

Effect of Vitamin D supplementation and outdoor activity on serum 25-Hydroxyvitamin D among children in North China: an observational study

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Abstract

Background

Living at high latitudes is one of the risk factors for vitamin D deficiency in children. However, evidence on vitamin D improvement for this pediatric population to date is limited. This study aims at evaluating the effect of different supplementation methods and outdoor activity time on the vitamin D status of children in North China.

Methods

A total of 55,925 children aged 1 month to 18 years old were recruited from pediatric outpatient departments from July 2016 to June 2017. Data on demographics, anthropometric measurements, vitamin D supplementation, and outdoor time were recorded. The serum levels of 25-hydroxycholecalciferol (25(OH)D) were determined by high performance liquid chromatography tandem-mass spectrometry. Logistic regression analysis was performed to assess the association of vitamin D supplementation or outdoor time with blood vitamin D status, adjusted for age, gender, BMI for age, and seasons.

Results

The overall rate of hypovitaminosis D was 65.60%. Of the children's outdoor time, 35.63%, 31.95%, and 32.42% were below 30 min/d, 30–60 min/d and over 60 min/d, respectively. Furthermore, the proportion of iatrogenic supplementation, voluntary supplementation and no vitamin D supplementation among the children was 16.48%, 32.87%, and 50.65%, respectively. After adjusted for confounding factors, vitamin D supplementation was associated with a lower risk of hypovitaminosis D, with OR (95% CI) of 0.191 (0.180, 0.202) in children with iatrogenic supplementation and 0.423 (0.404, 0.443) in those with voluntary supplementation, compared with children without vitamin D supplementation. In addition, longer outdoor time was associated with a lower risk of hypovitaminosis D [0.479 (0.456, 0.504) for 60 min/d, 0.737 (0.701, 0.776) for 30–60 min/d], independent of vitamin D supplementation.

Conclusions

High prevalence of vitamin D deficiency was found in children living at high latitudes. Vitamin D supplementation and outdoor time are all negatively associated with children's vitamin D deficiency. Routine 25(OH)D testing combined with vitamin D supplementation might be an effective approach to prevent hypovitaminosis D among children living at high latitudes.

Introduction

Vitamin D deficiency is a disorder mainly induced disorders of calcium and phosphorus metabolism, which causes defective chondrocyte differentiation, mineralization in growth plate and defects in osteoid mineralization among children^[1]. Vitamin D deficiency is also related to functions of muscles and immune organs, and hematopoiesis, which are associated with multiple extra-skeletal disorders, such as myopathy, anemia, and recurrent respiratory tract infections in children^[2-4].

Vitamin D deficiency or insufficiency are still of global public health concerns, particularly in developing countries^[5]. Approximately 30.00% of children suffer from hypovitaminosis D worldwide^[6]. Academic societies of China and other regions have released guidelines to emphasize the role of outdoor time and vitamin D supplement in physical health of children and adolescents, especially those with risk factors of deficiency^[7, 8]. Several studies have demonstrated that vitamin D supplementation significantly increased blood 25-hydroxyvitamin D (25(OH)D) level in children. A randomized, double-blinded study reported that vitamin D treatment in 600 IU/d for 6 weeks resulted in an increase in serum 25(OH)D in asthmatic children compared with placebo treatment (76.3 vs 48.2 nmol/l)^[9]. In a prospective observational study, 55 children with inflammatory bowel diseases were prescribed vitamin D 2000 IU/d for 2 to 3 months, and their serum 25(OH) D were increased from 58 nmol/L at the baseline to 85 nmol/L^[10]. Uysalol et al found that serum 25(OH)D levels in asthmatic children with inadequate sun exposure and vitamin D supplements were significantly lower than that of the healthy controls (16.6 vs 28.2 ng/mL) in Turkey^[11]. Therefore, most present studies focused on the impact of vitamin D supplements and outdoor time on pediatric patients. Yet the effect of vitamin D supplement and sun exposure on healthy children are not well documented given that few guidelines support serum 25(OH)D test for children^[12]. However, previous studies suggested that circulating vitamin D level should be measured even in healthy children with a risk of vitamin D deficiency mainly due to inadequate sun exposure^[13, 14], in order to early prevent vitamin D deficiency-related diseases.

