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Vitamin E intake, α-tocopherol levels and pulmonary function in children and adolescents with cystic fibrosis

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Abstract

Pancreatic insufficiency cystic fibrosis (CF) patients receive vitamin E supplementation according to CF-specific recommendations in order to prevent deficiencies. It has been suggested that higher serum α-tocopherol levels could have protective effects on pulmonary function (PF) in patients with CF. Whether current recommendations are indeed optimal for preventing deficiency and whether vitamin E has therapeutic benefits are subjects of debate. Therefore, we studied vitamin E intake as well as the long-term effects of vitamin E intake, the coefficient of fat absorption (CFA) and IgG on α-tocopherol levels. We also examined the long-term effects of serum α-tocopherol and serum IgG on forced expiratory volume in 1 s expressed as percentage of predicted (FEV_1% pred.) in paediatric CF patients during a 7-year follow-up period. We found that CF patients failed to meet the CF-specific vitamin E recommendations, but serum α-tocopherol below the 2·5th percentile was found in only twenty-three of the 1022 measurements (2 %). Furthermore, no clear effect of vitamin E intake or the CFA on serum α-tocopherol was found (both $P \geq 0{\cdot}103$). FEV_1% pred. was longitudinally inversely associated with age ($P < 0{\cdot}001$) and serum IgG ($P = 0{\cdot}003$), but it was not related to serum α-tocopherol levels. We concluded that in the present large sample of children and adolescents with CF, vitamin E intake was lower than recommended, but serum α-tocopherol deficiency was rare. We found no evidence that higher serum α-tocopherol levels had protective effects on PF. Adjustment of the recommendations to the real-life intake of these patients may be considered.

Key words: Vitamin E: α-Tocopherol: Cystic fibrosis: Coefficient of fat absorption: IgG

Cystic fibrosis (CF) is a life-threatening genetic disorder characterised by chronic pulmonary inflammation that causes a gradual, progressive decline in pulmonary function (PF) partly due to oxidative stress[1]. The antioxidant vitamin E is routinely prescribed[1,2]to prevent deficiencies associated with fat malabsorption, which is seen in more than 85 % of pancreatic insufficiency patients who have CF[3]. Vitamin E levels, which are measured as serum α-tocopherol, decrease during a pulmonary exacerbation[4,5] and normalise after intravenous antibiotic treatment[5–7]. Consequently, a low serum α-tocopherol level might be caused by inflammation rather than nutritional vitamin E deficiency. Likewise, the suggested association between serum α-tocopherol levels and PF[5,6] might be secondary. For this reason, the extent of chronic pulmonary inflammation should be considered when investigating the association between PF and serum α-tocopherol. IgG, which increases once chronic inflammation has developed[8,9], might be a good marker of chronic inflammation.

At present, little is known about daily vitamin E intake practices and serum α-tocopherol levels in large groups of CF patients; a previous study was rather small and conducted on patients who had a limited age range[10]. Moreover, the

Abbreviations: CF, cystic fibrosis; CFA, coefficient of fat absorption; FEV_1% pred., forced expiratory volume in 1 s expressed as percentage of predicted; NHANES, National Health and Nutrition Examination Survey; PF, pulmonary function.

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long-term relationship between serum α-tocopherol levels and PF is poorly understood because most studies have follow-up periods of less than three years and lack data on inflammation[5,6,11]. We therefore studied the association between vitamin E intake, the coefficient of fat absorption (CFA) and IgG on α-tocopherol levels. Additionally, the long-term effects of serum α-tocopherol and serum IgG on PF in paediatric CF patients during a 7-year follow-up period is described.

Methods

Study sample

The present retrospective study included Dutch children (born between 1989 and 2013) with proven CF who received medical care at the CF Centre at the University Medical Centre Utrecht. Each child was confirmed to have 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 α-tocopherol levels were obtained during annual check-ups. We used data obtained between January 2007 and December 2013 from children and adolescents who had provided at least one measurement of vitamin E intake (dietary intake plus prescribed supplementation) or serum α-tocopherol levels and who were receiving pancreatic enzyme replacement therapy at the time of reporting. All patients, or the parents or guardians in the case 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.

