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Original article

# Vitamin A intake and serum retinol levels in children and adolescents with cystic fibrosis

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SUMMARY

*Background:* Pancreatic insufficient cystic fibrosis (CF) patients receive vitamin A supplementation according to CF-specific recommendations to prevent deficiencies. Whether current recommendations are optimal for preventing both deficiency and toxicity is a subject of debate. We assessed the longitudinal relation between serum retinol levels and appropriate variables.
*Methods:* We studied vitamin A intake, and the long-term effects of vitamin A intake, coefficient of fat absorption (CFA) and immunoglobulin G (IgG) on serum retinol levels in 221 paediatrics CF patients during a seven-year follow up period.
*Results:* Total vitamin A intake, derived from 862 dietary assessments, exceeded the tolerable upper intake level in 30% of the assessments, mainly up to age six. Although CF patients failed to meet the CF-specific recommendations, serum retinol deficiency was found in only 17/862 (2%) of the measurements. Longitudinally, we observed no association to serum retinol levels for total vitamin A intake, CFA, gender or age but serum retinol levels were associated with serum IgG levels. Each g/L increase in serum IgG level would result in a 2.49% (95% CI -3.60 to −1.36%) reduction in serum retinol levels.
*Conclusion:* In this large sample of children and adolescents with CF, serum retinol deficiency was rare despite lower than the CF-specific recommendations. However, the TUL was commonly exceeded. A reduction in CF-specific vitamin A supplementation recommendations should therefore be considered. Moreover, serum retinol levels were not associated with vitamin A intake, CFA, gender or age, although a decreased serum retinol was associated with an increased serum IgG.


## 1. Introduction

Cystic fibrosis (CF) is a lethal genetic disorder, characterized by chronic pulmonary inflammation that causes a gradual, progressive decline in pulmonary function. Most patients in Northern Europe also have pancreatic insufficiency [1], leading to intestinal malabsorption of fat and fat-soluble vitamins. Therefore, lifelong treatment with pancreatic enzymes and fat-soluble vitamins such as vitamin A, has become standard care [2,3].

Vitamin A, which plays a role in immune function, vision, reproduction, growth and epithelial cell integrity, is generally routinely administered to all pancreatic insufficient patients, with a recommended daily dosage varying between 1500 and 10,000 international units [2,3]. This is considered to be sufficient to prevent deficiency, which indeed has become rare [4,5].

Moreover, supplementation may even be too high, as recent studies have reported serum retinol levels above the normal reference range in approximately half of CF patients [6,7]. Though, as it is know that serum retinol levels are affected during

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**Abbreviations**

| | |
|---|---|
| CF | cystic fibrosis |
| IgG | immunoglobulin G |
| CFA | coefficient of fat absorption |
| RAE | retinol activity equivalents |
| RDA | recommended daily advice |
| TUL | tolerable upper intake level for healthy referents |
| NHANES | National Health and Nutrition Examination Survey |
| LL | lower level |
| UP | upper level |

pulmonary exacerbations [8,9], the extent of chronic pulmonary inflammation should be included when describing the association between vitamin A intake and serum retinol levels. In this respect, serum immunoglobulin G (IgG), which level increases once a chronic infection has set in [10,11], may a good marker of the chronic inflammation in CF patients.

At present, the relation between vitamin A intake and serum retinol levels are poorly understood as most studies were rather small, encompassed small age ranges, were limited by a cross-sectional design, and lack data on fat malabsorption or inflammation [6,7]. We therefore studied the association between vitamin A intake, serum retinol levels, coefficient of fat absorption (CFA) and serum IgG levels in paediatric CF patients during a seven-year follow-up period.

## 2. Methods

### 2.1. Study sample

This retrospective study included Dutch children (born between 1988 and 2012) with proven CF and who received medical care in the CF Centre of the University Medical Centre Utrecht. Each child was confirmed as having CF by a positive sweat test and/or the presence of two CF mutations, as well as clinical signs of CF. Dietary data and serum retinol levels were obtained during annual check-up. We used data obtained between January 2007 and December 2013 in children and adolescents who had at least one measurement of vitamin A intake (dietary intake and prescribed supplementation) along with a measurement of serum retinol level and who were receiving pancreatic enzyme replacement therapy at the time of reporting. Excluded were transplant patients. All patients or the parents or guardians of young patients provided written informed consent for the storage and analysis of their data. The study was performed in accordance with the guidelines of the medical ethics board of the University Medical Centre Utrecht.

