Review Article

Vitamin D and asthma in children: A systematic review and meta-analysis of observational studies

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ABSTRACT

There is growing literature suggesting a link between Vitamin D deficiency and asthma in children, but systematic reviews are lacking. The aim of this study is to evaluate the prevalence of Vitamin D deficiency in asthmatic children and to assess the correlations of Vitamin D levels with asthma incidence, asthma control, and lung functions. PubMed, EMBASE, and Cochrane Library were searched for observational studies on asthma and Vitamin D. Two authors independently extracted data. Meta-analysis was performed using the Review Manager Software. A total of 23 (11 case–control, 5 cohort, and 7 cross-sectional) studies enrolling 13,160 participants were included in the review. Overall, Vitamin D deficiency and insufficiency were prevalent in 28.5% and 26.7% children with asthma, respectively. The mean 25-hydroxyvitamin D (25(OH)D) levels (10 studies) were significantly lower in asthmatic children as compared to nonasthmatic children with a mean difference of −9.41 (95% confidence interval [CI] −16.57, −2.25). The odds ratio of Vitamin D deficiency (eight case–control studies) was significantly higher among asthmatic children as compared to nonasthmatic children (odds ratio 3.41; 95% CI 2.04, 5.69). Correlations between Vitamin D levels and incidence of asthma, lung functions, and control of asthma had mixed results. To conclude, asthmatic children had lower 25(OH)D levels as compared to nonasthmatic children, but the correlations between 25(OH)D and asthma incidence, asthma control, and lung functions were varied. Well-designed randomized controlled trials are required to determine if children with asthma can benefit from Vitamin D supplementation.

KEY WORDS: Asthma, children, meta-analysis, observational studies, Vitamin D

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INTRODUCTION

Bronchial asthma is one of the most common diseases affecting the children worldwide.[1] Several observational studies suggest that serum Vitamin D deficiency is also common in children.[2-4] Vitamin D is an immunomodulator[5] and Vitamin D receptors (VDRs) are present in cells of the immune system such as macrophages, dendritic cells, monocytes, and activated T- and B-cells.[6] VDRs regulate the transcription of various genes implicated in inflammation and immunomodulation of respiratory epithelium.[7] Vitamin D suppresses the proinflammatory cytokines interleukin-17 (IL-17) and IL-13 and promotes the anti-inflammatory cytokines such as IL-10. Further, Vitamin D shifts the balance of T lymphocyte response from Th1 phenotype to Th2 phenotype.[8,9] Studies on Vitamin D and asthma in children had mixed results. The low maternal 25-hydroxyvitamin D (25(OH)D) levels[10,11] and low cord blood 25(OH)D levels[12] had been associated with increased risk of early childhood wheezing. However, in another study,

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.209227

How to cite this article: Jat KR, Khairwa A. Vitamin D and asthma in children: A systematic review and meta-analysis of observational studies. Lung India 2017;34:355-63.

higher Vitamin D levels during pregnancy were associated with increased risk of eczema at age of 9 months and asthma at age of 9 years in offspring.[13] Vitamin D deficiency has been associated with increased incidence[14] and severity[15] of childhood asthma. A few observational studies suggested association between low serum Vitamin D levels and poor asthma control and reduced lung function in children.[15-17] Whereas some other studies had adverse effects of Vitamin D in asthma.[13,18] In a study, Vitamin D supplementation during 1st year of life was associated with higher prevalence of allergic rhinitis, atopy, and asthma at age of 31 years of life.[18] The question of whether or not Vitamin D deficiency is a risk factor for pediatric asthma needs to be clarified. We conducted a systematic review and meta-analysis to evaluate the prevalence of Vitamin D deficiency in asthmatic children and to determine the correlation between Vitamin D levels and asthma incidence, asthma control, and lung functions in children.

MATERIALS AND METHODS

We searched the literature from PubMed, EMBASE, and Cochrane Library. The PubMed database was searched using MeSh terms for asthma and Vitamin D without any filters. The EMBASE database was searched with keywords "'vitamin d'/exp and 'asthma'/exp" without any filter. The Cochrane Library was searched with keywords "asthma" and "vitamin d" in title and abstract without any other filter. The last search for PubMed, EMBASE, and Cochrane was repeated on July 27, 2015. Reference list of eligible studies was hand searched for additional studies.