Dietary intake assessment

All CF patients received written instructions about completing a 3 d dietary food record in which they recorded the portion sizes or weights of all food and beverages consumed during two weekdays and one weekend day whenever possible. Registered dietitians coded and analysed the food records according to a standardised approach by using the Dutch Food Composition Table (2010) of the Dutch Nutrition Centre, and vitamin E intake was calculated for each assessment. The prescribed vitamin E supplements, as registered in the medical records, were considered as actual supplemental vitamin E intake. Vitamin E intake (dietary, prescribed supplementation and total) was expressed as mg α-tocopherol/d. The prescribed vitamin E intake was also expressed as a percentage of both the European[2] and North American[1] CF-specific vitamin E recommendations.

Clinical measurements

Serum α-tocopherol levels, which were expressed as μg/dl and also as μmol/l, were measured once a year and analysed by HPLC. The outcomes were compared with reference values for age-equivalent, Caucasian, healthy controls according to the US National Health and Nutrition Examination Survey (NHANES) from 2005–6[12].

A fat-balance study was performed to measure the fat excretion in faeces and to calculate the CFA. In conjunction with the 3 d dietary intake assessment, a home-based 72 h stool collection was obtained starting on day 2 of the dietary intake assessment and ending 1 d after dietary recording was completed (day 4) in order to determine the mean faecal fat content of the 3 d collection. The CFA was then calculated from the mean dietary fat intake of the 3 d dietary record and the mean daily faecal fat output and expressed as a percentage.

Serum IgG was also measured once per year and expressed as g/l.

PF, which was assessed as forced expiratory volume in 1 s (FEV_1), was obtained from maximal expiratory flow-volume curves (Masterscreen; Viasys Healthcare) and was expressed as the percentage of the predicted value for a given height, age and sex (FEV_1% pred.)[13]. For each child, the highest FEV_1% pred. measured in the preceding calendar year (beginning at 6 years of age) was used in the analysis.

Statistical analysis

Descriptive statistics of categorical variables were examined. All continuous variables were examined for normality and skewness. Because individual patients were repeatedly measured at different years of age, the children were stratified according to age (year 0 = birth to < 1 year, year 1 = 1 to < 2 years, etc.). The total vitamin E intake was expressed as a percentage of the lower level and the upper level of both the European and North American CF-specific recommendations. To assess whether total vitamin E intake and PF were related to serum α-tocopherol levels, the children were categorised on the basis of their serum α-tocopherol as having a level < 50th or > 50th percentile or a level between the 2·5th and 97·5th percentiles or > 97·5th percentile of the NHANES. The total vitamin E intake and FEV_1% pred. outcomes among the categories of serum α-tocopherol levels were compared using the Mann–Whitney test. For longitudinal analyses, linear mixed effects regression was performed to evaluate the effects of total vitamin E intake, the CFA, serum IgG, sex and age on serum α-tocopherol. This model allowed the inclusion of variable numbers of measurements per child as well as irregularly timed and missing observations. Fixed effects for total vitamin E intake, the CFA, serum IgG, sex and age of each child as well as a random intercept and random slope for the age of each child were also included to account for correlations between measurements within children. In the mixed effects model, serum α-tocopherol was log transformed to correct for right skewness. We also examined the longitudinal effects of serum α-tocopherol and serum IgG on PF: in this model, fixed effects for serum α-tocopherol, serum IgG, age and sex as well as a random intercept and random slopes for serum α-tocopherol and age were included. The significance level was set at $\alpha < 0{\cdot}05$. The statistical analyses were performed using the Statistical Package for the Social Sciences Computer Software version 20 (SPSS, Inc., IBM).

Results

Clinical characteristics

A total of 232 patients with proven CF (97 % Caucasian, 112 girls) were eligible for inclusion. In these patients, we

