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Original Article

Effect of Nutritional Status on Vitamin K2 in Children with Picky Eating Habits: A Retrospective Study

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Abstract ***Purpose:*** This study aimed to analyse the effect that nutritional status has on vitamin K2 (VK2) in picky children. ***Methods:*** This was a retrospective study of children aged <10 years who were picky eaters without organic diseases and visited the clinical nutrition clinic at a Chinese tertiary children's hospital between January 2021 and October 2021. We first analysed the influencing factors of VK2 deficiency, then compared the nutritional status when VK2 concentration were categorised into three different groups according to their severity. ***Results:*** The correlation analysis yielded the correlation coefficients of weight-for-age z-score (WAZ), height-for-age z-score (HAZ) and body mass index-for-age z-score (BAZ) as 0.306 (p=0.009), 0.129 (p=0.283), and 0.085 (p=0.478), respectively. The multiple comparison results revealed significant differences in terms of HAZ (p=0.007) and WAZ (p=0.024). ***Conclusion:*** The nutritional status of children was worse when VK2 is severely deficient. WAZ was positively correlated with VK2 concentration.

Key words *Body mass index-for-age z-score; Height-for-age z-score; Picky eating, Vitamin K2; Weight-for-age z-score*

Introduction

Picky eating is a common behaviour in early childhood and is also known as being fussy, faddy, choosy, or selective. The prevalence of picky eating varies widely in different areas, with 5.6% in 4-year-old in the Netherlands and up to 50% in 2-year-old in the United States.[1] It has been shown that age and economy may affect the prevalence of picky eating. Children who are picky eaters are prone to being underweight and having stunted growth.[2,3] A lower intake of vegetables or meat in picky eaters can cause micronutrient and vitamin deficiencies.[4,5] Vitamin A (VA) and vitamin D (VD) deficiencies are the two most common nutrient deficiencies worldwide and are linked to malnutrition. Adequate amounts of these essential vitamins can be obtained through dietary sources or supplements.

Vitamin K (VK) is an essential fat-soluble compound, which was identified as the key factor for blood coagulation in 1936 and was first discovered by a Danish biochemist Hendrik Dam.[6] In recent years, given the interest in extrahepatic effects of VK beyond coagulation, there has been growing research in this area. An increasing number of studies show the different roles of vitamin K1 (VK1) and vitamin K2 (VK2).[7] All forms of VK exert their biological functions as cofactors of gamma-glutamyl carboxylase.[8] VK isomers exist in the form of phylloquinone (VK1) and menaquinone (VK2) in nature. Menaquinone (MK) exists in multiple structures. It has been shown that all vitamin K homologues can be

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converted to MK-4 *in vivo*.[9] Studies have shown that VK2, as a cofactor for osteocalcin, regulates bone formation and mineralisation to improve the quality of bones[10-13] and can improve insulin sensitivity to stimulate insulin secretion.[14,15] Furthermore, VK2 acts as a cofactor for the matrix gamma-carboxyglutamic acid (Gla) protein, an inhibitor of vascular calcification, which can reduce the risk of cardiovascular disease.[16,17] VK2 acts as an antioxidant, which can be associated with a reduced risk of cancer[18,19] and may prevent the cytokine storm observed in coronavirus disease.[20] The Gla protein family includes 17 proteins. Apart from osteocalcin and matrix Gla proteins, the physiological functions of other VK2-dependent proteins are not yet fully understood.[21] VK2 confers many health benefits; however, the relationship between malnutrition and VK2 deficiencies has not been reported. In the past, because of the limitation of detection technology, the results of VK2 concentration in serum are often questionable. Studies have shown that mass spectrometry is a rapid and accurate method to measure the concentration of vitamin K.[22,23]

Therefore, the purpose of this study was to investigate the prevalence of fat-soluble vitamin deficiencies and to analyse the effect of nutritional status on VK2 concentration in children with picky eating habits. Based upon this study, investigators expected to raise awareness of the VK2 deficiencies in picky eaters and provide a reference for VK2 supplementation in this paediatric population.

Materials and Methods

Study Population and Design

All children younger than 10 years who were picky eaters were randomly selected from paediatric patients who visited the clinical nutrition clinic at the Children's Hospital of Zhejiang University School of Medicine between January 2021 and October 2021. The definitions of picky eating used in this research settings: limited number of food items in the diet, unwillingness to try new foods, limited intake of vegetables and some other food groups, strong food preferences (likes/dislikes), and special preparation of foods required.[1] All the included patients underwent a complete fat-soluble vitamin test. Since this was a study of the effect of nutritional status on VK2 in children with picky eating habits and without organic diseases, children with digestive system diseases, congenital heart disease, nervous system diseases, endocrine diseases and food allergies were excluded.

