



## **Severity of Asthma and Serum Vitamin D Levels in Asthmatic Children**

**Nasrin Bazargan<sup>1\*</sup> and Zeinab Nazari<sup>2</sup>**

<sup>1</sup>*Department of Pediatrics, Afzalipour Medical Center, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran.*

<sup>2</sup>*Imam Reza Hospital, Sirjan Faculty of Medical Sciences, Sirjan, Iran.*

### **Authors' contributions**

*This work was carried out in collaboration between both authors. Author NB designed the study. Authors NB and ZN performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NB and ZN managed the analyses of the study. Author ZN managed the literature searches. Both authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2019/v30i130257

Editor(s):

(1) Dr. Wenbin Zeng, Professor, Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, China.

Reviewers:

(1) Veeravan Lekskulchai, Srinakharinwirot University, Thailand.

(2) Luigi Nespoli, University of Insubria, Italy.

Complete Peer review History: <http://www.sdiarticle3.com/review-history/50527>

**Original Research Article**

**Received 05 June 2019**  
**Accepted 08 August 2019**  
**Published 17 September 2019**

### **ABSTRACT**

**Introduction:** Vitamin D deficiency has been rediscovered as a public health problem worldwide. It has been postulated that vitamin D deficiency explains a portion of the asthma epidemic. The purpose of this study was to assess the serum vitamin D levels in children with asthma as compared with the non-asthmatic population and to investigate the association of serum vitamin D levels with the severity of asthma.

**Materials and Methods:** We measured serum 25-hydroxyvitamin D (25-OH vitamin D) levels in 50 children with mild intermittent to moderate persistent asthma at the time of enrollment and 50 age- and sex-matched non-asthmatic children in a case-control study. The independent sample t-test,  $\chi^2$  test, and spearman correlation coefficient were used to analyze the data.

**Results:** Vitamin D level was  $13.6 \pm 1.1$  ng/ml and  $19.2 \pm 1.8$  ng/ml in asthmatic and non-asthmatic individuals, respectively. The mean ( $\pm$ SD) levels of serum vitamin D were statistically significant between asthmatic and non-asthmatic individuals. Females had lower levels of vitamin D than males. Asthma severity was inversely associated with serum vitamin D level.

\*Corresponding author: E-mail: [na.bazargan@iran.ir](mailto:na.bazargan@iran.ir);

**Conclusion:** Findings of the present study demonstrate the significance of vitamin D in asthma. Sufficient doses of vitamin D should be administered to pregnant mothers and the babies monitored for symptoms of wheezing or asthma during childhood. Clinical trials are needed to definitively answer questions about the role of vitamin D in asthma.

*Keywords: Asthma; vitamin D; vitamin D deficiency; 25-OH vitamin D.*

## 1. INTRODUCTION

Asthma is the most prevalent chronic respiratory disease in all age groups, affecting 300 million people worldwide. In children asthma is the most common chronic disease. The prevalence of asthma has been increased in recent years. According to ISAAC global asthma prevalence raised from 11.1 to 11.6% in children and 13.2 to 13.7% in adolescents [1].

In Iran, the prevalence of asthma among children under 18 years of age varies from 1.26% to 11.6% depending upon sex, ethnicity, geography, and other factors [2]. Many factors can influence the severity of asthma, such as viral respiratory infections, male gender, food allergy, atopy, and air pollution. The role of these factors has been clearly proven over the past years [3]. Some recent studies have been conducted to determine the role of some vitamins and microelements in asthma occurrence and prevention [4-6].

Among the vitamins, the roles of vitamins C and D in the occurrence of asthma have been studied more seriously. Low levels of vitamin C and  $\alpha$ -carotene are believed to be risk factors for asthma occurrence [5]. According to Chambers and Hawrylowicz supplementary vitamin D had an anti-inflammatory effect on the lungs and also increased the level of IL10, an anti-inflammatory mediator [7]. Vitamin D has a regulatory role in other inflammatory processes and diseases [8]. Some studies showed that low levels of vitamin D increases mortality in patients with breast and lung cancers [9-10]. Low levels of vitamin D are also correlated with some autoimmune disorders, such as type I diabetes mellitus [11] multiple sclerosis [12], rheumatoid arthritis [13] and inflammatory bowel diseases [14].

