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Vitamin D Deficiency as a Strong Predictor of Asthma in Children

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Key Words
Vitamin D · Asthma · Children · Allergy · Predictors · Qatar

Abstract
Background: Epidemiological studies suggest a link between vitamin D deficiency in early life and development of asthma in later life. ***Aim:*** The aim of this study was to measure serum vitamin D levels in asthmatic children and to compare these to healthy non-asthmatic controls. ***Methods:*** Asthmatic (n = 483) and healthy control (n = 483) children were recruited from the Pediatric Allergy-Immunology Clinics of Hamad General Hospital and the Primary Health Care Clinics in Qatar from October 2009 to July 2010. All children were below 16 years of age and asthma was diagnosed by a physician. Parents of all children completed extensive questionnaires documenting demographics, child's feeding practice and vitamin D intake. Serum vitamin D (25-hydroxyvitamin D), calcium, phosphorus, alkaline phosphatase, magnesium, creatinine and parathyroid hormone assays were performed. Subjects with serum containing less than 20 ng/ml vitamin D were deemed deficient. ***Results:*** Asthmatic children had significantly reduced serum vitamin D levels compared to non-asthmatic children ($p < 0.001$); 68.1% of all asthmatics were vitamin D deficient. Asthmatic children had significantly higher degrees of moderate (41.8 vs. 25.1%) and severe (26.3 vs. 11.0%) vitamin D deficiency compared to healthy controls ($p < 0.001$). Positive familial history of vitamin D deficiency (35.6%, $p = 0.005$) and asthma (36.4%, $p = 0.009$) were significantly higher in asthmatic children. Along with vitamin D deficiency, asthmatics also had reduced phosphorus ($p < 0.001$) and magnesium ($p = 0.001$) levels but elevated serum alkaline phosphatase ($p < 0.001$) and IgE ($p < 0.001$). The majority of asthmatic children had less exposure to sunlight (66.7%, $p = 0.006$) and less physical activity (71.3%, $p < 0.001$). Vitamin D deficiency was the strongest predictor of asthma in this population (OR 4.82; 95% CI 2.41–8.63, $p < 0.001$). ***Conclusion:*** The present study revealed that the majority of asthmatic children had vitamin D deficiency compared to control children. Vitamin D deficiency was the major predictor of asthma in Qatari children.

Introduction

Bronchial asthma remains the most common chronic disease of childhood [1–3] and is one of the leading causes of morbidity in children worldwide [4]. Currently, the burden of asthma in both the developed and the develop-

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ing world is significant and increasing rapidly with more than 300 million people affected worldwide. Industrialized countries farthest away from the equator such as Australia, New Zealand and the United Kingdom are said to have the highest prevalence [2]. The prevalence of asthma and allergies in some Western countries has reached alarming proportions, affecting more than one third of children from the general population [1–4].

Similar trends have recently been reported in the Asia-Pacific areas [5–7] and Arabian Gulf countries [1–4, 6, 8]. Asthma is one of the most common chronic diseases in Saudi Arabia, affecting more than 2 million people [9]. The prevalence of asthma in Saudi Arabia [10] (26.5%), Kuwait [11] (16.8%) and in the United Arab Emirates [12] (13.6%) appears to be similar to that of industrialized or Western countries.

Although it is well known that positive atopic status [8, 13–14], exposure and sensitisation to environmental allergens [5–6, 8, 15] and/or familial history of allergic disease [5–6, 8, 14, 15] are significant risks factors associated with the development of asthma, recent evidence suggests that vitamin D deficiency may also predispose to allergic phenotype. Vitamin D is a potent modulator of the immune system and is involved in regulating cell proliferation and differentiation [16–18]. Epidemiological evidence suggests that there is a worldwide epidemic of vitamin D deficiency [17, 18], and lack of vitamin D has been linked to increased incidence of asthma [19–22] and increased severity of asthma in children [23].

Vitamin D deficiency remains a major health problem in many parts of the world, particularly in Africa [24] and the Middle East (Qatar [24, 25], Oman [19] and the Indian subcontinent [20]). Prolonged breastfeeding without vitamin D supplementation, maternal vitamin D deficiency, poor diet and limited sunshine exposure have been suggested as major contributors to vitamin D deficiency [24, 25]. The aim of this study was to use a case-control design to examine whether there are differences in serum vitamin D levels between asthmatic and non-asthmatic, healthy children and to test for any associations between vitamin D deficiency and development of allergic disease (asthma) in young children.