### 2.2. Dietary intake assessment

All CF patients received written instructions on completing a 3-day dietary food record in which they recorded all food and beverages consumed in portion sizes or weights during two weekdays and one weekend day whenever possible. Registered dieticians coded and analysed the food records according a standardised approach, using the Dutch Food Composition Table (2010) of the Dutch Nutrition Centre, and the vitamin A intake was calculated for each assessment. The prescribed vitamin A supplements, as registered in the medical records, were considered as vitamin A administered. Vitamin A intake (dietary, prescribed supplementation and total), were expressed as microgram retinol activity equivalents (μg RAE) which allows direct comparison among different forms of vitamin A such as retinol and bèta carotene. The vitamin A intake was compared with gender- and age-based Dutch nutritional recommendations and expressed as % of gender- and age-based recommended daily advice (RDA) and as % of age-based tolerable upper intake level for healthy referents (TUL) [12]. Additionally, the vitamin A intake was expressed as % of both the European and North-American CF-specific vitamin A recommendations [2,3].

### 2.3. Clinical measurements

Serum retinol levels, expressed as micromole/liter (μmol/L), were measured once a year and analysed by high-performance liquid chromatography. Serum retinol levels <0.7 μmol/L were considered deficient, and concentrations >3.5 μmol/L toxic [13]. Outcomes were compared with reference values for age-equivalent white healthy controls according the US National Health and Nutrition Examination Survey (NHANES) 2005–2006 [14].

A fat balance study was performed to measure the fat excretion in faeces and to calculate the CFA. In conjunction with the 3-day dietary intake assessment, a home-based 72-h stool collection was obtained, starting on day two of dietary intake assessment and ending one day after dietary recording (day four), to determine the mean faecal fat content of this 3-day collection. CFA was then calculated from the mean dietary fat intake of the 3-day dietary record and the mean daily faecal fat output and expressed as a percentage. Serum IgG levels were also measured once a year and expressed as gram/liter (g/L).

### 2.4. Statistical analysis

Descriptive statistics of categorical variables were examined. All continuous variables were tested for normality and skewness. Due to repeated measures on individual patients in different years of age, children were stratified according age year (zero year = birth to < one year, one year = one to < two years, two year = two to < three years, etc.) for the cross sectional analyses. We described the dietary vitamin A intake, prescribed supplementation and the total vitamin A intake (dietary vitamin A plus prescribed supplementation), expressed as μg RAE. The total intake was also expressed as both %RDA and %TUL. Subsequently, we described the prescribed supplementation, expressed as % of the lower level (LL) and the upper level (UL) of both the European and North-American CF-specific recommendations. The serum retinol levels, CFA and serum IgG levels were also examined. To assess if total vitamin E intake was related to serum retinol levels, children were categorized on the basis of their serum retinol as having a level <50th or >50th percentile, or a level between <5th, between 5th and 95th, and >95th percentile of the NHANES. The total vitamin A intake among the categories of serum retinol levels were compared, using the Mann–Whitney test or Kruskal–Wallis test respectively.

For longitudinal analyses, the linear mixed effects regression was performed to evaluate the effect of the total vitamin A intake, CFA, serum IgG level, gender and age on serum retinol. This model allows inclusion of variable numbers of measurements per child and irregularly timed and missing observations. Included were fixed effect for total vitamin A intake, CFA, serum IgG level, gender and age of child and a random intercept and random slope for age of child to account for correlations between measurements within children. In the mixed effects model, serum retinol was log transformed to correct for right-skweness and the significance level was set at $\alpha < 0.05$. Statistical analyses were performed by using the Statistical Package for the Social Sciences Computer Software (SPSS Inc. version 20, IBM, Chicago, IL).