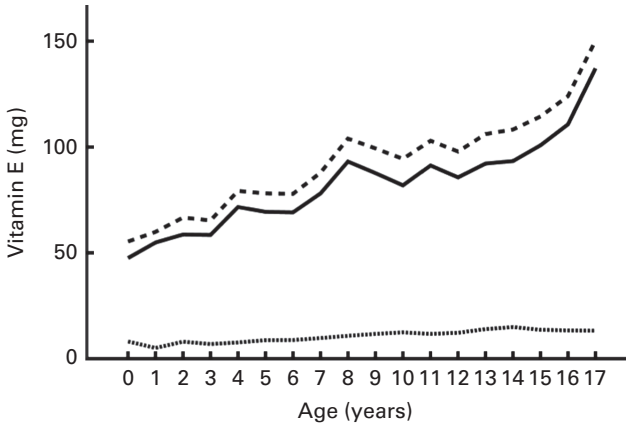

Fig. 1. Mean dietary vitamin E intake (·····), prescribed supplementation (——) and total vitamin E intake (- - -; dietary vitamin E intake plus prescribed supplementation), expressed as mg α-tocopherol/year of age, derived from 912 dietary measurements of 218 patients with cystic fibrosis.

obtained a total of 912 measurements of vitamin E intake and 1022, 672, 679 and 874 measurements respectively of serum α-tocopherol, CFA, serum IgG and FEV_1% pred.

Vitamin E intake

The mean total vitamin E intake (dietary vitamin E intake plus prescribed supplementation) of 218 patients in the different age groups was between 55 and 150 mg α-tocopherol/d. A gradual increase was seen with older children. The vitamin E intake was higher with supplements than with dietary sources (Fig. 1, Table 1). The European and North American lower level of the CF-specific vitamin E supplementation recommendations[1,2] were only met in adolescents aged 15 years and older and in children less than 1 year of age. In all age groups, the prescribed supplementation was far below the upper limits of both the European and the North American recommendations (Table 1).

Clinical measurements

The median serum α-tocopherol levels varied between 18 and 25 μmol/l (775 and 1079 μg/dl) and were all above the 50th percentile of the NHANES (Fig. 2). In children aged 6 and older, in twenty-three measurements (2%), a serum α-tocopherol level <2·5th percentile was found, and in 122 measurements (12%), a level >97·5th percentile was found. The median CFA varied between 89 and 94%. Serum IgG, which had medians between 3·9 and 12·4 g/l, gradually increased, whereas FEV_1% pred. gradually declined with age (online supplementary Table S1).

Vitamin E intake and α-tocopherol levels

Children were categorised for every year of age as having a serum α-tocopherol level either above or below the 50th percentile of the NHANES levels at the same age to asses if a higher vitamin E intake was related to higher serum α-tocopherol levels. We found no differences in total vitamin E

Table 1. Vitamin E intake (dietary intake, prescribed supplementation and total intake) derived from 912 measurements in 218 patients with cystic fibrosis (CF) expressed as mg α-tocopherol. The prescribed supplementation is also expressed as % of both the lower limit (LL) and upper limit (UL) of the European (EU) and North American (US) CF-specific vitamin E recommendations (Mean values and standard deviations)

		CF-specific recommendation for supplementation				Dietary intake		Supplementation		Total intake		Prescribed supplementation as % of CF-recommendations							
												EU LL		EU UL		US LL		US UL	
Age	*n*	EU LL	EU UL	US LL	US UL	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	6	100	400	40	50	8·1	1·5	47·5	5·6	55·3	6·6	48	6	12	1	119	14	95	11
1	18	100	400	80	150	5·0	2·5	54·9	16·7	60·0	16·2	55	17	14	4	69	21	37	11
2	22	100	400	80	150	8·0	4·9	58·6	24·6	66·7	25·3	59	25	15	6	73	31	39	16
3	36	100	400	80	150	6·9	4·0	58·4	28·9	65·3	28·3	58	29	15	7	73	36	39	19
4	35	100	400	100	200	7·7	3·7	71·6	41·6	79·3	41·4	72	42	18	10	72	42	36	21
5	46	100	400	100	200	8·7	4·8	69·4	38·8	78·1	39·1	69	39	17	10	69	39	35	19
6	50	100	400	100	200	8·8	5·7	69·1	39·0	77·9	38·4	69	39	17	10	69	39	35	19
7	56	100	400	100	200	9·7	5·5	78·0	52·5	87·8	52·2	78	53	20	13	78	53	39	26
8	63	100	400	100	200	10·8	6·4	93·2	84·6	104·0	85·2	93	85	23	21	93	85	47	42
9	73	100	400	200	400	11·7	7·4	87·7	75·9	99·3	77·9	88	76	22	19	45	42	22	19
10	76	100	400	200	400	12·4	6·9	81·9	58·4	94·4	59·2	82	58	20	15	41	29	20	15
11	81	100	400	200	400	11·7	6·1	91·3	77·7	103·0	78·0	91	78	23	19	46	39	23	19
12	78	100	400	200	400	12·2	7·5	85·6	63·5	97·9	63·2	86	64	21	16	43	32	21	16
13	72	100	400	200	400	14·0	7·0	92·2	66·9	106·1	67·6	92	67	23	17	46	33	23	17
14	64	100	400	200	400	14·9	8·4	93·4	65·8	108·3	64·7	93	66	23	16	47	33	23	16
15	50	100	400	200	400	13·6	7·9	100·8	89·1	114·4	89·1	101	89	25	22	50	45	25	22
16	52	100	400	200	400	13·3	6·2	110·7	97·7	124·1	96·6	111	98	28	24	55	49	28	24
17	34	100	400	200	400	13·2	9·2	137·2	111·6	150·3	111·2	137	112	34	28	69	56	34	28

