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A History of Cow's Milk Allergy Is Associated with Lower Vitamin D Status in Schoolchildren

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Keywords

Children · Cow's milk allergy · Supplementation · Vitamin D · Vitamin D fortification

Abstract

Background/Aims: Vitamin D insufficiency is common in children. We aimed to evaluate the main determinants of vitamin D status in Finnish school-aged children, including the history of allergic diseases. **Methods:** We conducted a cross-sectional study on 171 ten-year-olds where serum 25-hydroxyvitamin D (25[OH]D) levels were measured, and data on food consumption and use of vitamin D supplements were collected. The history of allergic diseases was evaluated with a validated questionnaire. **Results:** Vitamin D insufficiency (<50 nmol/L) was observed in 16% of the children. In children with a history of cow's milk allergy, the mean 25(OH)D levels were lower than in children without allergy (60.5 ± 12.6 nmol/L vs. 75.5 ± 22.3 nmol/L, $p = 0.004$). Lack of vitamin D supplementation, female gender, non-Caucasian ethnicity, and a history of milk allergy were associated with lower vitamin D status. **Conclusion:** The vitamin D status in our study sample of Finnish schoolchildren was sufficient, which suggests that health policy strategies – such as the

recommendation of vitamin D supplementation and the fortification of food products with vitamin D – have been successful in improving vitamin D status in children. Special concern should be given to children with a history of milk allergy to ensure their vitamin D sufficiency.

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Introduction

Vitamin D modulates bone health and growth and has several extra-skeletal effects, including the regulation of immune functions [1]. In epidemiological studies, vitamin D status has been associated with allergy and asthma and with other immune-mediated diseases such as type 1 diabetes and multiple sclerosis [2–4].

Vitamin D deficiency is a major health concern in many countries, especially in the northern latitudes where exposure to sunlight is limited [5]. In Finland, liquid milk products and fat spreads have been fortified with vitamin D since 2003. In 2010, the fortification of liquid milk products and fat spreads was doubled, the recommended vitamin D fortification is presently 1 µg (40 IU) per 100 mL for milk products and 20 µg (800 IU) per 100 g for

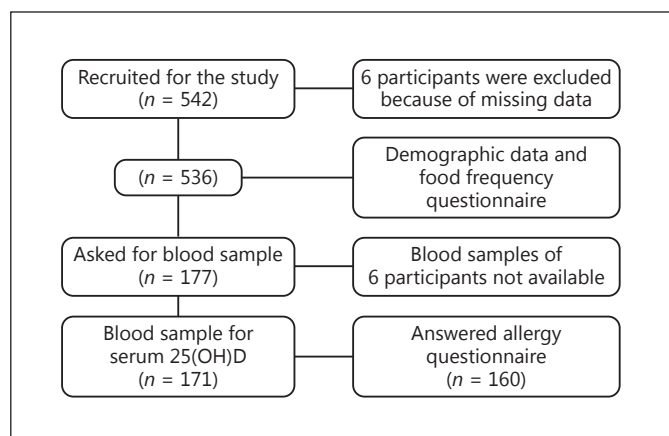


Fig. 1. Flow chart of data collection.

spreads. Finland also has a national recommendation of year-round vitamin D supplementation, which includes since 2011 all children from age 2 weeks to 18 years. Currently, all children aged 2 weeks to 2 years are recommended to take a daily supplement of 10 µg (400 IU) vitamin D₃, and 2- to 18-year-old children a daily supplement of 7.5 µg (300 IU) of vitamin D₃ [6].

Allergic diseases are among the most common chronic diseases in children in developed countries [7]. The lifetime self-reported prevalence of allergy to common foods in Europe ranges from 0.6 to 6% [8]. Food allergy may lead to extensive elimination diets that may affect nutrient intake and growth of children [9].

The aim of this study was to evaluate the overall vitamin D status in Finnish 10-year-old schoolchildren after the changes in the national policy of food fortification and vitamin D supplementation, and to examine the main determinants of vitamin D status and the role of allergic diseases therein.