## 3. Results

### 3.1. Clinical characteristics

Data of 221 patients with proven CF (98% Caucasian, 107 girls) were eligible for inclusion. In these patients, we obtained a total of 862 measurements of vitamin A intake along with serum retinol measurements, and 646 and 565 measurements respectively of CFA and serum IgG.

### 3.2. Vitamin A intake

The mean total vitamin A intake (dietary vitamin A intake plus prescribed supplementation) in the different age groups was between 1169 and 1546 μg RAE, providing 187–419% RDA, and was relatively stable over the age groups (Fig. 1, see also Table 1 for details). As recommendations for daily intake are lower for younger children, these children were more likely to surpass the RDA. An excessive total vitamin A intake, even above the TUL for healthy subjects, was seen in 30% of the assessments, especially in children up to six year of age. Nevertheless, apart from children less than one year of age, the mean prescribed supplementation in every year of age was lower than both the European, and the North-American, CF-specific vitamin A recommendations [2,3]. Moreover, in most age groups, mean total vitamin A intake was at the lower limit of the European CF-specific recommendation and far below both the upper limit of the European-, and the North-American recommendation (Table 1).

### 3.3. Clinical measurements

Serum retinol levels were more or less constant over the age groups, with median values between 1.2 and 1.6 μmol/L, and within the references values of the NHANES [14] (Fig. 2, Table 2). Serum retinol deficiency (values <0.7 μmol/L) was found in 2% of the measurements (17 measurements in 11 children) whereas 0.3% of the measurements (3 measurements in three children), showed a toxic value. i.e. >3.5 μmol/L. Children with a deficiency had a total vitamin A intake providing 293 ± 240% of RDA, while in children with toxic values the total vitamin A intake provided 224 ± 73% of RDA.

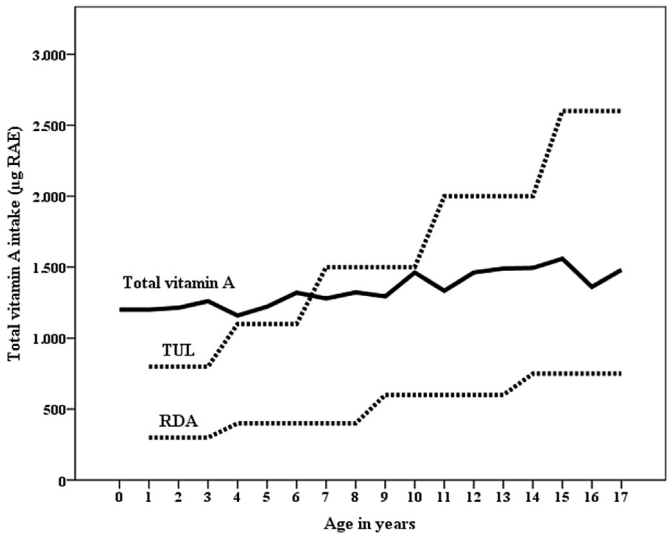


**Fig. 1.** Mean total vitamin A intake (dietary vitamin A intake plus prescribed vitamin A supplementation) expressed as μg retinol activity equivalent per year of age, derived from 862 measurements of 221 patients with cystic fibrosis set out against recommended daily advice (RDA) and tolerable upper intake level (TUL).

The median CFA varied from 89 to 95%, and median serum IgG levels from 3.9 to 12.7 g/L. In the latter, a gradual increase during the age years was seen (Table 2).

### 3.4. Vitamin A intake and serum retinol levels

Children were categorized for every year of age into those having a serum retinol level either above or below the 50th percentile of the NHANES levels at the same age to assess if a higher vitamin A intake was related to higher serum retinol levels. We found no differences in total vitamin A intake between patients above and below the 50th percentile. The exception was at age 16; the total vitamin A intake was significantly higher in those with lower serum retinol levels ($p = 0.046$) (Fig. 3). After categorizing patients as having a serum retinol level <5th, between 5th and 95th percentile and those with a level >95th percentile, we found no differences in total vitamin A intake among the categories (all $p \geq 0.088$).