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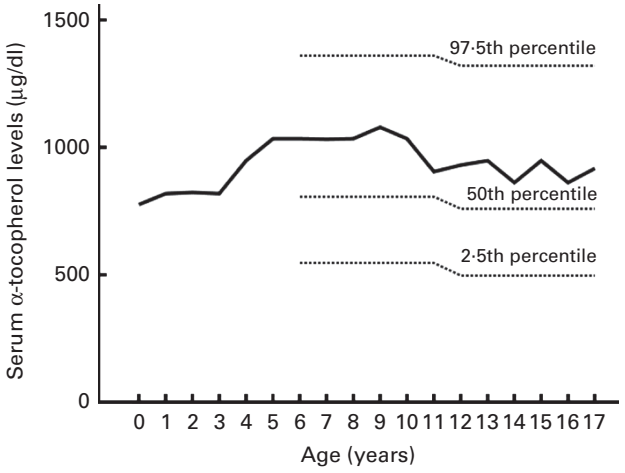

Fig. 2. Median serum α-tocopherol (—), expressed as μg/dl per year of age, derived from 1022 measurements of 229 patients with cystic fibrosis set out against the US National Health and Nutrition Examination Survey (NHANES) reference percentiles (·····)[12]. To convert α-tocopherol in μg/dl to μmol/l, multiply by 0·02322.

intake between patients above and below the 50th percentile. The exception was at age 13 years, when the total vitamin E intake was significantly higher in those with lower serum α-tocopherol levels (P=0·006). After categorising patients into those who had a serum α-tocopherol level between the 2·5th and 97·5th percentile and those with a level >97·5th percentile, we found no differences in total vitamin E intake between the categories (all $P \geq 0{\cdot}111$). Longitudinally, we found no significant association of serum α-tocopherol levels with total vitamin E intake (95% CI −0·01, 0·00; P=0·224), the CFA (95% CI −0·07, 0·81; P=0·103) or serum IgG levels (95% CI −0·95, 1·36; P=0·738).

Serum α-tocopherol levels and pulmonary function

To assess if better PF was related to higher serum α-tocopherol levels, the mean FEV_1% pred. outcomes among the serum α-tocopherol categories with levels <50th and >50th percentile of the NHANES for each year of age were examined. We found a difference in the distribution of FEV_1% pred. across the serum α-tocopherol categories for patients in age group 8 years (P=0·016), 11 years (P=0·028) and 12 years (P=0·004) and a lower FEV_1% pred. in the patients with a serum α-tocopherol >50th percentile. In addition, an overall trend towards a lower FEV_1% pred. in those with serum α-tocopherol levels >50th percentile was seen (Fig. 3; see also online supplementary Table S2 for detailed information). The distribution of FEV_1% pred. across serum α-tocopherol categories with levels between the 2·5th and 97·5th percentile and >97·5th percentile did not differ (all $P \geq 0{\cdot}102$) (data not shown).

