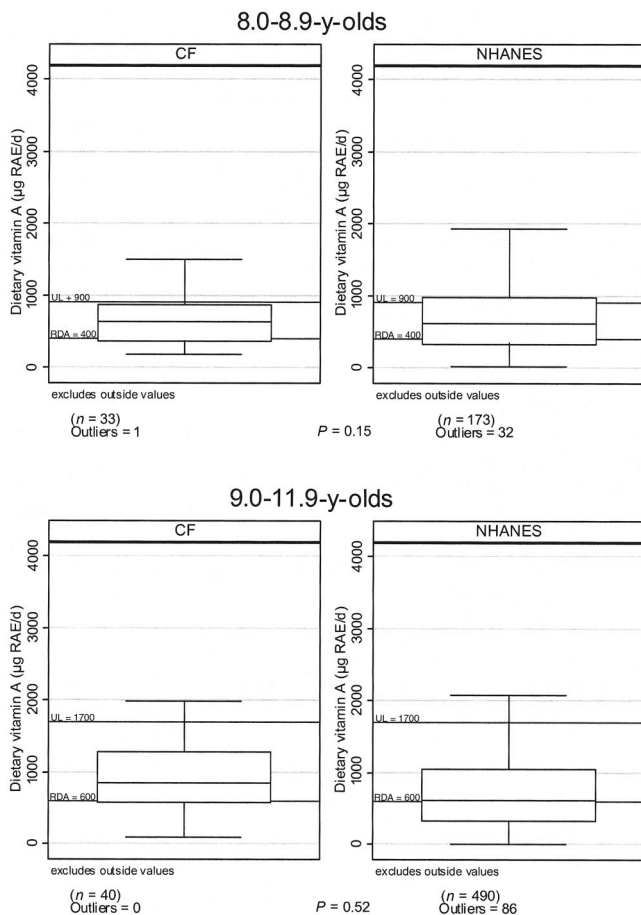
<sup>4</sup> All comparisons tested for the difference in mean intake between the CF and NHANES groups and were performed by using linear regression with appropriate statistical weighting to account for the complex sampling strategy of NHANES and were adjusted for age, race, and family income. The adjusted Wald test was used; all comparisons that involved diet used a randomly sampled 1-d dietary intake for the CF group compared with a 1-d dietary recall from NHANES.

<sup>5</sup>  $\bar{x}$  ± SD (all such values).

<sup>6</sup> Data not available.

<sup>7</sup> n = 169.

<sup>8</sup> n = 150.