Vitamin D has an important role in the suppression of the inflammatory response of Th2 cells in the lungs. In animal models, it can induce surfactant synthesis and stimulate lung maturation [15]. The role of vitamin D and the synthesis of surfactant in the human fetus is more complex [16]. The risk of wheezing can be

lowered in infants whose mothers have taken high doses of vitamin D during pregnancy [17].

Some studies have shown that vitamin D can be effective in regulating immune responses and can affect fetal lung growth [18]. Low levels of maternal serum vitamin D during pregnancy can increase the risk of occurrence of asthma during childhood [19]. Vitamin D supplementation can reduce asthma attack that requiring systemic corticosteroids for treatment [20]. However, some studies have presented contradictory results regarding the relationship between serum vitamin D levels and allergic diseases. Taking supplementary vitamin D can increase allergic diseases in children and an increased risk of asthma and allergies with high level of vitamin D was reported [21]. This study was designed to determine and compare the levels of serum vitamin D in children with asthma as compared with those of a control group. Moreover, the relationship between the severity of asthma and the level of serum vitamin D was investigated.

## 2. MATERIALS AND METHODS

In this cross sectional case-control study, 50 asthmatic children, aged 2–18 years, were enrolled via simple random sampling. The patients were referred to the Asthma and Allergy Clinic of Afzalipour Medical Center of Kerman University of Medical Sciences. Asthma was diagnosed and classified according to the National Asthma Education and Prevention Program's Expert Panel Report 3 [22].

Patients who suffered from disorders interfering with vitamin D metabolism or kidney disease and those who were taking antiepileptic drugs, supplementary vitamin D or other vitamins were excluded from the study. Fifty participants referring to the out-patient pediatric clinic of Afzalipour Medical Center due to simple and uncomplicated disorders, e.g., common cold and otitis media were selected as the control group. For each case, one control subject was randomly selected and matched to the index case according to age and gender. For each person, a data collection sheet containing name, age,

gender, asthma severity, and other demographic data was filled out. A 5-mL sample of peripheral venous blood was collected from each individual. After the separation of serum by centrifugation at 2000 rpm, the level of 25-OH vitamin D was measured using a commercial ELISA kit (DLD Diagnostica, GmbH) according to the manufacturer's instructions. Serum levels of 25 (OH) vitamin D were divided into three groups, including deficient (<20 ng/ml), insufficient (20–30 ng/ml), and sufficient ( $\geq$ 30 ng/ml) [23-24]. SPSS v.15 (SPSS Inc., Chicago, IL.) was used for statistical analysis of data. The independent sample t-test and chi-square analysis were used for comparison of the two groups. The Spearman correlation coefficient was calculated to identify the correlation between serum 25-OH vitamin D level and severity of asthma.  $P < 0.05$  was considered to indicate statistical significance.

### 3. RESULTS

Vitamin D level was  $13.6 \pm 1.1$  ng/ml and  $19.2 \pm 1.8$  ng/ml in asthmatic and non-asthmatic individuals, respectively. The mean ( $\pm$ SD) levels of serum vitamin D were statistically significant between asthmatic and non-asthmatic individuals ( $P = 0.01$ ). Amongst all participants, 52% of cases ( $n = 26$ ) and 62% ( $n = 31$ ) of controls were male. The mean ( $\pm$ SD) age was  $6.8 \pm 0.4$  years for cases and  $7.6 \pm 0.5$  years for the controls. The serum vitamin D levels was  $15.1 \pm 2$ ,  $13.6 \pm 1.4$  and  $10.2 \pm 3.8$  ng/mL in mild intermittent, mild persistent and moderate persistent asthma respectively. Vitamin D levels were lower in patients with moderate persistent asthma than in other groups, but this difference was not statistically significant. However, there was a significant negative correlation between serum

vitamin D level and asthma severity ( $r = 0.242$ ,  $P = 0.015$ ).