Additionally, with the linear mixed model analysis, we observed no significant relation between FEV_1% pred. and serum α-tocopherol levels (95% CI −0·00, 0·00; P=0·158), but FEV_1% pred. was associated with age and serum IgG. Each year, an increase in age was associated with a 1·84% (95% CI −2·22, −1·45; P<0·001) decline in FEV_1% pred., and each g/l increase in serum IgG was associated with a 0·53% (95% CI −0·89, −0·18; P=0·003) decline in FEV_1% pred.

Discussion

The present study of a large sample of children and adolescents with CF showed that both the European and the North American CF-specific recommendations for vitamin E intake were not met, but serum α-tocopherol deficiency was rare. Longitudinally, no associations of total vitamin E intake, CFA and serum IgG with serum α-tocopherol were found. Also, no correlation between serum α-tocopherol and FEV_1% pred. was observed, but decreasing FEV_1% pred. was associated with increased age and serum IgG.

A North American cross-sectional study of vitamin E status in sixty-nine subjects aged 7–10 years with CF reported a mean dietary vitamin E intake of 6 mg/d and a median CFA of 87%[10], both of which are slightly lower than the findings in the present study (dietary vitamin E intake between 9 and 12 mg/d, median CFA between 91 and 92%). The total vitamin E intake (dietary intake plus supplementation) in that North American study was in accordance with the North American CF-specific recommendation and much higher than the findings in the present study (a total intake of 224 *v.* 88–104 mg in the present group of 7–10-year-old children). Nevertheless, neither that study nor the present study found an association between serum α-tocopherol and vitamin E intake or between serum α-tocopherol and CFA. Also, serum α-tocopherol levels in that study were in the same range as the range found in the present study: respectively, 26 μmol/l (1131 μg/dl) *v.* levels between 24 and 25 μmol/l (1031 and 1079 μg/dl) for these 7–10-year-old children.

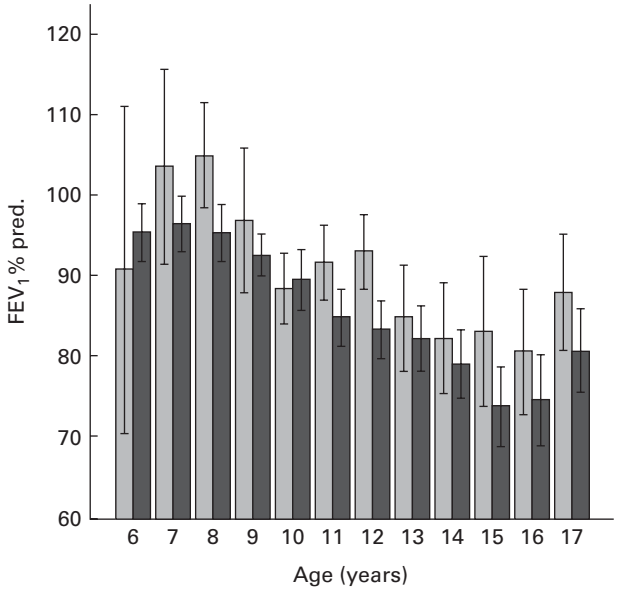

Fig. 3. Percentage of predicted forced expiratory volume in 1 s (FEV_1% pred.)/year of age, categorised for serum α-tocopherol levels above (■) or below (□) 50th percentile (according to the normal reference range of the US National Health and Nutrition Examination Survey (NHANES)) derived from 783 measurements of 194 patients with cystic fibrosis. Values are means and standard deviations represented by vertical bars.

In the present study sample, the current CF-specific recommendations for vitamin E supplementation were not met; nevertheless, median serum α-tocopherol levels were normal in all age groups. The vitamin E intake achieved in the present cohort seems to be sufficient to maintain a normal serum α-tocopherol level despite a supplementation of barely 50 % of the current recommendations. This suggests that both the European and North American CF-specific recommendations for vitamin E supplementation are higher than necessary to prevent deficiencies, and they may even lead to supranormal levels, which were found in 12 % of the present study's cohort. In this respect, it is noteworthy that vitamin E supplementation of more than 400 mg/d, the current upper recommended level in CF patients, may result in toxic effects, including an increased risk of death in adults[14] and an increased risk of haemorrhagic stroke[15]. Although vitamin E toxicity in children has not been described, the earlier studies may raise questions about the safety of the high levels of vitamin E supplementation that are recommended for children and adolescents with CF.