Inclusion criteria

Type of studies: Observational studies - cross-sectional studies, case–control studies, and cohort studies; population - children up to 18 years of age; content of study - related to asthma and Vitamin D.

Exclusion criteria

1. Randomized controlled trials (RCTs) assessing effect of Vitamin D supplementation on asthma as this was not the objective of the review
2. Studies comparing maternal serum level of Vitamin D with incidence of asthma in children.

The outcome measures of review were (1) mean Vitamin D levels among asthmatic and nonasthmatic children; (2) prevalence of Vitamin D deficiency and insufficiency among asthmatic and nonasthmatic children; and (3) relation between Vitamin D levels and incidence, lung functions, and control of asthma in children. Serum 25(OH)D levels of <20 ng/ml, between 20 and 30 ng/ml, and levels of 30–40 ng/ml are defined as Vitamin D deficient, Vitamin D insufficient, and Vitamin D sufficient levels in the review based on previously published studies, respectively.[19-22] Prevalence of Vitamin D deficiency and insufficiency was assessed using these definitions. Definition of incidence, lung functions, and asthma control were used as described by included studies.

Two authors independently assessed the title and abstract of electronic search results for potential eligible studies. The full texts of potential eligible studies were obtained and studies were selected for inclusion in the review as per inclusion criteria above. Two authors independently retrieved data in a predefined data collection proforma.

Quality assessment methods

The Newcastle–Ottawa Scale[23] (NOS) was used for assessing quality of nonrandomized studies (cohort and case–control studies).

Statistical methods

We analyzed dichotomous outcomes by calculating odds ratio (OR). Continuous outcome data were analyzed as mean differences (MDs). We presented overall results with 95% confidence intervals (CIs). Meta-analysis was performed using Cochrane RevMan 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.[24] Meta-analysis was only performed on studies of similar design and outcome measures and that comparison of different study types and outcomes are simply presented in the text.

The review was performed as per preferred reporting items for systematic reviews and meta-analyses statement for reporting systematic reviews and meta-analyses wherever applicable.

RESULTS

Study selection

The flow diagram for study selection is shown in Figure 1. The electronic database search revealed a total of 1822 records. Sixty potential eligible studies were identified after screening for titles and abstracts of all records. Full

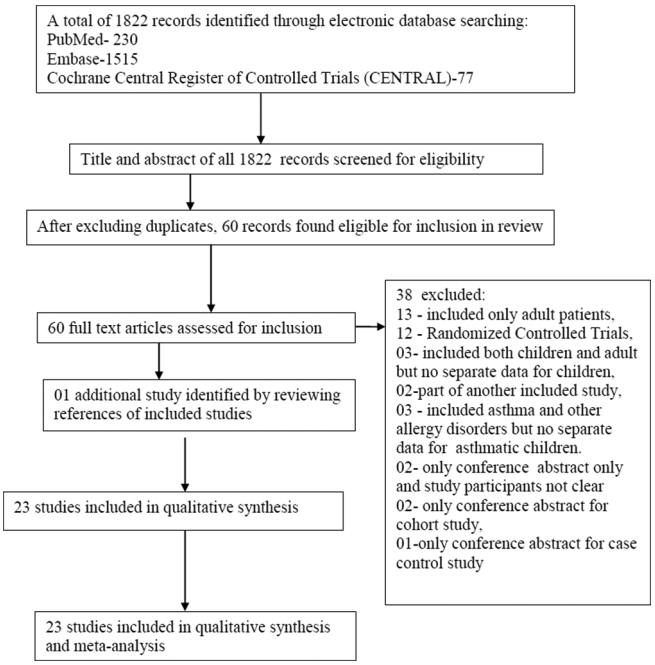

Figure 1: Study selection flow diagram

texts of 60 potential eligible studies were assessed for final inclusion in the review. One additional study was identified by reviewing references of included studies. Thirty-eight studies were excluded as per the reasons given in Figure 1 and remaining 23 studies were included in the review.

Included studies

The data extractions from 23 included studies are shown in Tables 1-3. There were 11 case–control studies[16,25-34] [Table 1], 5 cohort studies[9,14,35-37] [Table 2], and 7 cross-sectional studies[15,38-43] [Table 3]. A total of 13,160 subjects were enrolled in included studies: Case–control studies, 2979; cohort studies, 7830; and cross-sectional studies, 2351. Included studies were both from developed and developing countries: USA (n = 4), Italy (n = 2), Turkey (n = 2), one each from UK, Qatar, China, Tunisia, Iran, USA, Costa Rica, Egypt, The Netherlands, Australia, New Zealand, Canada, Germany, and Thailand. Origin of country was not known for a few studies where only conference abstracts were available.