Table 1 shows serum vitamin D levels in asthmatic and non-asthmatic female and male individuals. The serum vitamin D levels were  $10.6 \pm 1.4$  ng/ml and  $16.3 \pm 1.4$  ng/ml in female and male individuals, respectively. Statistically significant difference was documented between the two genders ( $P = 0.009$ ). Serum vitamin D levels were compared in asthmatic and non-asthmatic individuals according to age Table 2. The level of vitamin D was significantly lower in asthmatic patients under 5 years ( $P < 0.05$ ). However in older ages no significant difference was demonstrated between the two groups. In the case group, children >11 years had the lowest serum vitamin D levels ( $10.3 \pm 3.7$  ng/ml) and children <5 years had the highest levels ( $17.4 \pm 1.3$  ng/ml), a difference that was statistically significant ( $P = 0.02$ ). This difference was also found to be significant in the control group ( $P = 0.04$ ).

Serum vitamin D levels according to the type of dwelling and childcare situation are shown in Table 3. The serum vitamin D levels in home-cared children were significantly different in asthmatic ( $3.2 \pm 1.3$  ng/mL) and non-asthmatic subjects ( $20.9 \pm 2.1$  ng/mL,  $P = 0.004$ ).

There was statistically significant difference in serum vitamin D levels between asthmatic and non-asthmatic subjects in terms of the type of dwelling. Significantly lower vitamin D concentrations were detected in the asthmatic children living in villa buildings than the control group ( $P = 0.02$ ). However no significant difference was documented in those living in apartments.

**Table 1. Serum vitamin D levels in asthmatic and non-asthmatic subjects according to gender**

Gender (No.)	Vit. D level (ng/mL) asthmatics	Vit. D level (ng/mL) non-asthmatics	P value
Male	$16.3 \pm 1.4$	$21.3 \pm 2.1$	0.06
Female	$10.6 \pm 1.4$	$15.9 \pm 3.4$	0.18
P value	0.009	0.1	

**Table 2. Serum vitamin D levels in asthmatic and non-asthmatic individuals according to age**

Age group	Vitamin D level (ng/mL) Asthmatics	Vitamin D level (ng/mL) Non-asthmatics	P value
Below 5 yrs	$17.4 \pm 1.3$	$25.7 \pm 3.8$	0.05*
5–10 yrs	$11.5 \pm 1.6$	$15.7 \pm 2.1$	0.1
Above 11 yrs	$10.3 \pm 3.7$	$16.1 \pm 3.1$	0.27

**Table 3. Serum vitamin D level according to childcare situation, type of dwelling, maternal age, mother's education and history of taking vitamin D during infancy**

	Case	Control	P value
<b>Childcare situation</b>			
Kindergarten	14.8 ± 1.8	13.2 ± 2.8	0.65
Home	13.2 ± 1.3	20.9 ± 2.1	0.004
P value	0.5	0.04*	
<b>Type of dwelling</b>			
Villa building	14.1 ± 1.2	19.7 ± 2	0.02
Apartment	10.9 ± 2.6	15.3 ± 1.7	0.23
P value	0.3	0.4	
<b>Taking vitamin D during infancy</b>			
Complete	13.6 ± 1.5	18.3 ± 2.8	0.16
Incomplete	12.9 ± 1.9	17.3 ± 3	0.21
Not taking	15.1 ± 3.1	24.1 ± 2.6	0.046*
P value	0.8	0.4	

The mean level of vitamin D (95% CI) was measured according to the parental history of providing supplementary doses of vitamin D to children Table 3. Higher levels of vitamin D were shown in non-asthmatic children who were not taking supplementary vitamin D compared to the children with asthma (P=0.046).

#### 4. DISCUSSION

This study shows that the serum 25-OH vitamin D level in asthmatic children was lower than those in the controls. The role of vitamin D in the pathogenesis of asthma is not fully understood. Vitamin D can influence immune responses by affecting T helper type 1 and type 2 (Th1 and Th2) functions [25]. Polymorphisms in vitamin D receptor-coding genes can correlate with different phenotypes of asthma [26]. There was a significant negative correlation between the serum 25-OH vitamin D level and severity of asthma in this study. Alyasin et al. showed the serum 25-OH D3 levels and childhood asthma severity are inversely associated and suggested a direct relationship between pulmonary function test results and vitamin D deficiency in Iranian asthmatic children [27]. In Qatar, with a similar social and climate conditions to Iran, Bener et al found asthmatic children had significantly reduced levels of serum vitamin D compared to the non-asthmatic controls [28]. Brehm et al showed that the severity of asthma and increased markers of allergy are correlated with a low level of serum vitamin D [28].