Methods

Study Population

A total of 1,274 children were recruited for this study from October 2009 to July 2010. Asthmatic children (n = 671) were recruited from the Pediatric Allergy-Immunology Clinic, Hamad General Hospital in Qatar. The log book of this clinic was used for the selection of cases. This log book has all the names of children visiting this clinic. A total of 671 children below 16 years of age were selected by a simple random sampling procedure from this log book. Pediatric immunologists diagnosed asthma in children who were visiting the Pediatric Allergy-Immunology clinics. The Hamad General Hospital is the main tertiary care centre for children with referrals from primary health care centres.

Control subjects (n = 603) were identified from the primary health care centres. The control group is a random sample of healthy children who visited primary health care centres for acute or chronic diseases other than asthma or respiratory diseases. They were healthy, non-asthmatics and were taking no medication at the time of study. For the selection of controls, subjects were selected from the primary health care centres. This group involved a random sample of 603 healthy children below 16 years of age. The control subjects were selected in a way matching the age, gender and ethnicity of children to give a good representative sample. 483 children gave consent to take part in this study with a response rate of 80.1%.

Each subject received the regular routine of detailed medical history, comprehensive physical examination and appropriate laboratory tests including differential cell counts, serum IgE, skin prick tests, chest X-ray and lung function tests. The Research Ethics Committee at Hamad General Hospital of Hamad Medical Corporation approved this study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all participants.

Questionnaires

Health professionals and nurses interviewed all participants. Questionnaires involved collection of data on subjects' dietary intake (particularly vitamin D), history of allergic disease (if any), sociodemographics (age, gender, place of residence), socioeconomic status (household income), parental education and occupation, consanguinity as well as morphometric measures (height and weight). Body mass index (BMI) was calculated as the weight in kilograms (with 1 kg subtracted to allow for clothing) divided by height in meters squared. BMI <85th percentile was considered normal weight, 85–95th percentile as overweight and >95th percentile as obese [21]. Study participants were asked to list first names of all first-degree blood relatives, including parents, brothers, sisters, uncles and aunts, and determined their consanguinity. Familial history of vitamin D deficiency was collected from their medical files. Other variables like physical activity and sun exposure were collected from the study participants at the time of interview. With regard to diet, we collected information on dietary intake, vitamin D intake and type of feeding. One section of the questionnaire was 'assessment of dietary and vitamin D intake'. There were questions on food consumption like fortified food, sea food, fatty/oily fish, eggs, cod liver oil, milk fortified with vitamin D, and supplement consumption like multivitamin and vitamin D supplement. The children who were taking this food daily were considered as taking 'vitamin D supplement'.

The main investigator (A.B.) set up this questionnaire and criteria for vitamin D deficiency in a young population with asthma. A translated Arabic version was revised by a bilingual consultant. A major part of the designed questionnaire was validated in the previous study of Bener et al. [22]. In this questionnaire, variables related to asthma were inserted. This questionnaire was validated on 20 randomly selected children visiting paediatric asthma/allergy clinics of the Hamad General Hospital (cases) and 20 randomly selected healthy subjects from the children visiting primary health care clinics.

Blood Collection and Serum Measurements of Vitamin D

A trained phlebotomist collected venous blood sample, and serum was separated and stored at –70°C until analysis. Serum 25-hydroxyvitamin D [25(OH)D], a vitamin D metabolite, was measured using a commercially available kit (DiaSorin, Saluggia, Italy). The treated samples were then assayed using competitive binding radioimmunassay technique. Subjects were classified into four categories: (1) severe vitamin D deficiency, 25(OH)D <10 ng/ml; (2) moderate deficiency, 25(OH)D 10–19 ng/ml; (3) mild deficiency, 25(OH)D 20–29 ng/ml; (4) normal/optimal level is between 30–80 ng/ml [12]. According to the recommendations of other studies [10–12, 18–19], we categorized vitamin D levels as deficient if 25(OH)D was <20 ng/ml, insufficient if it was 20–29 ng/ml and sufficient if it was >30 ng/ml. We marked this classification in figure 1 in order to identify the deficient and insufficient vitamin D levels. Other baseline biochemical parameters measured from the serum included calcium, phosphorus, alkaline phosphatase, magnesium, creatinine and parathyroid hormone levels as previously described. Total and allergen-specific IgE (to a panel of common food and environmental allergens) levels were measured from serum.