Materials and Methods

Study Subjects

The ISCOLE study (International Study on Childhood Obesity, Lifestyle and the Environment) is a multinational cross-sectional study conducted in 12 countries aiming to determine the relationships between lifestyle behaviors and obesity [10]. ISCOLE's sample included children from semi-urban and urban areas, and they were recruited from schools stratified by indicators of socioeconomic status. In the present study, we used data collected in the allergy sub-study in Finland. Altogether, 542 ten-year-old 4th grade students from 13 primary schools in the capital region of Finland were recruited for the study. Vitamin D status was measured for 171 participants; and for 160 of them, the history of al-

lergic diseases was evaluated, as presented in the recruitment flow chart (Fig. 1). The main characteristics (sex, ethnicity, BMI, use of vitamin D supplement, and history of cow's milk allergy) of the 171 children did not differ from those of the ISCOLE cohort. This study was conducted according to the Declaration of Helsinki, and all procedures were approved by the Helsinki and Uusimaa Hospital District Ethics Committees. All children provided their assent to participate in the study, and the children's parents or legal guardians provided informed consent.

Data Collection

The participants' parents were invited to complete a questionnaire on basic demographics, ethnicity, family health, socioeconomic factors, and the use of vitamin D supplements. Data on food consumption was obtained from the participating children and included a validated food frequency questionnaire comprising 23 food and beverage groups [11]. The consumption of milk products and fish was inquired with 7 frequency alternatives: never; less than once a week; once a week; 2–4 days a week; 5–6 days a week; once a day, every day; and every day, more than once a day. The vitamin D content of the foods was calculated using the Finnish Food Composition Database (Fineli, version 2013, National Institute for Health and Welfare). The use of vitamin D supplements was inquired with 4 frequency alternatives: never; once a week or less; 2–5 days a week; and daily or almost daily. Time spent outdoors was reported in hours per day before and after school or on the weekend (<1 h, 1 h, 2 h, 3 h, 4 h, or >5 h).

Information on allergic symptoms and diagnosis of allergic diseases was obtained from a modified International Study of Asthma and Allergies in Childhood (ISAAC)-based questionnaire [12]. The parents were asked if the child had ever had allergies, asthma, atopic eczema, or allergic rhinitis diagnosed by a doctor. Regarding cow's milk allergy and wheat allergy, the parents were also asked to report whether the child still developed symptoms from the food in question.

Height (cm) and weight (kg) were measured, and the BMI was calculated and divided into BMI-for-age weight status categories (underweight, normal, overweight, obese) according to the Centers for Disease Control and Prevention (CDC) percentiles, as described in the ISCOLE protocol [10].

Vitamin D Status

Blood samples were collected from 171 children participating in the study between January 29th and June 3rd, 2013. Serum 25-hydroxyvitamin D (25[OH]D) levels were assayed with an immunochemiluminescence assay, which measures 25(OH)D₂ level and 25(OH)D₃ level as the total 25(OH)D level (Roche Diagnostics). All blood measurements were analyzed in the laboratory of Helsinki University Hospital.

Statistical Analyses

Due to the non-normal distribution of serum 25(OH)D levels, the variables were log-transformed. χ^2 test, independent sample *t* test, and analysis of variance (ANOVA) were used for group comparisons. Associations were tested with Pearson or Spearman correlation and further analyzed with multivariate linear regression analysis adjusted for potential confounders. The confounders were selected based on the associations found in the present study and in the previous literature. All statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 22).

Results

Subject Characteristics

The characteristics of the study subjects and the prevalence of allergic diseases are presented in Table 1. Altogether, 171 children participated in the study. The majority (94%) of them were of Caucasian origin. Atopic eczema, allergic rhinitis, and food allergy were the most frequently observed allergic diseases. The most commonly reported food allergy was cow's milk allergy. As many as 13% of the children had been diagnosed with cow's milk allergy sometime in earlier childhood, but the majority of them (81%) did not get allergic symptoms from milk anymore. The other most frequently reported food allergies were to various raw fruits (11%) and raw vegetables (9%), egg (7%), and peanut (5%).

Vitamin D Intake

In our study sample, 108/171 (63%) children reported to drink milk more than once a day. Eating fish according to recommendations (2–4 times a week) was reported by 46/171 (27%) of the subjects. Based on the frequency of milk product and fish consumption and use of vitamin D supplementation, we calculated that roughly 57% of the daily vitamin D dose was obtained from the use of vitamin D supplement, 27% from milk products, and 16% from fish. Daily or almost daily use of vitamin D supplement was observed in 60% of the children. Altogether, 13% of the children reported no regular use of vitamin D-containing supplements (Table 1).