Constant exposure of many parents to information on benefits of vitamin D supplementation during pregnancy and throughout childhood may contribute to voluntary daily intake of vitamin D in children.^[15, 16]. Voluntary supplementation of vitamin D helps prevent vitamin D deficiency in children, although few studies have been reported^[17]. With the spread of child health education, children are more likely to have regular clinic visits due to early recognition of nutritional rickets-related clinical symptoms by their parents, e.g. frontal bossing, rachitic rosary, and leg deformity. 25(OH)D test is routinely performed for children in North China as part of physical examination or assessment of suspected nutritional rickets. Once the diagnosis is confirmed, individualized intervention is provided by physicians/doctors to maintain or improve vitamin D status of their pediatric patients. Nevertheless, little research has been conducted on efficacy and feasibility of iatrogenic vitamin D supplementation to date. In our study, data of 55,925 children from our clinic were analyzed to investigate their vitamin D nutriture and possible causes, of which vitamin D supplementation and outdoor time were of particular interest, to explore the necessity of regular monitoring of 25(OH)D status and supplementation in children living at high latitudes.

Methods

Study design, data source, and patient selection

Heilongjiang is a province in North China at latitude 43°3' – 53°3' N and known as the coldest region in China, with an average annual sunshine of 1874 to 2761 h in 2016–2017, according to Heilongjiang Bureau of Statistics. The Sixth National Population Census of China indicated that the resident population in Heilongjiang was 383.14 million, in which 45.74 million (11.94%) were aged 0–14 years old.

In this cross-sectional study, children aged 0–18 years old were recruited who visited child health clinic in Harbin Children's Hospital between July 2016 and June 2017. All guardians completed questionnaires involving questions of their children's name, date of birth, date of visit, ethnic, and vitamin D supplementation. Children's outdoor time was reported by the parents as the number of hours during the last week (including the weekend)^[18].

Iatrogenic vitamin D supplementation is defined as vitamin D prescription in children who had physical examination or clinic visits in the past 3–6 months. Prophylactic and therapeutic dosage was recommended for pediatric patients with a normal level and in vitamin D deficiency, respectively according to the consensus of the Chinese Society of Osteoporosis and Bone Mineral Research, respectively^[19]. Voluntary vitamin D supplementation is defined as daily vitamin D intake in children asked by their parents in last 3–6 months (most of them had oral vitamin D3 intake of 400–800 IU/d), without being monitored for their serum 25(OH)D or a prescription from doctors. No vitamin D supplementation was defined as taking no vitamin D supplements in the past 3–6 months. Children were considered being supplemented with vitamin D if they were 1) aged over 6 months and given either iatrogenic or voluntary vitamin D supplementation for more than 3 months and 2) aged less than 6 months and received supplemental vitamin D in either aforementioned way for > 1 month. Children with the following conditions were excluded from our study: 1) using vitamin D metabolites and their analogs, e.g., alfacalcidol or calcitriol, for their routine supplementation. 2) suffering from hypophosphatemic rickets, organ dysfunction, congenital disorders, and inherited metabolic diseases. 3) for those over 6 months old, either aforementioned supplementation suspended for > 20 d in the past 3 months and 4) for children under 6 months, either aforementioned supplementary measure suspended for > 10 d in the past 1 month. Detailed information on the nature of this study was provided to the parents or guardians of participants before consent was written.

Anthropometric Measurements

Trained nurses measured twice the height and weight of the enrolled children within 0.1 cm and 0.1 kg respectively, and average the measurements for the final value. An anthropometric calculator obtained from World Health Organization (<http://www.who.int/en/>) was used to determine body mass index (BMI) for age. BMI for age < 90 percentile was considered normal, 90–97 percentile overweight and > 97 percentile obese.