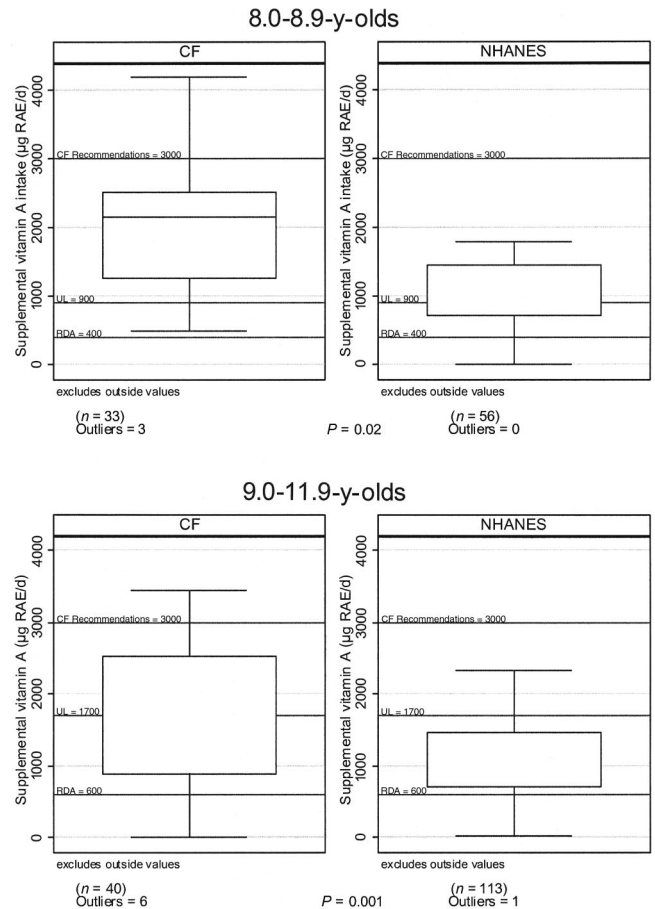


**FIGURE 1.** Dietary vitamin A intake in subjects with cystic fibrosis (CF) and in a representative sample of US subjects from the National Health and Nutrition Examination Survey (NHANES), presented by Dietary Reference Intake (DRI)-defined age groups. The top and bottom of each box correspond to the upper and lower quartiles of the distribution, respectively. The upper and lower whiskers identify the most remote high and low nonoutlier values within the distribution. Outlying values were excluded from the plot for easier visualization; their numbers are noted below each box. The horizontal line within each box corresponds to the median value. Age-specific DRI-defined recommended dietary allowance (RDA) and tolerable upper intake level (UL) reference values for healthy children are noted as labeled horizontal lines on each plot. The *P* values were derived from a Wald test of the survey sample-weighted linear regression of study group on dietary vitamin A intake, adjusted for age, race, and family income. RAE, retinol activity equivalents.

## DISCUSSION

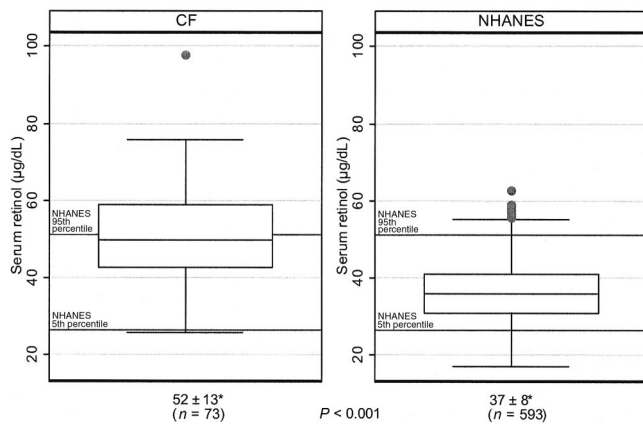
This sample of preadolescent children with CF, PI, and mild-to-moderate pulmonary disease had vitamin A intakes and serum retinol concentrations higher than those of a representative sample of US children of the same age range. Although it is clinically reassuring that vitamin A deficiency was not observed, the results suggest that children with CF cared for under current practice recommendations taking current vitamin formulations may be ingesting more supplemental vitamin A than necessary to prevent deficiency. This leads to concern that this population may be at-risk of chronic hypervitaminosis A.

Chronic hypervitaminosis A, which adversely affects liver and bone health in otherwise healthy persons, has occurred



**FIGURE 2.** Supplemental vitamin A intake in subjects with cystic fibrosis (CF) and in a representative sample of US subjects from the National Health and Nutrition Examination Survey (NHANES), presented by Dietary Reference Intake (DRI)-defined age groups. The top and bottom of each box correspond to the upper and lower quartiles of the distribution, respectively. The upper and lower whiskers identify the most remote high and low non-outlier values within the distribution. Outlying values were excluded from the plot for easier visualization; their numbers are noted below each box. The horizontal line within the box for the 8.0–8.9-y-olds with CF represents the median value. The absence of the median line in the other 3 boxes because of the skewness of the distribution. Age-specific DRI-defined recommended dietary allowance (RDA) and tolerable upper intake level (UL) reference values for healthy children and CF-specific recommendation reference values are noted as labeled horizontal lines on each plot. The *P* values were derived from a Wald test of the survey sample-weighted linear regression of study group on supplemental vitamin A intake, adjusted for age, race, and family income. RAE, retinol activity equivalents.

with long-term vitamin A supplementation in non-CF populations (24–32). In 1991, Geubel et al (32) reported 41 cases of hepatotoxicity after intake of 7500 µg RAE/d over 6 y in adults from Belgium. In 1998, Melhus et al (29) reported a lower bone mineral density and a greater risk of hip fracture (OR = 1.54, CI: 1.06 to 2.24) in Swedish women with a dietary retinol intake >1500 µg RAE/d than in women with an intake <500 µg RAE/d. In 2002, Feskanich et al (26) reported a greater risk of hip fracture in US postmenopausal women with a dietary retinol intake >2000 µg RAE/d than in women with an intake <500 µg RAE/d (relative risk: 1.89; 95% CI: 1.33, 2.68). In 2003, Michaëlsson et al (30) found a 64% greater