In children with a history of cow's milk allergy, the frequency of milk consumption was significantly lower compared to that of children without milk allergy. Only 7/21 (33%) of the children with a previously diagnosed milk allergy reported to drink milk more than once a day compared to 95/139 (68%) of the children with no such history ($p = 0.004$). Correspondingly, 5/21 (24%) of the children allergic to milk did not drink milk at all in comparison to 5/139 (4%) of those without milk allergy ($p = 0.004$). The consumption of fish, cheese, and other milk products was similar in both groups. The majority of children in both groups reported the use of daily vitamin D supplementation (71% of those with a history of milk allergy, and 58% of those without milk allergy, $p = 0.720$). The frequency of milk consumption did not differ between non-Caucasian and Caucasian children or according to gender ($p = 0.529$ and $p = 0.300$, respectively).

Table 1. Characteristics of the 171 schoolchildren in relation to serum 25(OH)D status

Characteristics	n (%)	25(OH)D $\pm$ SD, nmol/L	p value
Gender			
Boys	84 (49)	78.4 $\pm$ 20.8	<0.001
Girls	87 (51)	67.1 $\pm$ 21.4	
Ethnicity			
Caucasian	151 (94)	74.6 $\pm$ 21.6	0.003
Non-Caucasian	10 (6)	56.0 $\pm$ 18.2	
BMI			
Underweight/normal	139 (81)	73.9 $\pm$ 22.4	0.155
Overweight/obese	32 (19)	67.2 $\pm$ 18.0	
Parental education			
High school or less	43 (27)	72.2 $\pm$ 22.9	0.828
College degree	39 (24)	73.6 $\pm$ 20.2	
Bachelor's/postgraduate degree	79 (49)	74.0 $\pm$ 22.3	
Vitamin D supplement use			
No	20 (13)	59.1 $\pm$ 16.6	0.004
Once a week or less	19 (12)	69.7 $\pm$ 15.5	
2–5 days a week	24 (15)	75.0 $\pm$ 17.8	
Yes, daily or almost daily	95 (60)	77.1 $\pm$ 23.4	
Season of blood sampling			
Winter (January, February)	43 (25)	70.1 $\pm$ 23.3	0.537
Spring (March, April)	75 (44)	73.0 $\pm$ 21.3	
Summer (May, June)	53 (31)	74.2 $\pm$ 21.5	
Atopic eczema			
Yes	33 (21)	78.3 $\pm$ 22.7	0.126
No	127 (79)	72.3 $\pm$ 21.5	
Allergic rhinitis			
Yes	32 (20)	70.9 $\pm$ 18.1	0.585
No	128 (80)	74.2 $\pm$ 22.7	
Cow's milk allergy			
Yes	21 (13)	60.5 $\pm$ 12.6	0.004
No	139 (87)	75.5 $\pm$ 22.3	
Wheat allergy			
Yes	5 (3)	65.0 $\pm$ 9.8	0.484
No	153 (97)	74.0 $\pm$ 22.0	
Other food allergy			
Yes	30 (19)	74.0 $\pm$ 20.9	0.775
No	130 (81)	73.4 $\pm$ 22.1	
Other allergy			
Yes	18 (11)	69.0 $\pm$ 20.4	0.381
No	142 (89)	74.1 $\pm$ 22.0	
Asthma			
Yes	12 (8)	72.6 $\pm$ 20.9	0.114
No	148 (92)	84.8 $\pm$ 30.4	

Serum 25(OH)D levels were logarithmically transformed for analysis. Differences between means were tested by independent sample *t* tests or ANOVA (for more than two groups of cases).

Missing values: ethnicity – 6%, parental education – 6%, vitamin D supplement use – 8%, wheat allergy – 1%.

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; SD, standard deviation.