All procedures performed in this study involving human participants followed the ethical standards of the institutional research committee and complied with the Helsinki Declaration. This study was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine (no.2022-IRB-245), and the requirement for informed consent was waived due to the retrospective study design.

Data Collection

Anthropometric Data Collection

The weight and height (of children aged ≥2 years) or length (of children aged <2 years) measurements of all the patients were obtained preoperatively per unit protocols. A digital weighing scale with a height rod was used for the measurement of the weights and heights of children aged ≥2 years, whereas an infant weighing scale and a length mat were used for the measurement of children aged <2 years. Measurements of nutritional status included weight-for-age z-score (WAZ), height-for-age z-score (HAZ), and body mass index-for-age z-score (BAZ), which were derived from the weight and height measurements using the World Health Organization Anthro and AnthroPlus software. We defined WAZ, HAZ, or BAZ ≤-2 as malnutrition and >-2 as normal.

We measured vitamin K by a newly developed liquid-chromatography tandem mass-spectrometry method.[22] The criteria for Vitamins E (VE), D, A, and K deficiency were set according to the reference values provided by the laboratory. Prior to analysis, nondetectable concentration values of VK2 were replaced with an insignificant nonzero value below the limits of detection.

Statistical Methods

The data did not conform to a normal distribution; therefore, continuous and categorical variables are expressed as medians with interquartile ranges (IQRs) and as frequencies with percentages, respectively. Spearman's rank correlation coefficient was used to analyse the correlation between WAZ, HAZ, BAZ, and the VK2 concentration. The chi-squared distribution or Fisher's exact test was used to analyse categorical variables and the Kruskal-Wallis test for continuous variables. Pairwise comparisons p-values were Bonferroni-corrected (significance was evaluated with a Bonferroni-corrected p-value of 0.05). All analyses were performed using SPSS Statistics (version 26; IBM). P values <0.05 were considered statistically significant.

Results

Study Population and Nutritional Statuses of the Patients

Of the 200 children screened during the study period, 44 [62%] boys and 27 [38%] girls met the inclusion criteria and were included in this study (Figure 1). The median age of the patients was 47 (IQR, 20.00-67.50) months. The median WAZ, HAZ, and BAZ levels of the entire cohort were 0.94 (IQR -1.58 to -0.43), -1.45 (2.01 to -0.67), and -1.33 (-2.10 to -0.50), respectively. Eighteen (25.35%) patients had a WAZ ≤-2, 11 (15.49%) had an HAZ ≤-2, and 21 (29.5%) had a BAZ ≤-2. The median concentration of Vitamins A, D, E, K1, and K2 were 0.30 (IQR, 0.26-0.35) mg/L, 28.90 (IQR, 23.25-36.90) ng/mL, 9.85 (IQR, 8.10-11.75) mg/L, 0.61 (IQR, 0.31-1.86) ng/mL, and 0.12 (IQR, 0.06-0.18) ng/mL, respectively, whereas the deficiency rates were 47.4%, 15.49%, 0%, 1.4%, and 39.43%, respectively (Table 1).

Analysis of Nutritional Status and VK2

We compared the data collected for the VK2 deficiency group and VK2 normal group. The results showed that there was significant difference between pre-school children (≤36 months) and school children (>36 months) (p=0.040). There were no significant differences in sex, VA concentration, VD concentration, WAZ, HAZ, and BAZ (Table 1).

We categorised the levels of VK2 into normal (≥0.1), mild (≥0.05 to <0.1), and severe (<0.05) deficiency groups. The results showed that there were significant differences in HAZ (p=0.007) and WAZ (p=0.024) between the groups. There were no significant differences in age, sex, VA concentration, VD concentration, and BAZ (Table 2). There were significant differences in WAZ and HAZ between the severe deficiency group and the two other groups. There were no significant differences in WAZ, HAZ, and BAZ between the mild deficiency and normal groups (Figure 2). The correlation coefficients of WAZ, HAZ, and BAZ from the correlation analysis were 0.306 (p=0.009), 0.129 (p=0.283), and 0.085 (p=0.478), respectively (Figure 3).