Circulating 25(OH)D Level

Blood samples (3 ml) were taken by antecubital venipuncture and then stored in a cool box for < 2 h. After centrifugation at room temperature for 10 min at 1200 × g, the upper serum pipetted and stored at 4 °C for < 24 h. The samples were kept at room temperature for 30 min before analysis. The serum 25(OH)D levels were determined by high performance liquid chromatography tandem–mass spectrometry (HPLC–MS/MS, API 3200; AB SCIEX, American). The lower limits of 25-(OH)D₂ and 25-(OH)D₃ for detection were both 1.6 ng/mL. The test sensitivity was assessed with the inter-batch coefficient of variation (CV) of 6.59% and between batches CV of 6.98%.

Diagnostic Criteria of Serum Vitamin D Status

The consensus of the Chinese Society of Osteoporosis and Bone Mineral Research, Chinese Medical Association indicated that circulating 25(OH)D < 10 ng/mL was considered severely deficient, 10–20 ng/mL deficient, 20–29 ng/mL insufficient, and ≥ 30 ng/mL sufficient[19]. High levels of circulating 25(OH)D may have benefits for children’s extra-skeletal organs[20]. Thus, the cut-off points for defining low status of vitamin D is 30 ng/mL, which refers to hypovitaminosis D in this study^[14].

Statistical analysis

The serum level of 25(OH)D was expressed as mean ± SD. Comparison of the 25(OH)D levels between different groups was determined by ANOVA. The prevalence of vitamin D status was expressed as n (%). The statistical difference of the prevalence of vitamin D status between different groups was determined by chi-square test. Logistic regression analysis was performed to evaluate the association of vitamin D supplementation or outdoor time with blood vitamin D status, adjusted for age, sex, BMI for age, and season. Data were expressed as odds ratio (OR) and 95% confidence interval (CI). All analyses were performed using SPSS 21.0. A p value < 0.05 was considered statistically significantly.

Results

Participant Characteristics

A total of 55,925 participants were included in this study, in which 30,683 (54.86%) were male. Table 1 presented the basic characteristics of the participants. The average serum level of 25(OH)D for all participants was 26.13 ± 12.30 ng/mL. The median age of participants was 3.10 years old (interquartile range, 1.10–6.50 years old). Of the children’s outdoor time, 35.63%, 31.95%, and 32.42% were below 30 min/d, 30–60 min/d and over 60 min/d, respectively. Furthermore, 50.65% of the subjects had iatrogenic vitamin D supplementation, 32.87% voluntary vitamin D supplementation, and 16.48% no vitamin D supplementation. The vitamin D level was higher in boys, younger children, children recruited in summer, with prolonged outdoor time, and those with vitamin D supplementation ($P < 0.001$).

Table 1
25(OH)D concentration in children aged 0–18 years old

	N (%)	25(OH)D (ng/mL)	P value
Total	55,925	26.13 ± 12.30	
Gender			< 0.001
Boys	30,683 (54.86)	26.42 ± 12.07	
Girls	25,241 (45.13)	25.78 ± 12.56	
Age (year)			< 0.001
0–	11,953 (21.37)	33.25 ± 13.64	
1–	14,901 (26.64)	30.71 ± 11.44	
3–	13,124 (23.47)	23.74 ± 9.37	
6–	12,416 (22.20)	19.12 ± 8.70	
12–18	3531 (6.31)	16.24 ± 8.30	
Season			< 0.001
Spring	15,795 (28.24)	25.98 ± 11.77	
Summer	17,421 (31.15)	26.58 ± 13.07	
Autumn	10,205 (18.25)	26.51 ± 12.08	
Winter	12,504 (22.36)	25.37 ± 11.95	
Ethnic			0.050
Han	54,967 (98.29)	26.12 ± 12.29	
Ethnic minorities in China	958 (1.71)	26.91 ± 12.67	
Outdoor time			< 0.001
< 30 min/d	19,929 (35.63)	21.61 ± 11.81	
30–60 min/d	17,867 (31.95)	27.65 ± 11.47	
> 60 min/d	18,129 (32.42)	29.60 ± 12.11	
BMI for age			< 0.001
Normal	51,294 (91.72)	26.58 ± 12.26	
Overweight	2851 (5.10)	21.84 ± 12.43	

NOTE: P< 0.05 shows a significant difference between the groups.