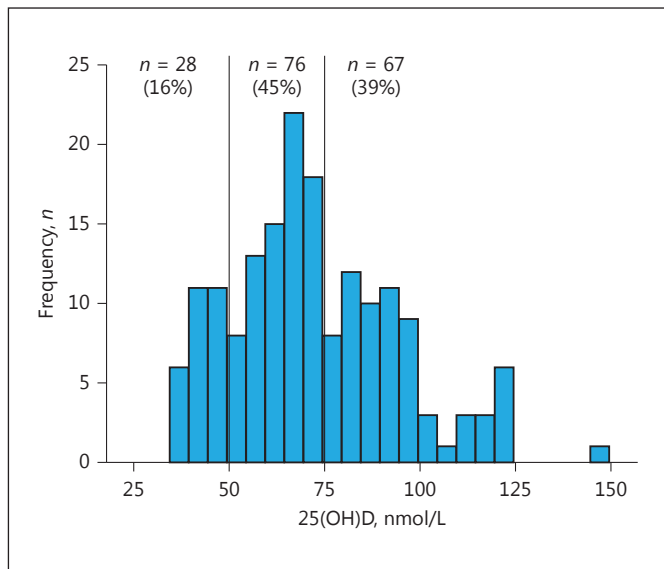


Fig. 2. Distribution of serum 25(OH)D levels among Finnish 10-year-olds ($n = 171$).

Vitamin D Status

Serum 25(OH)D levels were measured for 171 subjects between January and June. There was no seasonal variation in 25(OH)D levels. The mean serum 25(OH)D level was 72.6 ± 21.8 nmol/L (range 37–147 nmol/L). Vitamin D insufficiency (<50 nmol/L) was observed in 16% of the study population. None of the children had vitamin D deficiency (<30 nmol/L). In contrast, 39% of the children had serum 25(OH)D levels >75 nmol/L, only one child having a 25(OH)D level >125 nmol/L (Fig. 2).

Girls had lower mean serum 25(OH)D levels compared to boys as did children of non-Caucasian origin compared to Caucasian children (Fig. 3). Boys spent significantly more time outdoors after school than girls (<1 h: 12% of boys vs. 25% of girls; 4 h: 15% of boys vs. 3% of girls, $p = 0.007$). The BMI showed a negative correlation with serum 25(OH)D levels ($r = -0.161$, $p = 0.036$), but the mean serum 25(OH)D level did not differ between children with normal weight and overweight/obese children. The use of vitamin D supplement also correlated with serum 25(OH)D concentration ($r = 0.262$, $p = 0.001$), and daily users of vitamin D supplement had significantly higher serum 25(OH)D levels than non-users (Table 1).

The mean serum 25(OH)D level did not differ in subjects with previously diagnosed allergic rhinitis, atopic eczema, wheat allergy, or asthma from the serum 25(OH)D

level in those without these diagnoses (Table 1). However, in children with a history of cow's milk allergy, the mean serum 25(OH)D level was significantly lower than in subjects without milk allergy (Table 1, Fig. 3).

Major Determinants of Vitamin D Status

We evaluated the major determinants of vitamin D status by multivariate linear regression analysis. Female gender, a non-Caucasian ethnic background, the use of vitamin D supplements once a week or less (or never), and having been diagnosed with cow's milk allergy were associated with lower vitamin D levels (Table 2). BMI, the frequency of milk and fish consumption, the season when the sample was taken, parental education, or time spent outdoors were not associated with vitamin D status.

Discussion

Our study on 171 ten-year-olds shows that the vitamin D status of Finnish school-aged children is sufficient, as most children had a serum 25(OH)D level >50 nmol/L. Lower vitamin D levels were associated with female gender, non-Finnish ethnicity, a lack of vitamin D supplementation, and a history of diagnosed cow's milk allergy. Our novel finding is that even a cow's milk allergy without symptoms is reflected in a lower vitamin D status at school age.

In previous Nordic studies, the prevalence of vitamin D insufficiency was 71% in 7- to 19-year-old Finnish children and 82% in 13-year-olds in Sweden [13, 14]. In line with our findings, two recent Finnish studies showed increased 25(OH)D concentrations among 2- to 12-year-olds in 2003–2006 and 6- to 8-year-olds in 2007–2009 after the fortification of milk products with vitamin D began in 2003 [15, 16]. In their study, Mäkinen et al. [15] reported that the frequency of vitamin D insufficiency in Finnish children almost halved from 69.9% in 1998–2002 to 37.3% in 2003–2006. However, these studies were conducted before the increased fortification of fluid milk products and fat spreads in 2010, and before the 2011 recommendation of year-round use of vitamin D supplements in all children, actions which have further improved vitamin D status.