Discussion

This study was conducted to investigate the effect of nutritional status on VK2 in children with picky eating habits. In this study, 25.35% of the children who were picky eaters were underweight, 15.49% were stunted, and 29.58% were wasted. Nasreddine et al. investigated the nutritional statuses of children aged 0-12 years in the Eastern Mediterranean region and found that 7.3-9.3% of the children in the region showed stunting, 1.1-11.8% showed wasting, and 1.6-5.3% were underweight.[24] These results are lower than those of the present study, suggesting that malnutrition can easily occur in picky eaters. In addition, the rate of VA, VD, and VK2 deficiency among picky eaters in the present study was 47.4%, 15.49%, and 39.43%, respectively. In our study, the VD deficiency rate was improved compared with previous data from 2001 to 2004 in the United States.[25] However, the deficiency rate of VA was still very high. A systematic review and meta-analysis of VA deficiencies in preschool children in Ethiopia showed that the prevalence of subclinical VA deficiencies decreased by 55.7% (95% CI: 39.8%-71.6%) from 1990 to 2004 and a further 28.3% (95% CI: 9.8%-46.7%) from 2005 to 2019; however, these results were not statistically significant.[26] Despite considerable efforts being made to control VA deficiencies in recent years, both clinical and subclinical VA deficiencies remain a major public health problem worldwide. The prevalence of VK2 deficiency was surpassed only by that of vitamin A deficiencies in the present study. Due to limitations in technology, there has been no report on VK2 deficiency rates in the past. However, in this study, we used tandem mass spectrometry, which has been proven to be a rapid and accurate method for measuring VK2.[22,23] We should

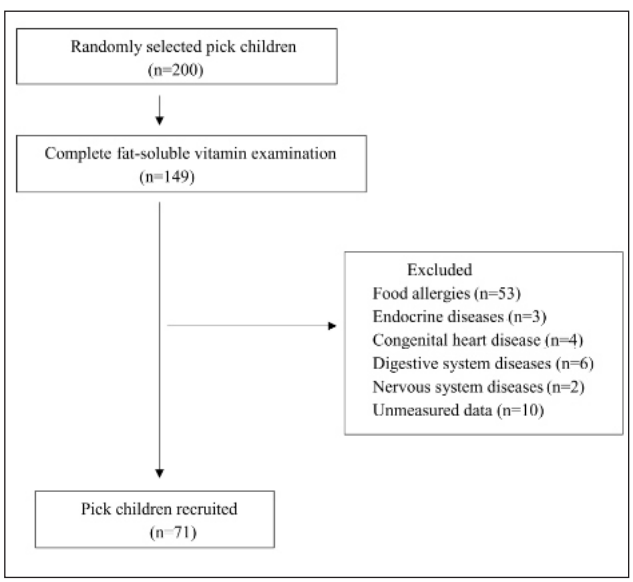

Figure 1. Study design.

Table 1 Characteristics of the study variables

Characteristics	Overall (n=71)	VK2 ≥0.1 (ng/mL) (n=43)	VK2 <0.1 (ng/mL) (n=28)	*P* value
	Median (IQR Q1,Q3) / N (%)			
Age (month)	47 (20.00, 67.50)			
≤36	30 (42.25%)	14 (32.6%)	16 (57.1%)	0.04
>36	41 (57.75%)	29 (67.4%)	12 (42.9%)	
Sex				
Boys	44 (62.00%)	27 (62.8%)	17 (60.7%)	0.86
Girls	27 (38.00%)	16 (37.2%)	11 (39.3%)	
VK2 (ng/mL)	0.12 (0.06, 0.18)			
<0.1	28 (39.43%)			
VK1 (ng/mL)	0.61 (0.31, 1.86)			
<0.1	1 (1.40%)			
VD (ng/mL)	28.90 (23.25, 36.90)	27.60 (21.25, 36.35)	25.6 (29.75, 37.62)	0.295
<30	11(15.49%)			
VA (mg/L)	0.30 (0.26, 0.35）	0.30 (0.27, 0.36)	0.30 (0.26, 0.33)	0.361
<0.3	34 (47.4%)			
VE (mg/L)	9.85 (8.10-11.75)			
<0.3	0%			
HAZ	-1.45 (-2.01, -0.67)	-0.67 (-1.41, -0.34)	-1.16 (-1.87, -0.51)	0.134
≤ -2	11 (15.49%)			
WAZ	-0.94 (-1.58, -0.43)	-1.51 (-2.01, -0.65)	-1.42 (-1.96, -0.74)	0.764
≤ -2	18（25.35%）			
BAZ	-1.33 (-2.10, -0.50)	-1.33 (-2.26, -0.41)	-1.41 (-1.78, -0.72)	0.477
≤ -2	21 (29.58%)			