**FIGURE 3.** Serum retinol concentrations in subjects with cystic fibrosis (CF) and in a representative sample of US subjects from the National Health and Nutrition Examination Survey (NHANES) of the same age range. The top and bottom of each box corresponds to the upper and lower quartiles of the distribution, respectively. The top and bottom whiskers identify the highest and lowest nonoutlier values. The dots above the top whiskers represent the outliers. The horizontal line within each box corresponds to the median value. The  $P$  value was derived from a Wald test of the survey sample-weighted linear regression of study group on serum retinol concentration, adjusted for age, race, and family income. \*Values are  $\bar{x} \pm$  SD.

fracture rate in Swedish men with a serum retinol concentration  $>76 \mu\text{g/dL}$  than in men with a serum retinol concentration between 62 and 67  $\mu\text{g/dL}$  (relative risk: 1.64; 95% CI: 1.12, 2.41).

Hypervitaminosis A in patients with CF taking vitamin A supplements has been described. In 1972, Underwood and Denning (6) reported significantly higher hepatic and lower serum retinol concentrations in 12 vitamin A-supplemented subjects with CF aged 8–23 y than in healthy control subjects ( $317 \pm 300$  compared with  $126 \pm 164 \mu\text{g/g}$  liver and  $22 \pm 14$  compared with  $38 \pm 11 \mu\text{g/dL}$ , respectively), which indicated an unexpected dissociation between liver and serum concentrations. In 1990, Eid et al (33) reported acute hypervitaminosis A after treatment of deficiency in an infant with CF. In contrast, in 1997, Lindblad et al (34) found normal hepatic retinol concentrations in 15 vitamin A-supplemented Swedish children and adults with CF compared with healthy control subjects ( $174 \pm 168$  and  $168 \pm 117 \mu\text{g/g}$  liver, respectively). None of these studies were sufficiently large to base recommendations for the optimal dose or form of vitamin A for persons with CF in the current care setting. However, they illustrate the complexity of vitamin A metabolism in this population, particularly because noninvasive biomarkers of vitamin A stores are not currently available.


The specific formulation of a vitamin A supplement affects its potential for toxicity, and water-soluble preparations pose more risk. In 2003, Myhre et al (35) showed in a meta-analysis of 259 cases of chronic hypervitaminosis A in children and adults without CF that water-soluble preparations given daily in small doses (200  $\mu\text{g}$  RAE/kg over weeks to months) induced toxicity similar to that of oil-based preparations given in larger doses (2000  $\mu\text{g}$  RAE/kg over months to years). One subject with CF in the present study ingested  $>200 \mu\text{g}$  RAE water-soluble vitamin A/kg daily. The subtype of vitamin A, preformed retinol or carotenoid, is also important to consider. Preparations with higher proportions of preformed retinol

pose more risk because retinol is insatiably absorbed, whereas  $\beta$ -carotene is less efficiently absorbed (2). CF-specific vitamins contain water-soluble vitamin A in a range of 987–2520  $\mu\text{g}$  RAE per dosage unit, 40–100% as preformed retinol (Table 1). Because many children with CF in this study took more than one dosage unit per day and some took more than one brand of supplement, higher intakes than required to prevent vitamin A deficiency were often taken.

Although several studies have speculated about altered vitamin A metabolism in CF, beyond inflammatory related-RBP depression and increased cellular demands, this has not been well characterized. In 1972, Underwood and Denning (6) proposed that children with CF may have defective mobilization of hepatic retinol stores on the basis of their findings of high hepatic and low serum retinol concentrations in 12 subjects with CF. In 1986, Rasmussen et al (9) hypothesized defective retinol absorption in CF but found normal enterocyte acyl-CoA retinol acyl-transferase concentrations in 5 subjects with CF compared with 16 healthy control subjects, which suggested normal mucosal function in CF. In 1990, Ahmed et al (36) reported fecal retinol losses out of proportion to the degree of steatorrhea in 11 children and young adults with CF, which suggested defective intestinal retinol absorption unrelated to fat malabsorption. The numerous steps in vitamin A metabolism provide many potential sites for defects, most of which have not been studied in CF. If the low serum retinol concentrations observed in persons with CF is due to low RBP concentrations, then hepatic retinol stores could still be high and potentially toxic.