To our knowledge, Finland is the only country worldwide where daily year-round vitamin D supplementation is recommended to children under 18 years of age [17]. Before the current recommendation, only 21% of all 6-year-old children used vitamin D supplements in Finland

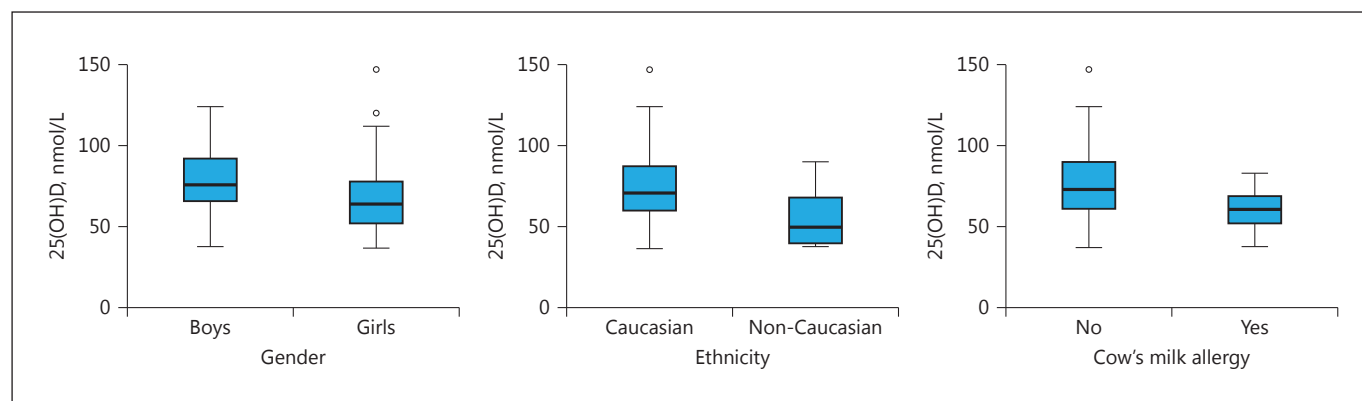


Fig. 3. Comparison of serum 25(OH)D levels according to gender, ethnicity, and history of cow's milk allergy. There is a significant difference in the serum 25(OH)D levels between boys and girls ($p < 0.001$), Caucasian and non-Caucasian children ($p = 0.003$), and children without and with a history of cow's milk allergy ($p = 0.004$).

Table 2. Determinants of vitamin D status in Finnish 10-year-olds ($n = 171$); multivariate linear regression analyses for serum 25(OH)D levels

Variable	Beta coefficient	95% CI	<i>p</i> value
Gender (girls vs. boys)	-0.133	-0.219, -0.048	0.002
Ethnicity (non-Caucasian vs. Caucasian)	-0.196	-0.382, -0.010	0.039
BMI	-0.010	-0.024, 0.005	0.183
Cow's milk allergy (present vs. no milk allergy)	-0.187	-0.313, -0.061	0.004
Use of vitamin D supplement (2–7 times a week vs. no or $\leq$ once a week)	0.140	0.039, 0.241	0.007

Serum 25(OH)D levels were logarithmically transformed for analysis. The model included all covariates presented in the Table. $R^2 = 0.210$, $F = 8.069$.

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval.

[18]. Our study is the first to indicate that after changing vitamin D supplement recommendations, the use of supplements has increased in children. Our results further indicate that the national recommendation of year-round use of vitamin D supplements and the fortification of foods with vitamin D can be effective strategies to improve the vitamin D status at the population level. Nevertheless, we observed that 40% of the children in our study did not follow the supplementation recommendation. Similar to other studies, a lack of vitamin D supplementation was associated with lower vitamin D levels [19]. This indicates that, to ensure sufficient intake of vitamin D, special attention should be paid to this subgroup of children. The reason for not using vitamin D supplementation can be related to e.g. parental education and other socioeconomic factors [20].