Abbreviations: VK2, Vitamin K2; VK1, Vitamin K1; VA, Vitamin A; VD, Vitamin D; VE, Vitamin E; WAZ, Weight-For-Age Z-Score; HAZ, Height -For-Age Z-Score; BAZ, Body Mass Index-For-Age Z-Score

Table 2 Comparison between vitamin K2 different groups

Characteristics	VK2 ≥0.1 (ng/mL) (n=43)	VK2=0.05-0.09 (ng/mL) (n=19)	VK2 <0.05 (ng/mL) (n=9)	*P* value
	Median (IQR Q1, Q3) / N (%)			
Age (month)	47 (20.00, 67.50)			
≤36	14 (32.6%)	12 (63.2%)	4 (44.4%)	0.86
>36	29 (67.4%)	7 (36.8%)	5 (55.6%)	
Sex				
Boys	27 (62.8%)	11 (57.9%)	6 (66.7%)	0.939
Girls	16 (37.2%)	8 (42.1%)	3 (33.3%)	
VD (ng/mL)	27.6 (20.40, 36.70)	31.40 (27.80, 38.30)	26.9 (22.25, 38.00)	0.440
VA (mg/L)	0.30 (0.26, 0.36）	0.30 (0.24, 0.33)	0.33 (0.27, 0.37)	0.285
HAZ	-0.67 (-1.44, -0.29)	-1.49 (-0.96, -0.47)	-2.22 (-2.39, -1.04)	0.007
WAZ	-1.51 (-2.02, -0.56)	-1.07 (-1.68, -0.04)	-2.13 (-2.61, -1.62)	0.024
BAZ	-1.33 (-2.29, -0.32)	-1.11 (-1.55, 0.23)	-1.92 (-2.29, -1.07)	0.074

Abbreviations: VA, Vitamin A; VD, Vitamin D; VE, Vitamin E; WAZ, Weight-For-Age Z-Score; HAZ, Height -For-Age Z-Score; BAZ, Body Mass Index-For-Age Z-Score

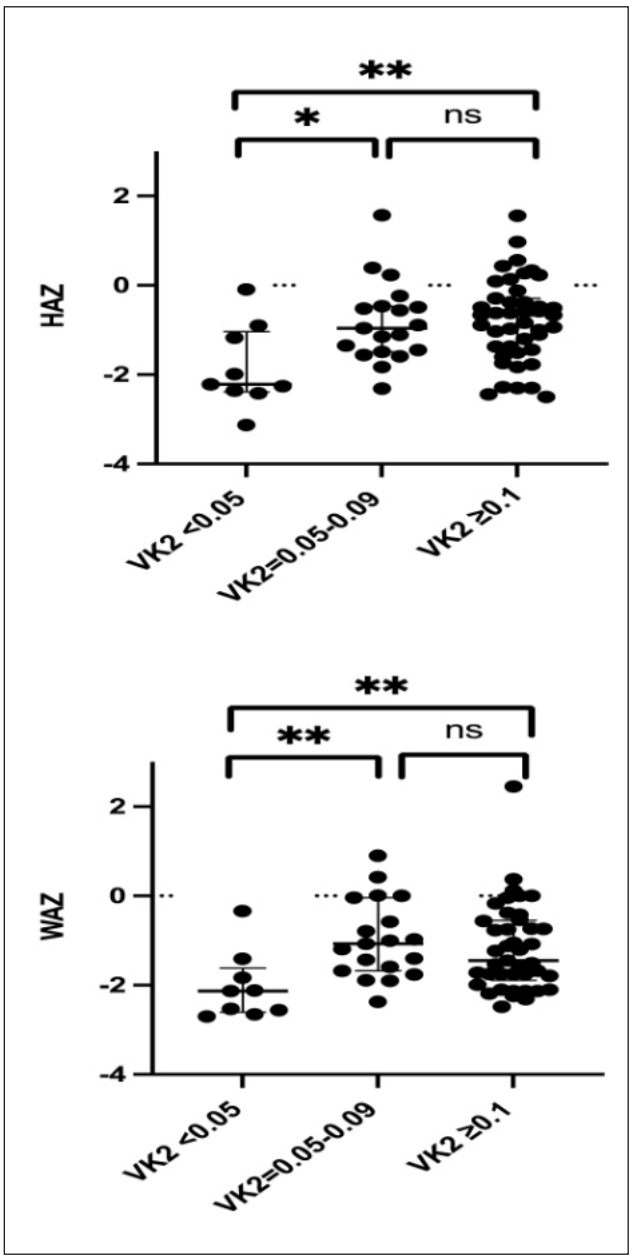

Figure 2. Pairwise comparison of WAZ and HAZ among VK2 different groups. P values <0.05 is meaned by *, P values <0.01 is meaned by **, P values ≥0.05 is meaned by NS.