Longitudinally, we found no significant association of serum retinol levels with total vitamin A intake (95% CI -0.04 to 0.01%, $p = 0.245$) or CFA (95% CI -39.98–55.83%, $p = 0.890$) but serum retinol levels was associated with serum IgG levels. Each g/L increase in serum IgG level would result in a 2.49% (95% CI -3.60 to −1.36%) reduction in serum retinol levels. The relatively large confidence interval for the effect of CFA indicated a high variability among individuals.

## 4. Discussion

The current study in this large sample of children and adolescents with CF, showed that the dietary vitamin A intake exceeded the RDA in all age groups. The total vitamin A intake (dietary vitamin A plus prescribed supplementation) exceeded the TUL for healthy subjects in 30% of the assessments, primarily before six year of age and, although it failed to achieve both the European and the North-American CF-specific vitamin A recommendations, serum retinol deficiency was rare. Longitudinally, no associations of total vitamin A intake, CFA, gender or age with serum retinol was found but decreasing serum retinol was associated with increasing serum IgG.

Vitamin A is comprised of preformed retinoids which are solubilised and esterified into retinyl esters in the intestine and stored in the liver as retinol. Excessive vitamin A intakes poses a risk of hepatotoxicity [15,16], presumably through activation of stellate cells. In this study we did indeed find an excessive vitamin A intake in patients with CF in all age years, as did some smaller studies [6,7,17]. Although the current study mainly found serum retinol levels within reference ranges, it is unknown whether excessive hepatic retinol levels were present. The best way to determine an abnormal vitamin A status would have been through hepatic biopsies [18]; however, this invasive procedure is unsuitable for population studies and the assessment of serum retinol levels is a generally accepted method for large clinical studies.

In our study serum retinol levels were not significantly dependent on vitamin A intake, as has also been found by others [6,7]. Nevertheless, two cross-sectional studies from the United Stated, including respectively 73 and 78 CF patients in an older age range (eight year up to respectively 12 and 25 year), found high serum retinol levels in patients with extremely high vitamin A intakes, in which respectively 49% and 73% of the patients exceeded the current recommendations [6,7]. The observation of high serum retinol levels in these cohorts suggest a causal relationship, although a direct correlation could not be found [7]. It is possible that with

**Table 1**
Vitamin A intake (dietary intake, prescribed supplementation and total intake) derived from 862 measurements in 221 patients with cystic fibrosis (CF) expressed as μg RAE. The total intake is also expressed as % of the recommended daily advice and tolerable upper intake level of vitamin A intake. The prescribed supplementation is also expressed as % of both the European and American CF-specific vitamin A recommendations.