Statistical Analyses

Statistical significance between two continuous variables was determined using Student's t test; the Mann-Whitney test was used for non-parametric data. χ^2 was performed to test for differences in proportions of categorical variables between two or more groups. Multivariate logistic regression analysis using the forward inclusion and backward deletion method was used to assess the relationship between dependent and independent variables and to adjust for potential confounders and orders the importance of risk factors (determinant) for asthma. A p value <0.05 was considered statistically significant.

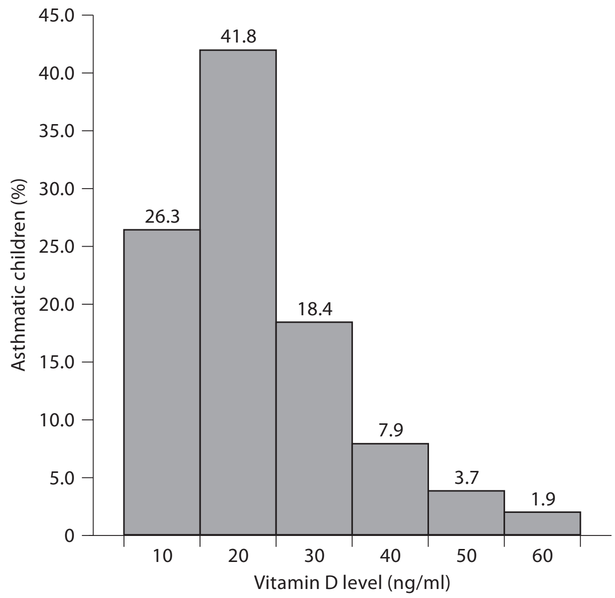

Fig. 1. Distribution of serum vitamin D in Qatari children with asthma. Vitamin D levels: deficient <20 ng/ml; insufficient 20–29 ng/ml; sufficient >30 ng/ml.

Results

Characteristics of our study population are illustrated in table 1. Mean age was similar between the two study groups, with equal numbers of males and females. Almost half (42.2%) the asthmatic children were younger than 5 years of age. Parental education ($p < 0.001$), parental occupation ($p < 0.01$), household income ($p = 0.005$) and the number of people living in the home ($p = 0.023$) were significantly different between asthmatics and control children. Consanguinity was significantly higher in parents of asthmatic children (38.5%) compared to parents of non-asthmatic controls (29.4%) ($p = 0.003$).

Prevalence of vitamin D deficiency in asthmatic and control children and their assessment of non-dietary covariates are shown in table 2. Moderate vitamin D deficiency was found in 41.8% of asthmatics and 25.1% of controls, while 26.3% of asthmatics had severe deficiency compared to 11% of controls. Moderate and severe degree of vitamin D deficiency was significantly higher in asthmatic children compared to controls ($p < 0.001$) (table 2). In this population of asthmatics, there was a strong familial risk of allergic disease ($p = 0.009$) and familial history of vitamin D deficiency was more prevalent in asthmatic children compared to non-asthmatics ($p = 0.005$). Looking at the non-dietary covariates, asthmatics were more likely to have a wheatish skin complexion compared to controls ($p < 0.001$), they participated in less physical activity ($p < 0.001$), had lower exposure to sunlight ($p = 0.006$) and were more likely to be overweight or obese than their age-matched non-asthmatic counterparts ($p = 0.008$).

Figure 1 reveals the distribution of serum vitamin D in Qatari children with asthma; 329/483 (68.1%) of all asthmatic children had vitamin D deficiency, 18.4% had insufficient levels (20–30 ng/ml) and only 13.5% of asthmatics had sufficient serum vitamin D levels (>30 ng/ml).

Feeding practices and vitamin D supplementation with breast milk in the asthmatic or control group are described in table 3. Of control children, 81% were breastfed for longer than 6 months compared to 67.3% of asthmatics ($p < 0.001$). A trend for earlier introduction of formula was observed for asthmatic children compared to controls ($p = 0.052$). There was no difference in the level ($p = 0.561$) or duration ($p = 0.434$) of vitamin D supplementation during breastfeeding between the two groups.