Quality of studies

Assessment of quality of case–control and cohort studies using NOS is shown in last row of Tables 1 and 2, respectively. A majority of studies were of moderate to high quality.

Outcomes

Meta-analysis of included studies was performed using Review Manager and results are shown in Table 4 and Figures 2-4. There was significant heterogeneity among studies; therefore, random effect model was used for meta-analysis.

Mean Vitamin D levels among asthmatic and nonasthmatic children

Mean 25(OH)D levels were available from 10 case–control studies enrolling 2383 participants. Five studies[25,27,29,31,34] had significantly lower mean 25(OH)D levels in asthmatic children as compared to nonasthmatic children [Figure 2]. In other five studies,[19,26,28,30,33] mean 25(OH)D levels were not different between the groups. After pooling data from the 10 studies, the mean 25(OH)D levels were significantly lower in asthmatic children as compared to nonasthmatic children with MD of −9.41 (95% CI −16.57, −2.25) [Table 4 and Figure 2].

Prevalence of Vitamin D deficiency and insufficiency among asthmatic and nonasthmatic children

Vitamin D status was extracted from cohort and case–control studies. Prevalence of Vitamin D deficiency and insufficiency varied markedly between different studies ranging from 3.4% to 77.4% and 4.1% to 85.8%, respectively [Tables 1 and 3]. Overall, on an average, 28.5% and 26.7% children were Vitamin D deficient and insufficient, respectively.

Data regarding proportion of children having Vitamin D deficiency among asthmatic versus nonasthmatic children were available from eight case–control studies enrolling 1795 patients. After pooling data, OR of asthmatic children being Vitamin D deficient (levels <20 ng/ml) was 3.41 (95% CI 2.04, 5.69) [Table 4 and Figure 3]. OR of asthmatic children having Vitamin D levels below 30 ng/ml (after combining subjects with both insufficiency and deficiency) was 2.34 (95% CI 1.23, 4.43) [Table 4 and Figure 3].

Children without asthma had Vitamin D levels more sufficient as compared to asthmatic children [Figure 4].

Relation between Vitamin D levels and incidence of asthma

Four cohort studies reported relation of Vitamin D levels with incidence and prevalence. van Oeffelen *et al.*[14] assessed relation between serum micronutrient concentrations including Vitamin D and prevalence of asthma in children and found that there was inverse associations between serum Vitamin D concentrations and asthma and severe asthma at age of 4 years with OR of 0.49, 95% CI: 0.25–0.95, although there was no association between serum Vitamin D concentrations and severe asthma at 8 years of age in the same study.[14] Camargo *et al.*[9] assessed association between cord blood Vitamin D levels and respiratory outcome at 5 years of age and found that there was increased incidence of