| Age | N | | | CF recommendation supplementation | | | | Dietary intake | Supple-mentation | Total intake | | | Prescribed supplementation as % of CF- recommendations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EU | | US | | | | | | | EU | | US | |
| | | RDA | TUL | LL | UL | LL | UL | μg RAE | μg RAE | μg RAE | %RDA | %TUL | LL | UL | LL | UL |
| 0 | 11 | nd | nd | 1200 | 3000 | 450 | | 548 ± 137 | 739 ± 628 | 1287 ± 612 | | | 62 ± 52 | 25 ± 21 | 164 ± 140 | |
| 1 | 26 | 300 | 800 | 1200 | 3000 | 1500 | | 607 ± 273 | 645 ± 545 | 1238 ± 598 | 413 ± 199 | 155 ± 74 | 54 ± 45 | 21 ± 18 | 43 ± 36 | |
| 2 | 24 | 300 | 800 | 1200 | 3000 | 1500 | | 596 ± 268 | 573 ± 461 | 1169 ± 500 | 390 ± 167 | 146 ± 63 | 45 ± 38 | 19 ± 15 | 38 ± 31 | |
| 3 | 35 | 300 | 800 | 1200 | 3000 | 1500 | | 599 ± 333 | 658 ± 648 | 1256 ± 651 | 419 ± 217 | 157 ± 81 | 55 ± 54 | 22 ± 22 | 44 ± 43 | |
| 4 | 38 | 400 | 1100 | 1200 | 3000 | 1500 | 3000 | 645 ± 283 | 615 ± 578 | 1260 ± 580 | 315 ± 145 | 115 ± 53 | 51 ± 48 | 21 ± 19 | 41 ± 39 | 21 ± 19 |
| 5 | 42 | 400 | 1100 | 1200 | 3000 | 1500 | 3000 | 725 ± 263 | 471 ± 485 | 1196 ± 539 | 299 ± 135 | 109 ± 49 | 39 ± 40 | 16 ± 16 | 31 ± 31 | 16 ± 16 |
| 6 | 46 | 400 | 1100 | 1200 | 3000 | 1500 | 3000 | 814 ± 365 | 488 ± 451 | 1301 ± 546 | 325 ± 136 | 117 ± 49 | 41 ± 38 | 16 ± 15 | 33 ± 30 | 16 ± 15 |
| 7 | 50 | 400 | 1500 | 1200 | 3000 | 1500 | 3000 | 849 ± 357 | 501 ± 547 | 1350 ± 605 | 337 ± 151 | 91 ± 41 | 42 ± 46 | 17 ± 18 | 33 ± 36 | 17 ± 18 |
| 8 | 56 | 400 | 1500 | 1200 | 3000 | 3000 | | 906 ± 414 | 441 ± 352 | 1343 ± 503 | 336 ± 126 | 90 ± 34 | 37 ± 29 | 15 ± 12 | 15 ± 12 | |
| 9 | 62 | 600 | 1500 | 1200 | 3000 | 3000 | | 883 ± 440 | 416 ± 354 | 1293 ± 520 | 216 ± 87 | 86 ± 35 | 35 ± 30 | 14 ± 12 | 14 ± 12 | |
| 10 | 71 | 600 | 1500 | 1200 | 3000 | 3000 | | 1014 ± 543 | 474 ± 477 | 1488 ± 738 | 248 ± 123 | 99 ± 49 | 39 ± 40 | 16 ± 15 | 16 ± 15 | |
| 11 | 71 | 600 | 2000 | 1200 | 3000 | 3000 | | 1015 ± 490 | 442 ± 371 | 1451 ± 637 | 242 ± 106 | 73 ± 32 | 37 ± 31 | 15 ± 12 | 15 ± 12 | |
| 12 | 73 | 600 | 2000 | 1200 | 3000 | 3000 | | 1002 ± 436 | 445 ± 414 | 1464 ± 671 | 244 ± 112 | 73 ± 34 | 37 ± 35 | 15 ± 14 | 15 ± 14 | |
| 13 | 68 | 600 | 2000 | 1200 | 3000 | 3000 | | 1068 ± 524 | 406 ± 292 | 1474 ± 725 | 244 ± 122 | 74 ± 36 | 34 ± 24 | 14 ± 10 | 14 ± 10 | |
| 14 | 55 | 750[a] | 2000 | 1200 | 3000 | 3000 | | 1141 ± 581 | 415 ± 392 | 1530 ± 652 | 204 ± 86 | 75 ± 32 | 35 ± 33 | 14 ± 13 | 14 ± 13 | |
| 15 | 47 | 750[a] | 2600 | 1200 | 3000 | 3000 | | 1126 ± 617 | 406 ± 328 | 1532 ± 797 | 204 ± 108 | 61 ± 36 | 34 ± 27 | 14 ± 11 | 14 ± 11 | |
| 16 | 48 | 750[a] | 2600 | 1200 | 3000 | 3000 | | 993 ± 539 | 406 ± 386 | 1399 ± 659 | 187 ± 90 | 54 ± 25 | 34 ± 32 | 14 ± 13 | 14 ± 13 | |
| 17 | 39 | 750[a] | 2600 | 1200 | 3000 | 3000 | | 1131 ± 655 | 416 ± 445 | 1546 ± 817 | 203 ± 107 | 59 ± 31 | 35 ± 37 | 14 ± 15 | 14 ± 15 | |

RDA: recommended daily advice, RAE: retinol activity equivalent, LL: lower limit, UL: upper limit, UL = tolerable upper intake level, nd = not defined.
[a] RDA girls (700 μg) and boys (800 μg) averaged.

moderate vitamin A intake, as was found in our study, the correlation with serum retinol levels is minimal or non-existent, while with a very high intake serum retinol levels might indeed be boosted to above normal levels.