Litonjua shows that the use of supplementary vitamin D in the diet can play a primary preventive role in the incidence of asthma, reduce the severity of asthma, and improve

recovery from steroid-resistant asthma. In this study, there was no significant difference in the serum vitamin D levels in children with a history of taking sufficient amounts of vitamin D in supplemental form with those who did not take supplementary vitamin D (at least 400 IU per day) during infancy. Failing to remember vitamin D supplementation by mothers is a factor that should be taken into consideration. An unexpected finding in Table 3 is the higher serum Vit D levels in the children not supplemented with Vit D. One possible explanation for this finding is the vitamin D supplementation through enriched formula during infancy.

Studies showed that children who have taken supplementary vitamin D during the first year of life have a lower risk of asthma at 31 years of age, but there was no report of vitamin D levels during this period [29]. A meta-analysis of randomized trials show the rate of asthma exacerbation can reduce by vitamin D supplementation especially in patients with vitamin D insufficiency [30]. Litonjua (2019) suggested vitamin D supplementation can prevent asthma and wheeze in early life, and may help in treatment of asthma [31].

Gale shows that the prevalence of asthma at the end of the first decade of life has a negative correlation with the serum vitamin D levels of mothers in the third trimester of pregnancy [32]. A deficiency of vitamin D in the prenatal period can influence the development of the fetal lungs and immune system [18].

This study shows that serum vitamin D levels were lower in female than in male patients, this

difference may be due to body coverage in female patients. In one study conducted in Turkey, the lowest serum vitamin D levels were found in women who cover their whole body from sunlight [33]. Gender is a significant factor in vitamin D insufficiency as indicating in our findings as well as in a study carried out in Tehran by Rabbani et al. They found the prevalence of vitamin D insufficiency in healthy subjects was 53.6% in girls and 11.3% in boys [24]. A study in Saudi Arabia showed the levels of vitamin D in asthmatic and non-asthmatic females was lower than males which is in accordance with the results of the present study [34]. Despite higher sunny days in the region throughout the year, these findings can be attributed to the body coverage of females due to the social, cultural and behavioral aspects of this issue. Findings of the present study indicate that in children living in villa dwellings the serum vitamin D level was lower in asthmatic than non-asthmatic group. This difference might be due to limited outdoor activities and lower sun exposure time in asthmatic children.

Mirsaeid Ghazi et al showed that children under 10 years of age have higher serum vitamin D levels in contrast to older age groups and the level of serum vitamin D decreases with increasing age [35]. These data are in accordance with our findings. The difference in the serum vitamin D levels in the early years of life in contrast to later years can be due to more attention given by parents to vitamin D supplementation of children in the early years of life and more exposure to sunlight due to more time spent on outdoor activities by this age group.

It has been shown that low levels of serum vitamin D are correlated with more severe forms of asthma. Brehm demonstrated that vitamin D insufficiency can develop more severe forms of asthma exacerbation in Puerto Rican children [36]. Tabak et al reported that using some foods, such as fish, containing high amounts of vitamin D can protect children from asthma [37]. Vitamin D deficiency is common in different parts of Iran [38]. Twenty-six percent of primary school children in Isfahan had vitamin D deficiency [39]. In Shiraz 81.3% of healthy children were vitamin D efficient [40]. In Zahedan, southeast of Iran, vitamin D deficiency was reported in 94.7% of apparently health subjects [41]. High prevalence of vitamin D deficiency may be due to the low dietary intake of vitamin D, reduced sunlight exposure and low physical activity [40-41].

## 5. CONCLUSIONS

In conclusion findings of the present study demonstrate the significance of vitamin D in asthma. The level of serum vitamin D in asthmatic patients was significantly lower than those in controls. The severity of asthma had a significant negative correlation with serum vitamin D levels. Further studies are required to determine the role of vitamin D in the prevention of asthma and in decreasing its severity. To this end, sufficient doses of vitamin D should be administered to pregnant mothers and the babies monitored for symptoms of wheezing or asthma during childhood in future years.

## CONSENT

Written and informed parental consent was obtained from all cases and controls.