Measurements of baseline serum vitamin D, minerals, isoenzymes and hormones in asthmatic and control children are shown in table 4. Asthmatics had a significantly lower concentration of serum vitamin D ($p < 0.001$), phosphorus ($p < 0.001$) and magnesium ($p = 0.001$) compared to control children. The levels of alkaline phosphatase were elevated in serum of asthmatics compared to controls ($p < 0.001$), suggesting increased bone turnover. Asthmatics had significantly elevated serum IgE compared to controls ($p < 0.001$). Calcium, creatinine and parathyroid hormone concentrations were similar between the two groups.

Table 5 shows predictors for development of asthma in children using multivariate logistic regression analysis. Deficiency in vitamin D level (OR 4.82; 95% CI 2.41–8.63; $p < 0.001$) and low duration of time spent outdoors (OR 3.13; 95% CI 1.50–5.75; $p < 0.001$) were the major predictors of asthma in Qatari children. Familial history of vitamin D deficiency was a significant contributing risk factor amongst asthmatic children ($p = 0.011$). As previously reported in other populations, familial history of asthma and elevated serum IgE are both strong predictors ($p < 0.001$ and $p = 0.003$, respectively) of the disease. Reduced physical activity ($p < 0.001$), elevated child's BMI ($p = 0.004$) and parental consanguinity ($p = 0.005$) were considered as other contributing risk factors.

Discussion

The present case-control study provides an epidemiological support for the association between vitamin D deficiency and asthma, as most children with asthma were either vitamin D deficient or insufficient. To date, only a handful of studies have directly evaluated the role of vitamin D in asthma. To our knowledge, this is the first epidemiological study in the Middle East region which has investigated the association between vitamin D deficiency and the risk of asthma in children. Among the asthmatic children, 68.1% were deficient in vitamin D.

Bener et al. [22] reported that the prevalence of vitamin D deficiency was high in Qatari children and this deficiency increased with age. The high prevalence of vitamin D deficiency in Qatari children supports the hy-

Table 1. Sociodemographic characteristics of the studied asthmatic and control children

	Asthmatics (n = 483)	Controls (n = 483)	p
Age group			
<5 years	204 (42.2)	183 (37.9)	
5–10 years	125 (25.9)	118 (24.4)	0.159
11–16 years	154 (31.9)	182 (37.7)	
Sex			
Male	247 (51.1)	266 (55)	0.245
Female	236 (48.9)	198 (45)	
Education of father			
Illiterate	37 (7.7)	52 (10.8)	
Primary	56 (11.6)	84 (17.4)	
Intermediate	90 (18.6)	70 (14.5)	<0.001
Secondary	137 (28.4)	167 (34.6)	
University	163 (33.7)	110 (22.8)	
Education of mother			
Illiterate	14 (2.9)	36 (7.5)	
Primary	57 (11.8)	63 (13.0)	
Intermediate	101 (20.9)	156 (32.2)	<0.001
Secondary	149 (30.8)	130 (26.9)	
University	162 (33.5)	98 (20.3)	
Occupation of father			
Not working	27 (5.6)	18 (3.7)	
Sedentary/professional	201 (41.6)	127 (26.3)	
Manual/clerk	30 (6.2)	26 (5.4)	<0.001
Businessman	134 (27.7)	181 (37.5)	
Government officer	91 (18.8)	131 (27.1)	
Occupation of mother			
Sedentary/professional	143 (29.6)	111 (23.0)	
Manual/clerk	36 (7.5)	21 (4.3)	0.010
Businesswoman	38 (7.9)	46 (9.5)	
Housewife	266 (55.1)	305 (63.1)	
Place of living			
Urban	439 (90.9)	448 (92.8)	
Semi-urban	44 (9.1)	35 (7.2)	0.348
Household income			
5,000–9,999 QR	131 (27.1)	91 (18.9)	
10,000–14,999 QR	153 (31.7)	187 (38.7)	0.005
>15,000 QR	199 (41.2)	205 (42.4)	
People living at home			
≤5	118 (24.4)	135 (28.0)	
6–10	270 (59.9)	284 (58.8)	0.023
>10	95 (19.7)	64 (13.3)	
Consanguineous relatives			
None	247 (51.1)	300 (62.1)	
First-degree relatives	186 (38.5)	142 (29.4)	0.003
Second-degree relatives	50 (10.4)	41 (8.5)	

Figures in parentheses are percentages. 1 USD = 3.65 QR.