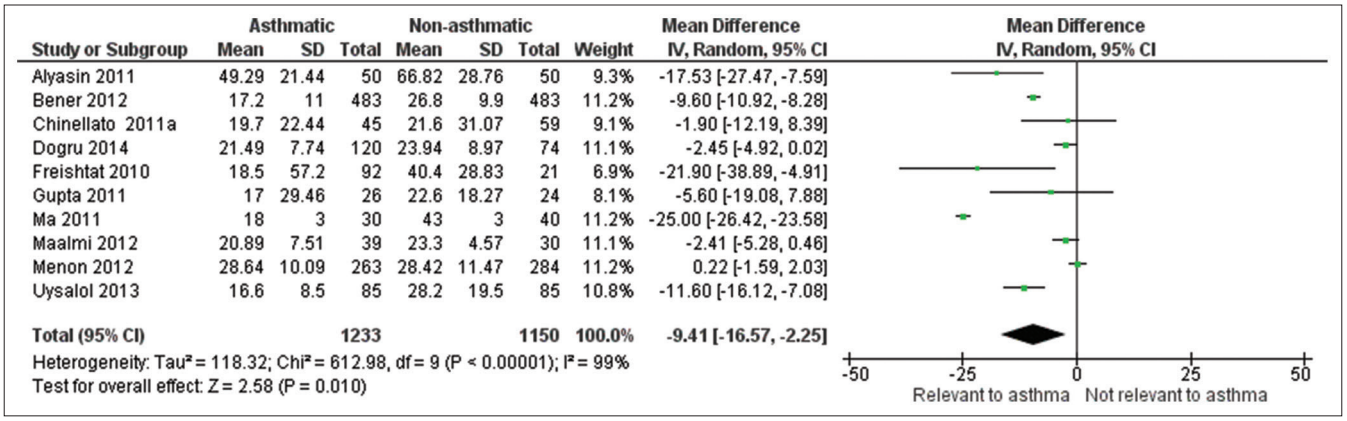

Figure 2: Forest plot of comparison of mean 25-hydroxyvitamin D levels in asthmatic and nonasthmatic children

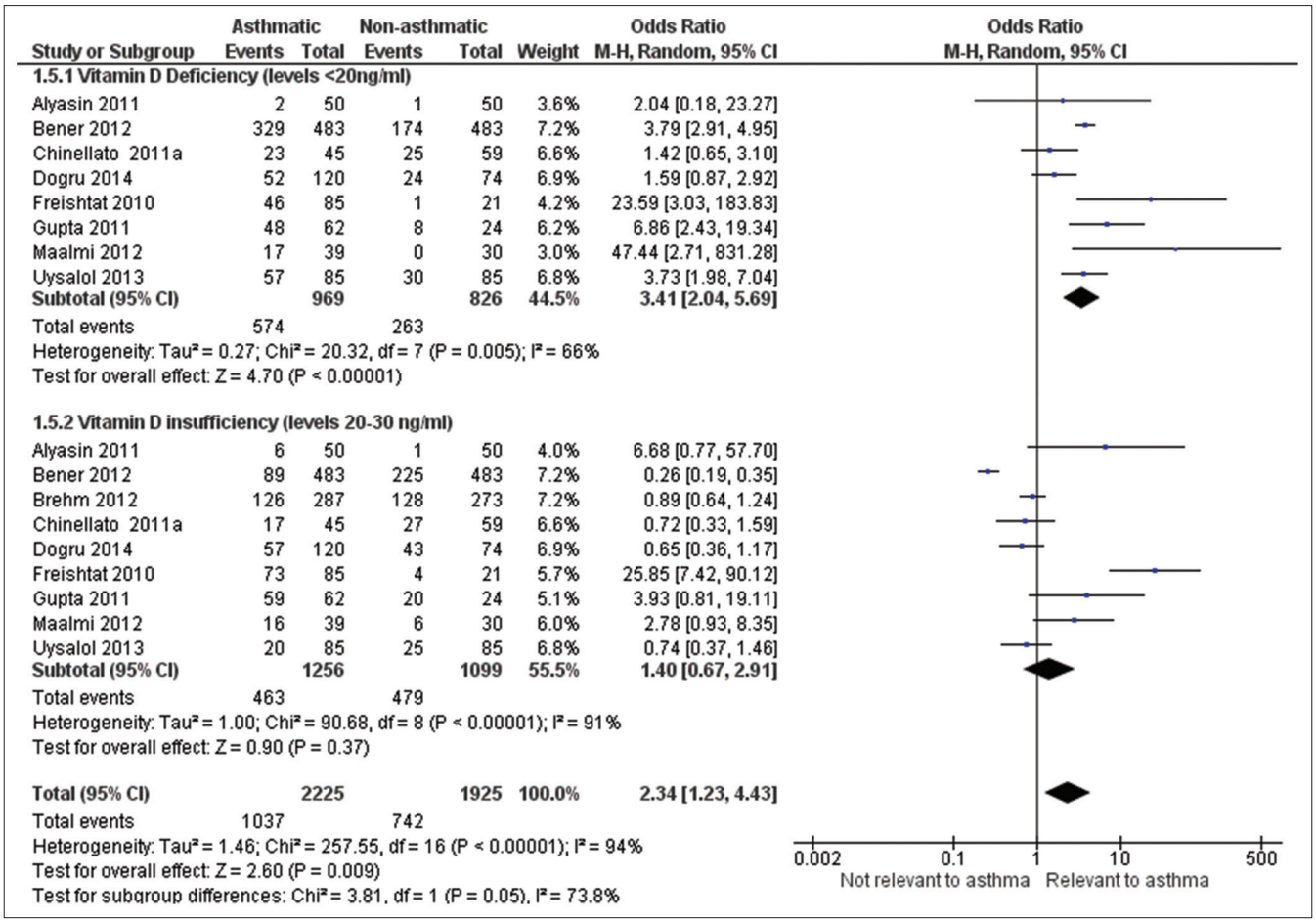

Figure 3: Forest plot of proportion of asthmatic and nonasthmatic children with Vitamin D deficiency and insufficiency