## ETHICAL APPROVAL

The study was approved by the research ethics committee of the University.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Ferrante G, La Grutta SL. The burden of pediatric asthma. *Frontiers in Pediatrics*. 2018;6:186.
2. Hassanzadeh J, Mohammadbeigi A, Mousavizadeh A, Akbari M. Asthma prevalence in Iranian guidance school children: A descriptive meta-analysis. *Journal of Research in Medical Sciences*. 2012;17(3):293.
3. Liu AH, Covar RA, Spahn JD, Sicherer SH. Childhood Asthma, In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF. *Nelson Textbook of Pediatrics*. Philadelphia. 2016;1095-6.
4. Somashekar AR, Prithvi AB, Gowda MV. Vitamin D levels in children with bronchial asthma. *Journal of Clinical and Diagnostic Research: JCDR*. 2014;8(10):PC04.
5. Radia I, Denisc H-than, Wise MR. Serum vitamin levels and the risk of asthma in children. *AM Journal Epidemiol* 2004;159: 351-7.
6. Brehm JM, Celedón JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, Laskey D, Sylvia JS, Hollis BW, Weiss ST,

- Litonjua AA. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *American Journal of Respiratory and Critical Care Medicine*. 2009;179(9):765-71.
7. Chambers ES, Hawrylowicz CM. The impact of vitamin D on regulatory T cells. *Current Allergy and Asthma Reports*. 2011; 11(1):29-36.
  8. May E, Asadullah K, Zugel U. Immunoregulation through 1, 25-dihydroxyvitamin D 3 and its analogs. *Current Drug Targets-Inflammation & Allergy*. 2004;3(4):377-93.
  9. Crew KD, Gammon MD, Steck SE, Hershman DL, Cremers S, Dworakowski E, Shane E, Terry MB, Desai M, Teitelbaum SL, Neugut AI. Association between plasma 25-hydroxyvitamin D and breast cancer risk. *Cancer Prevention Research*. 2009;2(6):598-604.
  10. Zhou W, Heist RS, Liu G, Asomaning K, Neuberg DS, Hollis BW, Wain JC, Lynch TJ, Giovannucci E, Su L, Christiani DC. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. *Journal of Clinical Oncology*. 2007;25(5):479-85.
  11. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: A birth-cohort study. *The Lancet*. 2001;358 (9292):1500-3.
  12. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006;296(23):2832-8.
  13. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: Results from the Iowa Women's Health Study. *Arthritis & Rheumatism*. 2004;50(1):72-7.
  14. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Progress in Biophysics and Molecular Biology*. 2006;92 (1):60-4.
  15. Nguyen TM, Guillozo H, Marin L, Tordet C, Koite S, Garabedian M. Evidence for a vitamin D paracrine system regulating maturation of developing rat lung epithelium. *American Journal of Physiology-Lung Cellular and Molecular Physiology*. 1996;271(3):L392-9.
  16. Phokela SS, Peleg S, Moya FR, Alcorn JL. Regulation of human pulmonary surfactant protein gene expression by 1 $\alpha$ , 25-dihydroxyvitamin D3. *American Journal of Physiology-Lung Cellular and Molecular Physiology*. 2005;289(4):L617-26.
  17. Camargo Jr CA, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, Kleinman K, Gillman MW. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *The American Journal of Clinical Nutrition*. 2007;85(3):788-95.
  18. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. *Current Opinion in Allergy and Clinical Immunology*. 2009;9(3):202.
  19. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *Journal of Allergy and Clinical Immunology*. 2007;120(5):1031-5.
  20. Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo Jr CA, Kerley CP, Jensen ME, Mauger D, Stelmach I, Urashima M, Martineau AR. Vitamin D supplementation to prevent asthma exacerbations: A systematic review and meta-analysis of individual participant data. *The Lancet Respiratory Medicine*. 2017;5 (11):881-90.
  21. Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. *Current opinion in allergy and clinical immunology*. 2012;12(2):179.
  22. National Asthma Education and Prevention Program. Expert panel report 3: Guidelines for the diagnosis and management of asthma. NIH pub no 07-4051. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2007. Available:<http://www.nhlbi.nih.gov/guidelines/asthma/>.
  23. Thomas GO, Tutar E, Tokuc G, Oktem S. 25-hydroxy vitamin D levels in pediatric asthma patients and its link with asthma severity. *Cureus*. 2019;11(3):e4302.
  24. Rabbani A, Alavian SM, Motlagh ME, Ashtiani MT, Ardalan G, Salavati A, Rabbani B, Rabbani A, Shams S, Parvaneh N. Vitamin D insufficiency among children and adolescents living in Tehran, Iran. *Journal of Tropical Pediatrics*. 2008;55(3):189-91.
  25. Mahon BD, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *Journal of Cellular Biochemistry*. 2003;89(5):922-32.