In our cohort, the current CF-specific recommendations for vitamin A intake were only met in infants. Nevertheless, median serum retinol levels were within the references values of the NHANES at all ages. Moreover, comparable number of patients had serum retinol levels <5th or >95th NHANES percentile. The vitamin A intake achieved in our cohort seems to be sufficient to maintain a normal serum retinol level, as was also found in another European study [17]. This was surprising, since the supplementation prescribed was only half or less of the current recommendations. In addition, mean total vitamin A intake was in the bottom of the lower limit of the European CF-specific recommendation and far below both the upper limit of the European- and North-American CF-specific recommendations. This suggests that both the European and North-American CF-specific recommendations for vitamin A intake are higher than necessary to prevent deficiencies and may even lead to excessive vitamin A intake. Moreover not only in our study but especially in two American studies [6,7], many patients exceeded the TUL, considered the maximum daily intake above which toxicity in healthy children might be seen. It seems therefore appropriate to reduce the recommendations for vitamin A supplementation in CF, at least in infants and young children.

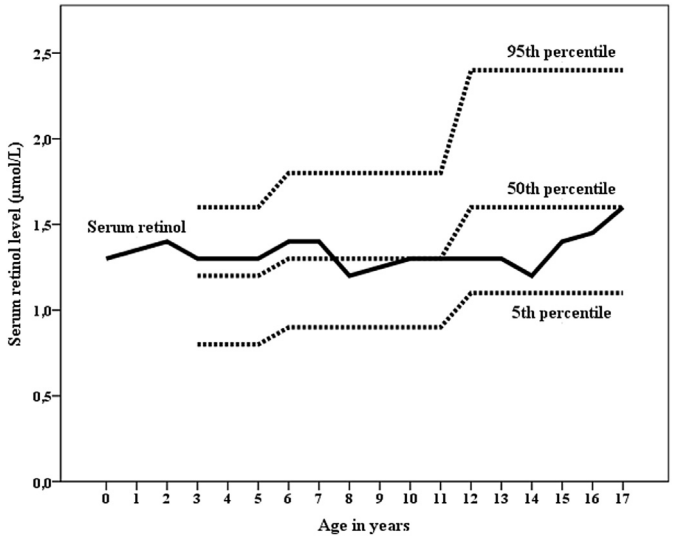


**Fig. 2.** Median serum retinol level, expressed as μmol/L per year of age, derived from 862 measurements of 221 patients with cystic fibrosis set out against the US National Health and Nutrition Examination Survey (NHANES) percentiles.

We found no association between CFA and serum retinol levels, which is in line with a study in CF patients in whom identical serum retinol levels were found in both pancreatic sufficient and pancreas insufficient patients [19]. Previously, serum retinol deficiency was described in patients with severe steatorrhoea. In our study and others (near) normal CFA in patients who get prescribed pancreatic enzyme dosages primarily tailored to their individual dietary fat intake [20,21]. Thus fat malabsorption is nowadays most often well-treated, which reduces the loss of fat-soluble vitamins and making an effect on retinol levels hard to detect.

In healthy people serum retinol levels are reduced by 11–24% during an infection, as a result of the increased consumption of retinol and recover subsequently [9]. Likely, in patients with CF, serum retinol concentrations are transiently depressed during acute inflammation [8,22,23]. Indeed, we found a gradual increase in serum IgG levels during the age years. These higher IgG levels were associated with declined serum retinol levels which may have been the result of an increased incidence of chronic pulmonary inflammation with increasing age as also was found by others [8]. It can be assumed that a lowering in serum retinol levels might be due to acute inflammation rather than a nutritional vitamin A deficiency as we observed no significant correlation between serum retinol levels and total vitamin A intake.