	N (%)	25(OH)D (ng/mL)	P value
Obesity	1780 (3.18)	20.07 ± 9.90	
Supplementation			< 0.001
None	28,328 (50.65)	20.60 ± 8.65	
Voluntary	18,383 (32.87)	29.80 ± 9.49	
Iatrogenic	9214 (16.48)	35.80 ± 17.14	

NOTE: $P < 0.05$ shows a significant difference between the groups.

Characteristics of Children with Different Vitamin D Statuses

The overall rate of hypovitaminosis D was 65.60%. 6.57%, 25.51%, and 33.52% of the children included were found with severe deficiency, deficiency and insufficiency, respectively. Moreover, 18.11% children with severe deficiency were overweight or obese, compared with 11.34% and 8.17% in those with deficiency and insufficiency, respectively. However, the rate of overweight and obesity decreased to 4.21% in children with vitamin D sufficiency ($P < 0.001$). Children who have outdoor time of 30–60 min/d and over 60 min/d showed a percentage of 34.31% and 39.97% in the vitamin D sufficiency group, whereas it dropped to 25.72% in the < 30 min/d group ($P < 0.001$). In children with normal vitamin D status, 46.70% and 27.12% had voluntary and iatrogenic vitamin D supplementation, respectively; in contrast, 26.18% took no supplements, accounting for 90.31% patients with severe vitamin D deficiency (Table 2). Among the influential factors, outdoor activity time and supplementation methods are possibly causal factors determine the vitamin D status in children, and also changeable factors for prevention of hypovitaminosis D.

Table 2
Characteristics of children with varying serum levels of 25(OH)D

	Severe deficient	Deficient	Insufficient	Sufficient	P value
Vitamin D (ng/mL, $\bar{x} \pm s$)	7.45±2.19	15.35±2.87	25.04±2.81	38.74±10.57	< 0.001
Percentage (%)	6.57	25.51	33.52	34.40	
Male (%)	51.20	53.07	55.42	56.34	< 0.001
Age (years, $\bar{x} \pm s$)	7.54 ± 4.99	6.65 ± 3.94	4.18 ± 3.38	2.09 ± 2.39	< 0.001
Ethnic (Han, %)	98.31	98.49	98.28	98.14	0.063
Overweight and obesity (%)	18.11	11.34	8.17	4.21	< 0.001
Season (%)					< 0.001
Spring	30.50	29.82	31.12	32.29	
Summer	26.53	29.33	28.19	27.83	
Autumn	16.31	17.35	18.69	18.85	
Winter	26.66	23.50	22.00	21.03	
Outdoor activity time (%)					< 0.001
< 30 min/d	58.69	56.23	25.63	25.72	
30–60 min/d	23.56	22.14	38.63	34.31	
> 60 min/d	17.75	21.63	35.74	39.97	
Supplementation methods (%)					< 0.001
No supplement	90.31	74.10	50.16	26.18	
Voluntary supplement	7.27	17.94	35.06	46.70	
Iatrogenic supplement	2.43	7.96	14.79	27.12	

$\bar{x} \pm s$ and percentage (%) were used to describe the continuous and categorical variables, respectively;
 $P < 0.05$ was regarded as statistically significant.

Association of Supplementation Methods with Vitamin D Status

After adjusting for age, sex, BMI for age, season, and outdoor activity time, an inverse association of vitamin D supplementation with hypovitaminosis D was observed. The OR (95% CI) of hypovitaminosis D was 0.423 (0.404, 0.443) in children with voluntary supplementation and 0.191 (0.180, 0.202) in children with iatrogenic supplementation compared with children with no supplements (P for trend < 0.001, Table 3).

Table 3
Association of three types of vitamin D supplementation with hypovitaminosis D analyzed by logistic regression

Supplementation	Model 1	Model 2	Model 3
No supplements	1	1	1
Voluntary supplementation	0.435 (0.415, 0.455)	0.435 (0.415, 0.455)	0.423 (0.404, 0.443)
Iatrogenic supplementation	0.202 (0.191, 0.214)	0.202 (0.191, 0.214)	0.191 (0.180, 0.202)
P for trend	< 0.001	< 0.001	< 0.001

Associations were examined with multivariable logistic regression. Model 1: adjusted for age and sex. Model 2: adjusted for BMI for age on the basis of model 1. Model 3: adjusted for season and outdoor time on the basis of model 2.