26. Raby BA, Silverman EK, Lazarus R, Lange C, Kwiatkowski DJ, Weiss ST. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. *Human Molecular Genetics*. 2003;12(16):1973-9.
27. Alyasin S, Momen T, Kashef S, Alipour A, Amin R. The relationship between serum 25 hydroxy vitamin d levels and asthma in children. *Allergy, Asthma & Immunology Research*. 2011;3(4):251-5.
28. Bener A, Ehlayel MS, Tulic MK, Hamid Q. Vitamin D deficiency as a strong predictor of asthma in children. *International Archives of Allergy and Immunology*. 2012; 157(2):168-75.
29. Hyppönen EL, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, Järvelin MR. Infant vitamin d supplementation and allergic conditions in adulthood: Northern Finland birth cohort 1966. *Annals of the New York Academy of Sciences*. 2004; 1037(1):84-95.
30. Wang M, Liu M, Wang C, Xiao Y, An T, Zou M, Cheng G. Association between vitamin D status and asthma control: A meta-analysis of randomized trials. *Respiratory Medicine*. 2019;150:85-94.
31. Litonjua AA. Vitamin D and childhood asthma: causation and contribution to disease activity. *Current Opinion in Allergy and Clinical Immunology*. 2019;19(2):126-31.
32. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, Godfrey KM, Cooper C. Maternal vitamin D status during pregnancy and child outcomes. *European Journal of Clinical Nutrition*. 2008;62(1):68.
33. Alagöl F, Shihadeh Y, Boztepe H, Tanakol R, Yarman S, Azizlerli H, Sandalci Ö. Sunlight exposure and vitamin D deficiency in Turkish women. *Journal of Endocrinological Investigation*. 2000;23(3): 173-7.
34. Al-Daghri NM, Al-Attas OS, Yakout SM, Alnaami AM, Wani K, Alokail MS. The association of serum 25-OH vitamin D with asthma in Saudi adults. *Medicine*. 2018; 97(36).
35. Ghazi AM, Zadeh FR, Pezeshk P, Azizi F, Cacicedo L. Seasonal variation of serum 25 hydroxy D3 in residents of Tehran. *Journal of Endocrinological Investigation*. 2004;27(7):676-9.
36. Brehm JM, Acosta-Pérez E, Klei L, Roeder K, Barmada M, Boutaoui N, Forno E, Kelly R, Paul K, Sylvia J, Litonjua AA. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. *American journal of respiratory and critical care medicine*. 2012;186(2):140-6.
37. Tabak C, Wijga AH, de Meer G, Janssen NA, Brunekreef B, Smit HA. Diet and asthma in Dutch school children (ISAAC-2). *Thorax*. 2006;61(12):1048-53.
38. Heshmat R, Mohammad K, Majdzadeh SR, Forouzanfar MH, Bahrami A, Ranjbar Omrani GH. Vitamin D deficiency in Iran: A multi-center study among different urban areas. *Iran Journal of Public Health*. 2008; 37(1):72-8.
39. Ardestani PM, Salek M, Keshteli AH, Nejadnik H, Amini M, Hosseini SM, Rafati H, Kelishadi R, Hashemipour M. Vitamin D status of 6-to 7-year-old children living in Isfahan, Iran. *Endokrynologia Polska*. 2010;61(4):377-82.
40. Saki F, Dabbaghmanesh MH, Omrani GR, Bakhshayeshkaram M. Vitamin D deficiency and its associated risk factors in children and adolescents in southern Iran. *Public Health Nutrition*. 2017;20(10): 1851-6.
41. Kaykhaei MA, Hashemi M, Narouie B, Shikhzadeh A, Rashidi H, Moulaei N, Ghavami S. High prevalence of vitamin D deficiency in Zahedan, southeast Iran. *Annals of Nutrition and Metabolism*. 2011; 58(1):37-41.

© 2019 Bazargan and Nazari; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*  
*The peer review history for this paper can be accessed here:*  
<http://www.sdiarticle3.com/review-history/50527>