The limitations of this study include its cross-sectional design, which did not allow for assessing the effect of above-normal serum retinol concentrations on long-term liver and bone health. The exclusion of the most ill subjects with CF could introduce selection bias if excluded subjects had more systemic inflammation and lower serum retinol concentrations. This exclusion also limits the generalizability of the results to the complete CF population but does make them more applicable to the typical pre-adolescent child with CF and PI. The use of 2 different dietary assessment methods was a limitation but was addressed by using data from one random day for each subject with CF in the comparisons with the NHANES population. The serum retinol concentration is better understood as an indicator of vitamin A deficiency than is vitamin A excess, and noninvasive markers of vitamin A excess do not exist. Although extrahepatic tissues (ie, epithelial, adipose, renal, and lung tissue) store small amounts of RE, they likely provide a short-term local supply for conditions of increased demand (37), and expected extrahepatic concentrations in humans in the setting of total-body retinol excess is unknown (4, 38). Other samples—such as serum RE, RBP, and hepatic retinol concentrations—are needed to better describe the total-body vitamin A status of subjects with CF and PI. The strengths of this study include the research-quality 7-d dietary data assessing the dietary and supplement intake of the CF population, the focus on preadolescent children with mild-to-moderate lung disease before the decline of nutritional and pulmonary status associated with adolescence, the multiple CF centers and geographic areas represented, and the use of a recent nationally representative sample for comparison.

In conclusion, the results of this study suggest that the combination of food and supplements provided a high vitamin A

intake in this group of preadolescents with CF and PI. The associated high serum retinol concentrations suggest that this intake may be more than necessary to prevent deficiency and may pose a risk of vitamin A toxicity. Future studies are needed to determine whether these intakes and serum concentrations are associated with high hepatic concentrations, liver disease, bone deficits, and other indicators of hypervitaminosis A. The overlapping signs of chronic hypervitaminosis A and longstanding CF, namely hepatic fibrosis, cirrhosis, osteoporosis, anorexia, and weight loss, make vitamin A toxicity of particular concern in this population. Because children with CF and PI require fat-soluble vitamin replacement throughout their lives, they should be carefully monitored for excess vitamin A. This task may prove difficult until noninvasive tests of vitamin A stores are developed. Until further information specific to CF patients is available, we recommend that this population receive the minimum vitamin A supplementation necessary to maintain normal serum retinol concentrations. In addition, we urge the dietary supplement industry to provide labels that state the content of vitamin A as  $\mu\text{g}$  RAE, the proportion of retinoid and carotenoid compounds, and the fat or water solubility of their products. 

We thank the participating children and their families, the 13 CF centers who made this study possible (Albany Medical Center, Albany, NY; Children's Hospital of Buffalo, Buffalo, NY; Children's Hospital of Philadelphia, Philadelphia, PA; Children's Medical Center, Dayton, OH; Children's National Medical Center, Washington, DC; Eggleston Center at Emory University, Atlanta, GA; Hershey Medical Center, Hershey, PA; Johns Hopkins Children's Center, Baltimore, MD; Long Island College Hospital, Long Island, NY; Schneider's Children's Hospital, New Hyde Park, NY; St Christopher's Hospital for Children, Philadelphia, PA; State University of New York, Stony Brook, NY; and University of Florida, Gainesville, FL), the General Clinical Research Center at the Children's Hospital of Philadelphia, the Nutrition and Growth Laboratory staff at the Children's Hospital of Philadelphia, and the Nutrition Assessment Laboratory at the University of California Davis School of Medicine.

RCG-M, JIS, BSZ, and VAS were responsible for the conception and design of the study. JIS, BSZ, and VAS were responsible for the acquisition of data and the writing of the manuscript. All authors read and approved the final version of the manuscript to be submitted for publication. None of the authors had a conflict of interest.

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