Association of the three Supplementation Methods with Vitamin D Status in Children with Varying Outdoor Time

We conducted logistic regression to further eliminate the influence of outdoor activity time on the relationship between supplementation methods and serum 25(OH)D level. Both iatrogenic and voluntary supplementation reduced the risk of hypovitaminosis D regardless of outdoor time compared to those with no vitamin D supplementation. In children whose outdoor time was > 60 min/d, the OR was 0.196 (0.178, 0.216) in the former way, whereas 0.508 (0.470, 0.550) in the latter way, compared with those who took no supplements (Table 4).

Table 4

Logistic regression analysis of the association of vitamin D supplementation methods with hypovitaminosis D in children with varying outdoor time

Supplementation methods	Model 1	Model 2	Model 3
> 60 min/d			
No supplement	1	1	1
Voluntary supplementation	0.508 (0.470, 0.549)	0.508 (0.469, 0.549)	0.508 (0.470, 0.550)
Iatrogenic supplementation	0.196 (0.177, 0.216)	0.196 (0.177, 0.216)	0.196 (0.178, 0.216)
P for trend	< 0.001	< 0.001	< 0.001
30–60 min/d			
No supplement	1	1	1
Voluntary supplementation	0.362 (0.332, 0.394)	0.362 (0.332, 0.394)	0.361 (0.332, 0.394)
Iatrogenic supplementation	0.183 (0.164, 0.205)	0.184 (0.164, 0.205)	0.183 (0.164, 0.205)
P for trend	< 0.001	< 0.001	< 0.001
< 30 min/d			
No supplement	1	1	1
Voluntary supplementation	0.376 (0.345, 0.411)	0.377 (0.346, 0.411)	0.377 (0.346, 0.411)
Iatrogenic supplementation	0.176 (0.160, 0.194)	0.174 (0.159, 0.192)	0.174 (0.159, 0.192)
P for trend	< 0.001	< 0.001	< 0.001
Associations were examined using multivariable logistic regression. Model 1: adjusted for age and sex. Model 2: adjusted for BMI for age on the basis of model 1. Model 3: adjusted for season on the basis of model 2.			

Association of Outdoor Time with Vitamin D Status

We found another inverse association of prolonged outdoor time with hypovitaminosis D after age, sex, BMI for age, season, and supplementation methods were adjusted. The OR (95% CI) of hypovitaminosis D was 0.737 (0.701, 0.776) in children with outdoor time of 30–60 min/d and 0.479 (0.456, 0.504) in those with 60 min/d. (P for trend < 0.001, Table 5).

Table 5
Logistic regression analysis of the association of outdoor time with hypovitaminosis D

Outdoor time (min/d)	Model 1	Model 2	Model 3
< 30	1	1	1
30–60	0.696 (0.663, 0.731)	0.697 (0.663, 0.732)	0.737 (0.701, 0.776)
> 60	0.533 (0.508, 0.560)	0.534 (0.508, 0.560)	0.479 (0.456, 0.504)
P for trend	< 0.001	< 0.001	< 0.001

Associations were examined using multivariable logistic regression. Model 1: adjusted for age and sex. Model 2: adjusted for BMI for age on the basis of model 1. Model 3: adjusted for season and supplementation methods on the basis of model 2.

Association of Outdoor Time with Vitamin D Status in Various Supplementation Methods

The results of logistic regression models suggested that there was a decline in the risk of hypovitaminosis D with increased outdoor time whether vitamin D supplementation was used [0.858 (0.769, 0.957) for 30–60 min/d and 0.469 (0.420, 0.525) for over 60 min/d compared with below 30 min/d in children with iatrogenic vitamin D supplement, *P* for trend ≤ 0.001 , Table 6].