We found no association between the CFA and serum α-tocopherol, which is in line with a study in which identical serum α-tocopherol levels were found in both pancreatic sufficient and pancreatic insufficient CF patients[16]. In the present study sample, near-normal CFA was encountered, although smaller proportions of older patients completed fat-balance studies. The available CFA outcomes suggested that in current practice, fat malabsorption is usually well treated, which reduces the loss of fat-soluble vitamins and makes a potential effect of fat malabsorption on serum α-tocopherol hard to detect, at least in those patients who completed fat-balance studies.

The preventive use of high-dose vitamin E as an antioxidant is a subject of debate, because contradictory, but generally disappointing, findings have been reported[17]. *In vivo,* it has been shown that serum α-tocopherol has no protective function against oxidative damage[18]. This is supported by the present study's results and those of previous studies[10,11]: no evidence was obtained that higher serum α-tocopherol levels have a protective effect on PF in patients with CF. However, a French longitudinal study that included 312 paediatric and adult patients with CF reported a positive correlation between FEV_1% pred. and higher serum α-tocopherol levels[6]. The age range in that study differed from the present study (one–45 years of age in that cohort[6] *v.* zero–18 years of age in the present cohort), although serum α-tocopherol levels were in the same range as that found in the present study: respectively, 21 μmol/l (about 908 μg/dl) *v.* levels between 18 and 25 μmol/l (755 and 1079 μg/dl). An association between a low serum α-tocopherol and a compromised PF may be present in adults, who generally have a more severely reduced FEV_1% pred. than children do as a result of the prolonged nature of the disease. Because only a few patients in the present study had a severely decreased PF, we could not reliably assess whether there is a potentially protective effect of serum α-tocopherol when FEV_1% pred. is already severely compromised. Nevertheless, within the serum α-tocopherol distribution seen in the present cohort, where almost all patients had serum α-tocopherol levels within or even, in 12 % of the measurements, above the normal NHANES reference ranges, we found the opposite: a trend towards higher serum α-tocopherol levels in patients with lower PF. This once again casts doubt on the hypothesis that vitamin E boosts antioxidant defences and thus offsets oxidant damage, at least in the age range in the present study's sample.

It has been proposed that the serum α-tocopherol:total lipid ratio is a more correct index of vitamin E status than serum α-tocopherol measurement alone[19]. Nevertheless, studies that have used both the ratio of plasma vitamin E to total plasma lipids and the serum α-tocopherol level to detect patients with a vitamin E deficiency only find minor differences between the two methods[20–22], but it is unclear which method is superior. Consequently, there is no consensus for reporting vitamin E status in CF patients[23]. In the present study, we were interested in examining serum α-tocopherol levels which were clinically available and which could be compared with reference values obtained in healthy counterparts of the same age.

Because this was a single-centre study, the results might not be generalisable to other CF treatment centres and populations. Moreover, keeping food records can be burdensome and can lead to alterations of the diet and to over- and/or under-reporting, which affects the validity. Lastly, patient adherence to vitamin supplementation could have lead to overestimation of the true total vitamin E intake in the present study and may have prevented us from observing a correlation between total vitamin E intake and serum α-tocopherol levels.

Conclusion

In the present large sample of children and adolescents with CF, the current international recommendations for vitamin E supplementation in CF were not met. Nevertheless, the median serum α-tocopherol levels were within reference values. We found no evidence that higher serum α-tocopherol levels had protective effects on PF. Adjustment of the recommendations to the real-life intake of these patients may be considered.

Supplementary material

To view supplementary material for the present article, please visit http://dx.doi.org/10.1017/S0007114515000215

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Contributions of authors were as follows: J. W. W. conceived of the study, carried it out, analysed the data and drafted the manuscript; N. B. carried out the study and helped draft the manuscript; R. K. S. participated in statistical analysis and helped draft the manuscript; H. G. M. A.

participated in the design of the study and helped draft the manuscript; C. K. v. d. E. conceived of the study, participated in its design and helped draft the manuscript; R. H. J. H. conceived of the study, participated in its design and coordination and helped draft the manuscript; All authors read and approved the final manuscript.

None of the authors has any conflicts of interest to declare.

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