Table 2. Prevalence of vitamin D deficiency and assessment of the non-dietary covariates in studied asthmatic and control children

	Asthmatics (n = 483)	Controls (n = 483)	p
Mean age ± SD, years	7.37 ± 4.03	8.01 ± 4.59	0.210
Vitamin D status			<0.001
Sufficient (30–80 ng/ml)	65 (13.5)	84 (17.4)	
Mild deficiency (20–29 ng/ml)	89 (18.4)	225 (46.6)	
Moderate deficiency (10–19 ng/ml)	202 (41.8)	121 (25.1)	
Severe deficiency (<10 ng/ml)	127 (26.3)	53 (11.0)	
Familial history of asthma			0.009
Yes	176 (36.4)	137 (28.4)	
No	311 (63.6)	346 (71.6)	
Familial history of vitamin D deficiency			0.005
Yes	172 (35.6)	131 (27.1)	
No	311 (64.4)	352 (72.9)	
Color of skin			<0.001
White	113 (23.4)	153 (31.7)	
Wheatish	267 (55.3)	207 (42.9)	
Brown or black	103 (21.3)	123 (25.5)	
Physical activity			<0.001
Vigorous physical activity	139 (28.7)	226 (46.8)	
Less physical activity	344 (71.3)	257 (53.2)	
Exposure to sunlight			0.006
Yes	161 (33.3)	203 (42)	
No	322 (66.7)	280 (58)	
Birth order			0.003
1st or 2nd	173 (35.8)	130 (26.9)	
3rd or 4th	196 (40.6)	231 (47.8)	
≥5th	114 (23.6)	122 (25.3)	
BMI			0.008
Normal (<85th percentile)	335 (69.3)	376 (77.8)	
Overweight (85–95th percentile)	121 (25.1)	92 (19)	
Obese (>95th percentile)	27 (5.6)	15 (3.1)	

Figures in parentheses are percentages.

pothesis that there is a strong association between vitamin D deficiency and asthma risk. Freishtat et al. [26] also reported a similar proportion of inner-city African-American asthmatic children living in Washington, D.C., to be vitamin D deficient (86%), with only 19% of non-asthmatics having the deficiency. The distribution of vitamin D deficiency among our cohort of asthmatic children was considerably higher than that of a recently reported study in a Costa Rican population in which only 28% had a deficient level [18]. Litonjua and Weiss [16] found that 35% of American children were vitamin D deficient and these children were at a greater risk of severe asthma attacks. Together these epidemiological studies suggest a possible association between vitamin D deficiency and asthma and support our current observations.

Ginde et al. [27] have presented evidence to show that low vitamin D levels are associated with higher frequency of respiratory tract infections in asthmatic patients and with increased asthma severity. The reasons for widespread vitamin D deficiencies in various populations are not completely understood. However, it is speculated that increased prosperity and adoption of a Western lifestyle (increased time spent indoors resulting in less exposure to sunshine) may be contributing to our vitamin D deficiency, resulting in a predisposition to the development of allergic diseases including asthma. Our results have shown that asthmatic children have significantly reduced exposure to sunlight and are less physically active. We know that cutaneous synthesis of vitamin D is dramatically reduced amongst individuals who spend time in-

Table 3. Feeding practices and vitamin D supplement with breast milk in the studied asthmatic and control children

	Asthmatics (n = 483)	Controls (n = 483)	p
Type of feeding			
Breastfeeding			
≤6 months	158 (32.7)	92 (19)	<0.001
>6 months	325 (67.3)	391 (81)	
Formula feeding			
Never	142 (29.4)	111 (23.0)	0.052
≤6 months	37 (7.7)	33 (6.8)	
>6 months	304 (62.9)	339 (70.2)	
Vitamin D supplements during breastfeeding			
Yes	227 (47)	217 (45)	0.561
No	256 (53)	266 (55)	
Duration of vitamin D supplements, months	13.4 ± 8.0	12.8 ± 7.5	0.434

Results are expressed as means ± SD for continuous variables, and numbers of subjects (percentage of group in parentheses) for categorical variables.