Table 6

Logistic regression analysis of the effect of outdoor time on hypovitaminosis D in children with the three vitamin D supplementation methods

Outdoor time (min/d)	Model 1	Model 2	Model 3
Iatrogenic supplementation			
< 30	1	1	1
30–60	0.849 (0.762, 0.947)	0.857 (0.768, 0.956)	0.858 (0.769, 0.957)
> 60	0.464 (0.415, 0.519)	0.469 (0.420, 0.525)	0.469 (0.420, 0.525)
P for trend	< 0.001	< 0.001	< 0.001
Voluntary supplementation			
< 30	1	1	1
30–60	0.704 (0.650, 0.761)	0.704 (0.650, 0.762)	0.704 (0.650, 0.762)
> 60	0.608 (0.557, 0.663)	0.608 (0.558, 0.663)	0.608 (0.558, 0.663)
P for trend	< 0.001	< 0.001	< 0.001
No supplementation			
< 30	1	1	1
30–60	0.798 (0.728, 0.874)	0.797 (0.728, 0.874)	0.796 (0.727, 0.873)
> 60	0.422 (0.390, 0.455)	0.421 (0.390, 0.455)	0.427 (0.390, 0.455)
P for trend	< 0.001	< 0.001	< 0.001
Associations were examined using multivariable logistic regression. Model 1: adjusted for age and sex. Model 2: adjusted for BMI for age on the basis of model 1. Model 3: adjusted for season on the basis of model 2.			

Discussion

This observational study was the first to assess circulating 25(OH)D in over 50,000 children by HPLC-MS/MS, the current gold standard in vitamin D level assessment^[21]. Our data showed that (1) hypovitaminosis D was prevalent (65.60%) among children in Heilongjiang; (2) voluntary and iatrogenic vitamin D supplementation were inversely associated with the rates of pediatric hypovitaminosis D; (3) increased outdoor activity time was also linked with a lower risk of hypovitaminosis D, and (4) supplementation combined with outdoor time over 60 min/d may be a better way in preventing hypovitaminosis D among children in North China.

Latitude has a clear impact on the vitamin D status in children. However, we still lack of data for the vitamin D nutriture of children from different latitudes. Previous hospital-based cross-sectional studies

indicated that 23.28% children in Huzhou (southeastern China, $30^{\circ}2' - 31^{\circ}1'$ N)^[22] and 33.60% in Hangzhou (southeastern China, $29^{\circ}1' - 30^{\circ}3'$ N)^[23] were found with hypovitaminosis D, whereas the prevalence increased to 65.91% in this study, which is consistent with early research focusing on children in high latitudes. Data from Hutterite communities (Canada, $49^{\circ}2' - 54^{\circ}8'$ N) suggested that 76.00% of children suffered from hypovitaminosis D^[24], indicating that hypovitaminosis D might be a common and serious problem in children in high latitudes. Skin is a key organ in vitamin D synthesis because 80–90% vitamin D that the human needs per day is produced in the skin from ultraviolet-B-activated 7-dehydrocholesterol^[25]. Evidence from Spain ($36^{\circ}0' - 43^{\circ}2'$ N) suggested that production of over 1000 IU/d vitamin D in spring and summer depends on regular sunlight exposure^[26], making outdoor activity an optimal way of getting vitamin D. However, our results showed that still 17.75% and 21.63% of the enrolled children whose outdoor time was over 60 min/d had a deficient and insufficient vitamin D status, respectively. Moreover, excessive ultraviolet radiation exposure throughout childhood appears to be particularly harmful^[27]. Children with sun protection by their parents are much less exposed to ultraviolet radiation^[28]. Therefore, vitamin D supplementation might be taken into account to prevent hypovitaminosis D among children living in Heilongjiang.