Cow's milk allergy is one of the most common food allergies affecting children [21]. The prevalence of self-reported lifetime milk allergy in Europe has been reported to be 6.0% [8]. In our study the prevalence of ever diagnosed milk allergy was as high as 13%; however, a majority of the children had developed tolerance to milk. A limitation of this study is that the information on allergy diagnosis relied on parents' reports. Milk hypersensitivity can also be caused by other factors such as lactose intolerance [22]. With the development of Finnish Current Care Guidelines on Food Allergy, the diagnostic criteria for food allergy have changed [23]. Previously, positive reactions to specific immunoglobulin E tests could lead to an allergy diagnosis and the children were put on elimination diets more easily, whereas currently the diagnosis relies on elimination-provocation tests [24]. These reasons

can also explain the high prevalence of milk allergy observed in this study.

There are a limited number of studies evaluating the nutrient status of children allergic to milk, but in a sample of 2- to 17-year-old US children, cow's milk allergy was associated with decreased growth and a trend toward lower vitamin D intake [25]. In our study, milk allergy was associated with a lower vitamin D status. Children once diagnosed with milk allergy during childhood consumed less dairy products, even though most of them no longer had allergic symptoms. This suggests that restrictive dietary habits established in early childhood may track into later life [26, 27]. In our study, the majority of the children with milk allergy took vitamin D supplements, and the frequency of their fish consumption did not differ from that of the other children, but still their 25(OH)D levels were significantly lower. Our finding is similar to that of a recent study on 6- to 8-year-old Finnish children, where the strongest determinant of vitamin D status was consumption of milk, and it implies that vitamin D obtained from fortified dairy products is an effective means of improving the vitamin D status [16]. Those children who do not regularly consume fortified milk products are at risk of a lower vitamin D status and might benefit from higher vitamin D supplementation. However, the number of children with a milk allergy included in our study was relatively small and limits our ability to draw strong conclusions. Furthermore, the lower vitamin D status of children allergic to milk may also be related to a lower calcium intake, as calcium intake may affect 25(OH)D concentration [28]. Children on a milk-elimination diet face an increased risk of suboptimal intake of calcium [29].

Other factors associated with a lower vitamin D status were female gender and a non-Caucasian ethnicity. Dark skin pigmentation may be a risk factor for vitamin D deficiency [30]. Also, there may be a genetic variation in vitamin D-binding protein levels in different ethnic groups. Female gender has also been associated with a lower vitamin D status in other studies [19, 31]. This could be due to the finding that girls spend less time outdoors than boys, as was also seen in our study [32]. However, in our cohort, this is an unlikely explanation, as most of the 25(OH)D measurements were performed during the season when sunlight exposure outdoors is limited. Biological differences may play a role. Girls have an increased fat mass compared to boys, and this may increase the proportion of vitamin D stored in the adipose tissue, at the expense of circulating levels of 25(OH)D [33].

We recognize some limitations of our study. This was a cross-sectional study with a relatively small number of

subjects with measured 25(OH)D levels. Furthermore, we could not calculate accurate estimates for vitamin D intake due to the food frequency questionnaire we used, which lacked information on consumed portion sizes and the use of vitamin D-fortified fat spreads. Further, no parathormone or vitamin D-binding protein measurements were available.

Conclusion

The overall vitamin D status of Finnish school-aged children is sufficient after the increased vitamin D fortification of dairy products and the initiation of the national guidelines of daily year-round vitamin D supplementation to all children. This indicates that public health strategies are an important means to increase the vitamin D status in children. A lower vitamin D status was associated with female gender, a non-Caucasian ethnicity, and a lack of regular vitamin D supplementation. The vitamin D status was significantly lower in children with a history of cow's milk allergy, indicating that restricting the diet of an allergic child may have long-term consequences on dietary habits and subsequently on vitamin D status in later childhood.

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Disclosure Statement

The authors declare no conflicts of interest.

Author contributions are as follows: J.R., M.E., and M.F. participated in the study design, data collection, and analysis of the data. J.R. performed the statistical analysis and drafted the article. M.E. and O.M. revised the manuscript. All authors critically reviewed the manuscript and approved the final version and submission of the manuscript.

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