Table 4. Baseline serum laboratory parameters among the studied asthmatic and control children

Laboratory parameter	Asthmatics (n = 483)	Controls (n = 483)	t test	p
Serum vitamin D, ng/ml	17.2 ± 11.0	26.8 ± 9.9	–8.719	<0.001
Calcium, mmol/l	2.4 ± 0.15	2.4 ± 0.14	0.9089	0.364
Phosphorus, mmol/l	1.56 ± 0.3	1.65 ± 0.3	–4.572	<0.001
Alkaline phosphatase, U/l	258.8 ± 38.4	229.3 ± 34.7	3.511	<0.001
Magnesium, mmol/l	0.77 ± 0.13	0.82 ± 0.11	–3.440	0.001
Creatinine, μmol/l	46.7 ± 13.4	48.2 ± 2.1	–0.658	0.511
Parathyroid hormone, mmol/l	44.4 ± 5.1	46.6 ± 4.1	–0.345	0.733
Log_{10} IgE	2.0 ± 0.7	1.7 ± 0.6	5.369	<0.001

Results are expressed as means ± SD.

Table 5. Predictors of asthma in the studied children using multivariate logistic regression analysis

Independent variables	OR	95% CI	p
Vitamin D deficiency	4.82	2.41–8.63	<0.001
Low duration of outdoor time	3.13	1.50–5.75	<0.001
Familial history of asthma	2.45	1.30–4.19	<0.001
Less physical activity	2.37	1.77–3.18	<0.001
Breastfeeding >6 months	2.26	1.47–4.12	0.001
Serum IgE level	1.89	1.24–2.84	0.003
Parental consanguinity	1.78	1.15–2.62	0.005
Familial history of vitamin D deficiency	1.66	1.15–2.45	0.011
Child BMI	1.54	1.09–2.13	0.004

doors and those who use protective clothing and sunscreen against ultraviolet radiation (sunlight). For this reason, vitamin D deficiency has been documented in many populations around the world regardless of the degree of sun exposure [28] and is more common among the non-White population [29]. In our study, 55.3% of asthmatic children had a wheatish skin complexion and 21.3% had darker skin. Dark skin is known to reduce the penetration of sunlight and these individuals, therefore, need a longer duration of sunlight exposure to the skin to achieve adequate vitamin D levels compared to the fair-skinned population. A recent study in infants and toddlers from an urban population, in which the majority had darker skin pigmentation, found that 40% of these children were vitamin D insufficient (<30 ng/ml) [30]. Similarly, 42% of healthy urban adolescents with darker skin pigmentation had vitamin D levels less than 20 ng/ml [31]. Inadequate sun exposure and skin pigmentation might be the reasons for the low level of vitamin D in asthmatic children.

Epidemiologic data suggest a possible association between maternal intake of vitamin D during pregnancy and risk of childhood wheezing/asthma in offspring [32, 33]. In this study, we have shown that familial history of vitamin D deficiency was significantly higher in parents of asthmatic children and was a significant risk factor in the development of the disease, suggesting that pregnant and/or lactating mothers are at a significant risk to develop vitamin D deficiency. Supplementing mothers during pregnancy or the lactating period with vitamin D might be a safe and effective strategy for reducing the risk of developing asthma in infants. Although vitamin D deficiency was thought to be eradicated with fortification of foods [33], widespread vitamin D deficiency has been rediscovered and associations with many disorders are being recognized. Here we describe, for the first time, a relationship between low levels of vitamin D and exacerbation of allergic disease in Qatari children. Prolonged breastfeeding without vitamin D supplementation can have long and detrimental effects on the development of early immune function. Improving vitamin D status holds promise in the primary prevention of asthma and in decreasing exacerbations of the disease. Given the emerging association between low vitamin D levels and asthma, strong consideration should be given to routine vitamin D testing in children, particularly those with asthma, and supplementation should be provided accordingly.

Conclusion

The present study revealed that a high proportion of Qatari children were deficient in vitamin D. This deficiency was more frequent in children suffering from asthma compared to non-asthmatic controls. Vitamin D deficiency was the strongest predictor of asthma (stronger than familial history of asthma or serum IgE levels) with a familial history of vitamin D deficiency also being a predictor of asthma.

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