Numerous programs or health policies for vitamin D supplementation are available in almost all countries to prevent vitamin D deficiency or hypovitaminosis D in children^[29–32]. In the guidelines aforementioned, some risk factors for vitamin D deficiency are recognized, including vegan diet, malabsorption syndromes, and reduced sunlight exposure; meanwhile, regular vitamin D supplementation and routine 25(OH)D testing are recommended for children. However, living at high latitude as an identified risk factor for vitamin D deficiency has not been explicitly mentioned for routine 25(OH)D testing in these guidelines. Despite of high incidence of hypovitaminosis D among children living in high latitudes was found in previous studies^[18], few of them focused on related improvements. Approximately 30% of the total world population lives from 40° N to 60° N. Given the vitamin D status of children living at high latitudes, it is necessary to determine whether they need to be routinely screened for serum 25 (OH) D levels, followed by appropriate vitamin D supplementation as required. In this study, we found that vitamin D supplementation and outdoor time were all negatively associated with children's vitamin D status, and routine 25(OH)D testing combined with vitamin D supplementation might be an effective approach for the prevention of hypovitaminosis D among children living at high latitudes, which were of great significance of addressing this global public health issue.

The pediatric health care system in China has been improved and consists of a proper examination interval and routine monitor network of serum 25(OH)D levels in children^[22, 33]. Prescriptions were given by health professionals according to vitamin D status and the supplementary recommendation in the consensus of the Chinese Society of Osteoporosis and Bone Mineral Research. To the best of our knowledge, this was the first study to describe and evaluate the effect of iatrogenic supplementation on prevention of hypovitaminosis D among children, and iatrogenic supplementation had a 2.21-, and 5.24-fold decreased risk of hypovitaminosis D compared with voluntary supplementation and no supplementation, respectively. Besides, health professionals urge the parents to keep regular vitamin D

supplementation[34]. Minkowitz et al. reported that better adherence of guardians with low serum vitamin D levels to physicians' orders to remind their children of daily intake of vitamin supplements^[35]. Although there were some unfavorable factors causing poor response to oral supplementation^[36], pediatricians could improve the oral doses according to the follow-up serum 25(OH)D test results until the doses reached optimum. Noticeably, however, compliance of children with follow-up blood collection varied. No vitamin D supplementation due to guardians' lack of awareness that might be the main cause[34], was like to expose their children to the increased risk of hypovitaminosis D and acute and chronic diseases including infectious diseases, autoimmune disorders and childhood dental caries^[37]. Thus, although iatrogenic supplementation has shown a better effect in preventing hypovitaminosis D than voluntary supplementation, which prevention strategy to follow depends on certain factors, in particular the local health policy and compliance of guardians with blood collection.

This study had several limitations. First, the vitamin D doses in the iatrogenic supplementation group remained inconsistent. Individualized vitamin D supplementations were prescribed by doctors according to the medical conditions of healthy children and those with vitamin D deficiency. Second, outdoor time might be a confounder. However, duration and sun-exposed skin areas of each child was not investigated in this study. Third, < 10–20% vitamin D that human needed per day was from diet^[38], which played an important role in the vitamin D status of children. However, such information was unavailable in our study. We assumed that children in the same region had similar dietary patterns. A prospective study is warranted to explore the role of diet in addition to other confounders. Fourth, as the subjects in this study were all recruited from the outpatient department instead of the general pediatric population, their parents might be more concerned about their children's vitamin D status or health condition, and their health status may be better. Therefore, demographic characteristics of the participants in this study could not represent that of the whole population of children living in North China.

Conclusions

In summary, we strongly recommended routine risk screening of low serum 25(OH)D for early prevention of vitamin D deficiency in children living at high latitudes. Voluntary and iatrogenic vitamin D supplementation were all promising strategies and prolonged outdoor time was negatively associated with pediatric vitamin D deficiency, the combination of which might be an optimal way to prevent hypovitaminosis D in children; nevertheless, guardian's compliance should be considered for a practical prevention strategy.

Abbreviations

25(OH)D, 25-hydroxycholecalciferol; BMI, body mass index; OR, odds ratio; high performance liquid chromatography tandem-mass spectrometry, HPLC–MS/MS.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Harbin Children's Hospital on May 17, 2016 (No. HRYLL 201605).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XZ and LN designed the study, writing, prepared the original draft, and acquired funding. XZ, YC, XB, DC, DZ and LL collected the data; HJ and SJ analysed and interpreted data. All authors read and approved the final manuscript.

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