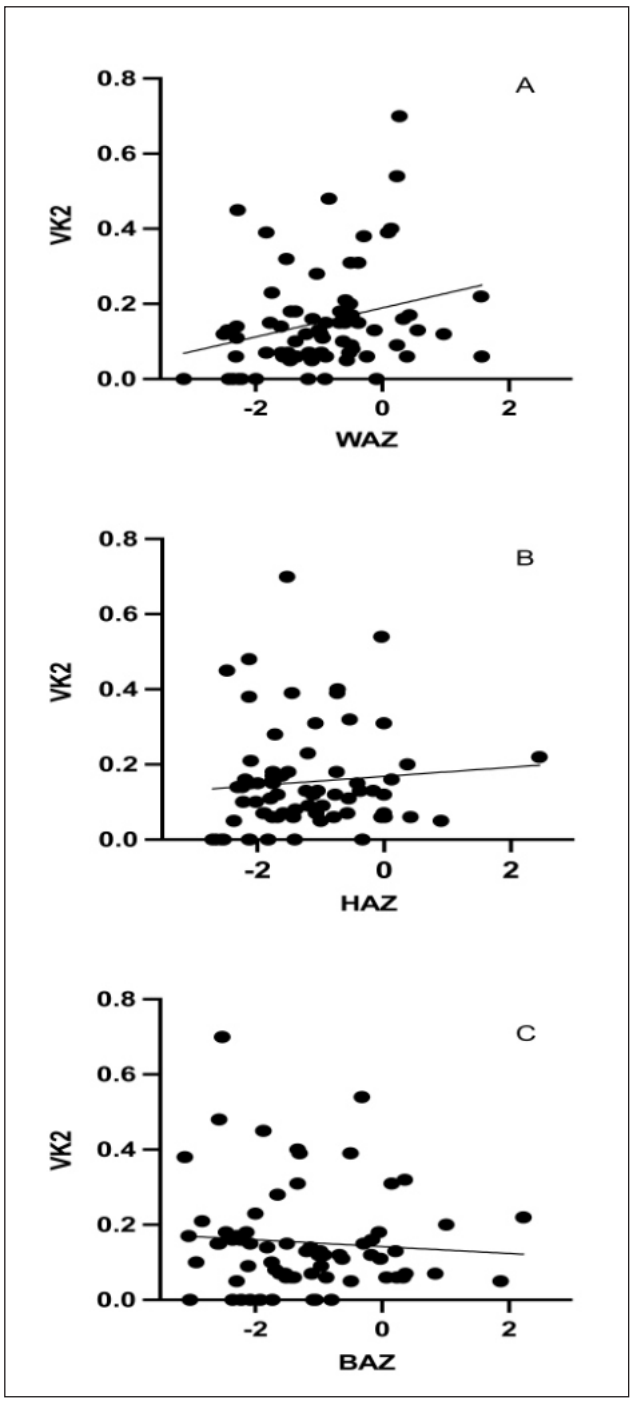

Figure 3. Correlation of VK2 concentration with WAZ, HAZ and BAZ. (A) Correlation between WAZ and VK2 concentration (r=0.306, p=0.009). (B) Correlation between HAZ and VK2 concentration (r=0.129, p=0.283). (C) Correlation between BAZ and vitamin VK2 concentration (r=0.085, p=0.478).

raise awareness of the rate of VK2 deficiency in the future. In the present study, there were significant difference between pre-school children (≤36 months) and school children (>36 months) (p=0.040). We found that pre-school children had a greater likelihood of VK2 deficiency than school children. Chilman et al reported a review on picky children, which showed that extrinsic features which appear to increase the likelihood of picky eating are authoritative parenting, rewards for eating, and pressuring the child to eat.[27] Therefore, we not only need to pay attention to the dietary intake and nutritional status of pre-school children, but also need to pay attention to the effect of parental discipline. However, there was no significant decline in WAZ, HAZ, and BAZ (p=0.764, p=0.134, and p=0.477, respectively) in children with VK2 deficiency. Children who are picky eaters are prone to being underweight and having stunted growth.[2,3] A cross-sectional study analysed the growth and development of Chinese pre-schoolers with picky eating behaviour and reported lower energy and protein intake among picky eaters.[28] This may explain why the effect of nutritional status on VK2 was not observed.