Because this was a single centre study, the results might not be generalized to other CF treatment centres and populations.

**Table 2**
Serum retinol levels, coefficient of fat absorption (CFA), immunoglobulin G (IgG), z-score weight-for-age (WFA), z-score height-for-age (HFA) and z-score weight-for-height (WFH), derived from 862 measurements of 221 patients with cystic fibrosis.

| Age | N (girls) | Serum retinol (μmol/L)* | CFA (%)* | IgG (g/L)* | z-score WFA** | z-score HFA** | z-score WFH** |
|---|---|---|---|---|---|---|---|
| 0 | 11 (7) | 1.3 (1.1–1.7) | 95 (n = 3) | 3.9 (2.9–7.1) (n = 4) | −0.3 ± 1.0 | −0.4 ± 1.1 | −0.0 ± 0.6 |
| 1 | 26 (12) | 1.4 (1.2–1.5) | 94 (90–95) (n = 8) | 5.7 (4.8–8.2) (n = 10) | −0.9 ± 0.9 | −0.6 ± 0.9 | −0.6 ± 0.8 |
| 2 | 24 (13) | 1.4 (1.1–1.6) | 92 (85–94) (n = 6) | 6.8 (5.1–7.4) (n = 17) | −0.7 ± 1.0 | −0.6 ± 0.9 | −0.5 ± 1.2 |
| 3 | 35 (23) | 1.3 (1.1–1.5) | 91 (85–96) (n = 20) | 6.5 (5.2–7.3) (n = 23) | −0.1 ± 0.9 | −0.3 ± 0.8 | 0.1 ± 1.0 |
| 4 | 38 (21) | 1.3 (1.1–1.5) | 91 (86–94) (n = 31) | 7.5 (6.5–10.0) (n = 22) | −0.3 ± 1.0 | −0.5 ± 1.1 | 0.1 ± 1.0 |
| 5 | 42 (20) | 1.3 (1.0–1.5) | 91 (86–96) (n = 32) | 7.5 (6.7–9.7) (n = 28) | −0.4 ± 1.1 | −0.5 ± 1.1 | −0.3 ± 1.0 |
| 6 | 46 (19) | 1.4 (1.2–1.6) | 89 (86–94) (n = 37) | 8.0 (6.3–10.2) (n = 29) | −0.3 ± 1.0 | −0.5 ± 1.0 | −0.2 ± 1.0 |
| 7 | 50 (25) | 1.4 (1.1–1.7) | 92 (85–94) (n = 44) | 9.1 (6.8–11.3) (n = 36) | −0.1 ± 1.0 | −0.5 ± 1.0 | 0.2 ± 0.8 |
| 8 | 56 (24) | 1.2 (1.0–1.5) | 92 (89–95) (n = 49) | 9.1 (6.5–10.9) (n = 34) | −0.2 ± 0.9 | −0.6 ± 1.0 | 0.1 ± 0.8 |
| 9 | 62 (30) | 1.3 (1.1–1.4) | 90 (85–95) (n = 51) | 9.6 (7.9–12.5) (n = 41) | −0.2 ± 0.9 | −0.5 ± 1.0 | −0.0 ± 0.9 |
| 10 | 71 (33) | 1.3 (1.0–1.6) | 92 (88–95) (n = 61) | 10.8 (7.2–12.6) (n = 46) | −0.2 ± 0.9 | −0.6 ± 1.0 | −0.0 ± 0.9 |
| 11 | 71 (36) | 1.3 (1.1–1.4) | 92 (88–95) (n = 58) | 11.0 (8.1–12.0) (n = 41) | −0.2 ± 0.9 | −0.5 ± 1.0 | −0.1 ± 0.8 |
| 12 | 73 (37) | 1.3 (0.9–1.5) | 91 (87–95) (n = 59) | 11.0 (8.4–13.2) (n = 56) | −0.4 ± 1.0 | −0.6 ± 1.0 | −0.1 ± 0.8 |
| 13 | 68 (39) | 1.3 (1.1–1.7) | 93 (89–96) (n = 56) | 10.5 (8.0–13.2) (n = 46) | −0.4 ± 0.9 | −0.4 ± 0.9 | −0.2 ± 0.7 |
| 14 | 55 (27) | 1.2 (1.1–1.7) | 93 (87–96) (n = 43) | 10.8 (9.2–14.6) (n = 36) | −0.3 ± 0.8 | −0.5 ± 1.0 | −0.0 ± 0.7 |
| 15 | 47 (23) | 1.4 (1.2–1.8) | 92 (89–95) (n = 30) | 12.0 (9.7–13.9) (n = 32) | −0.4 ± 0.8 | −0.4 ± 0.9 | 0.0 ± 0.7 |
| 16 | 48 (23) | 1.5 (1.2–1.8) | 90 (84–93) (n = 33) | 12.7 (10.8–14.4) (n = 33) | −0.3 ± 0.7 | −0.5 ± 0.7 | 0.3 ± 0.7 |
| 17 | 39 (14) | 1.6 (1.2–2.0) | 90 (83–93) (n = 25) | 12.1 (10.6–15.5) (n = 31) | −0.1 ± 0.8 | −0.5 ± 0.9 | 0.6 ± 0.7 |

*Median (25th − 75th percentile).
**Mean ± SD.

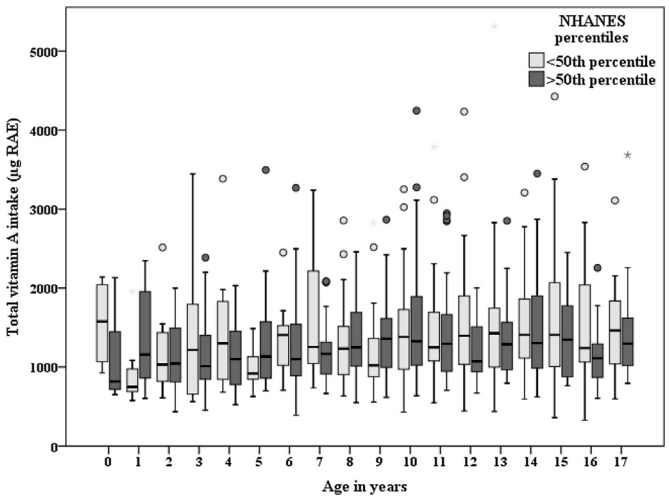


**Fig. 3.** Total vitamin A intake (dietary intake plus prescribed vitamin A supplementation), expressed as microgram retinol activity equivalents (μg RAE) per year of age, categorized for serum retinol levels above or below 50th percentile (according to the normal reference range of the US National Health and Nutrition Examination Survey (NHANES)) derived from 862 measurements of 221 patients with cystic fibrosis.

Moreover, keeping food records can be burdensome, leading to alterations of the diet and to over- and/or under-reporting, which affects the validity. Furthermore, we did not measure the adherence to vitamin supplementation, which could have led to overestimation of the true total vitamin A intake. The commonly used vitamin supplementation contain water-miscible vitamin A, although the use of other vitamin supplement products was not ruled out and thus may affected the calculated vitamin A intake. Also taking additional supplements containing vitamin A or vitamin A enriched food, which had not been reported by patients, may underestimate the vitamin A intake in the present study.

## 5. Conclusions

In this large sample of children and adolescent with CF, the current recommendations for vitamin A supplementation in CF were not met. Nevertheless, the serum retinol distribution was normal. It seems that the current vitamin A specific recommendations are no longer appropriate and a reduction in CF-specific vitamin A supplementation recommendations should therefore be considered.

## Statement of authorships

JW conceived of the study, contributed to the database construction, carried out the study and data analyses and drafted the manuscript.

NB contributed to the database construction and helped to draft the manuscript.

RS contributed to the database construction and data analyses and helped to draft the manuscript.

BA helped to draft the manuscript.

CE conceived of the study, participated in the design of the study and helped to draft the manuscript.

RH conceived of the study, participated in the design of the study and helped to draft the manuscript.

All authors read and approved the final manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

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