Interestingly, when categorising VK2 deficiencies into three groups, we observed significant differences in HAZ and WAZ between the severe deficiency group and the other groups (the normal and mild groups). VK exists as phylloquinone (VK1) and menaquinone (VK2). VK1 is mainly found in green leafy vegetables, whereas VK2 is mainly produced by bacteria. Thus, a high amount of VK2 is found in fermented foods and the meat of certain farm animals.[29,30] Food sources containing the most abundant long-chain MKs are animal liver and foods prepared with a bacterial fermentation stage such as cheeses (mainly MK-8 and MK-9) and natto (MK-7). The most common subtype in humans is the short-chain MK-4, which is not commonly synthesised by bacteria but can be synthesised *in vivo* given a suitable naphthoquinone precursor such as menadione or phylloquinone by invertebrates and vertebrates.[9] It can be seen that because children who are picky eaters consume a smaller variety of foods, the more likely they are to become deficient in VK2. However, weight loss in picky eaters is often caused by a decrease in food intake. The decrease in food intake tends to lead to insufficient energy intake, which induces the decomposition of fat to meet the energy demand of the body.[31] Fat-soluble vitamins are absorbed in the intestines, which involves a series of metabolic processes and requires the presence of fat.[32] Thus, children who are underweight and picky about what they eat are more likely to experience a severe VK2 deficiency. Long-term inadequate oral intake will affect the growth in height.

In recent years, an increasing number of studies have shown that VK2 can improve bone health.[10-13] All VK forms exert their biological functions as cofactors of gamma-glutamyl carboxylase, an enzyme that allows for the conversion of the amino acid, glutamic acid, to Gla residues in certain proteins. These proteins are known as 'vitamin K-dependent proteins' and can integrate calcium through their Gla residues once activated.[8] This proves that VK2 deficiency does not favour good bone health and may lead to a poor growth rate in height. Moreover, previous studies have shown that osteocalcin can also regulate the metabolism of glucose and fat through adiponectin produced by fat secretion.[14] Low adiponectin levels in underweight children can cause metabolic disorders and are not beneficial to energy balance and weight gain. However, a number of studies suggest this might be insignificant.[33-35] This disparity may be attributed to methodological differences in existing studies, such as detection technology, bioavailability, and distribution of different isomers of VK2. In addition, the Gla protein family includes 17 proteins with physiological functions not yet fully understood, except for osteocalcin and matrix Gla proteins.[21] Therefore, the mechanism underlying the action of VK2 in the human body requires further study. Further analysis in our study also confirmed that WAZ was positively correlated with VK2 concentration (r=0.306, p=0.009). However, HAZ was not correlated with VK2 concentration (r=0.129, p=0.283). This may be because height is a complex trait that is determined by a combination of genetic and environmental influences. The studies on twins have indicated that the heritability of height is high (>80%), suggesting that genetic variation is the main determinant of stature.[36]

This study had some limitations. This was a cross-sectional study, a design with its own inherent limitations. First, the retrospective nature of our research did not allow for the adoption of other nutritional parameters such as serum biomarkers (zinc, iron, haemoglobin, pre-albumin, or albumin). These data may cause confusion on our research results due to its association with growth and nutrition assessment. Second, the sample size of this study was small. Third, dietary evaluation of the children was not conducted. Fourth, we included only children who were picky eaters and may not be able to extend our results to other populations.

Conclusion

In summary, the nutritional status of picky eaters should be frequently monitored and the necessary fat-soluble vitamin screenings should be made readily available, especially pre-school children. The nutritional status of children is worse when VK2 is severely deficient. We should raise awareness of the rate of VK2 deficiency in the future. Furthermore, WAZ is positively correlated with Vit K2 concentration. In the future, we can do more research on the relationship between VK2, malnutrition, and intestinal flora to provide more evidence for vitamin K2 supplementation.

Ethical Statement

This study was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine (no.2022-IRB-245). and strictly followed the institution's ethical guidelines.

Declaration of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Informed consent was not obtained because the study was conducted retrospectively.

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