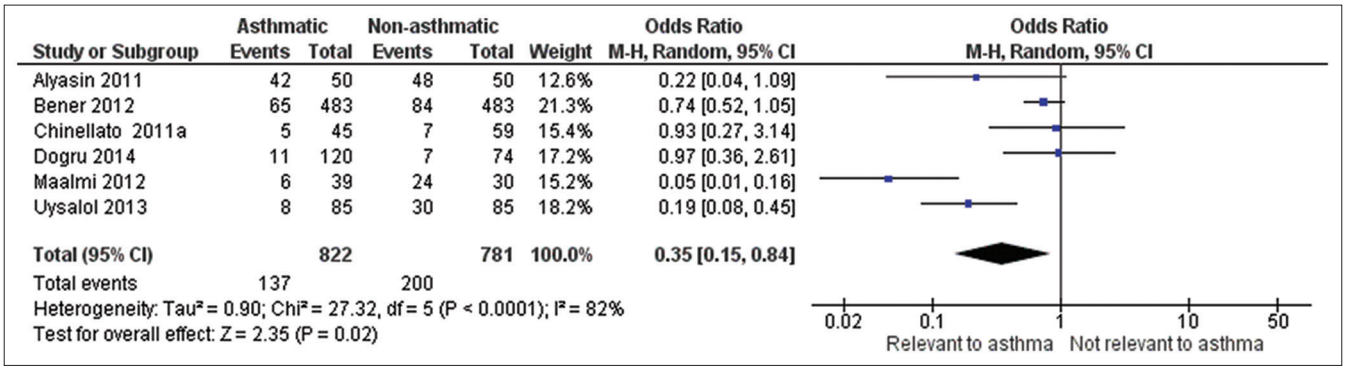

Figure 4: Forest plot of proportion of asthmatic and nonasthmatic children with Vitamin D sufficiency

cumulative wheezing (OR [95% CI] = 1.63 [1.17, 2.26] and 2.15 [1.39, 3.33]) for insufficiency and deficiency, respectively, as compared to sufficiency at 5 years of age but there was no association between cord blood Vitamin D levels and incidence of asthma at 5 years of age with OR of 1.19 (95% CI 0.78, 1.83) and 0.94 (95% CI 0.53, 1.64) for insufficiency and deficiency as compared to sufficiency, respectively.[9] In a West Australian pregnancy cohort study by Hollams *et al.*,[36] asthma at age of 14 years was not related to Vitamin D levels with OR of 0.39 [95% CI 0.09, 1.62; $P = 0.1930$].

Relation between Vitamin D levels and lung functions

Five studies[26,16,31,39,43] reported significant association between Vitamin D levels and lung functions in asthmatic children including forced expiratory volume in 1 s (FEV_1),[16,26,31,39,43] FEV_1/forced vital capacity (FVC),[31,39,43] bronchodilator response,[26] and exercise-induced bronchoconstriction[16] in asthmatic children. On the other side, there was no correlation between Vitamin D levels and FEV_1 and FEV_1/FVC in asthmatic children in the study by Brehm *et al.*,[15] Maalmi *et al.*,[30] Wu *et al.*,[35] Chinellato *et al.*,[38] Krobtrakulchai,[41] and Neagu.[42]

Table 1: Case–control studies for asthma and Vitamin D in children

Study ID	Bener *et al*., 2012[25]		Gupta *et al*., 2011[26]		Chinellato *et al*., 2011[16]		Freishtat *et al*., 2010[27]		Menon *et al*., 2012[28] (abstract)		Brehm *et al*., 2012[32] (abstract)		Ma and Zhen 2011[29] (abstract)		Maalmi *et al*., 2012[30]		Alyasin *et al*., 2011[31]		Dogru *et al*., 2014[33]		Uysalol *et al*., 2013[34]	
Study site (s)	Qatar		London		Italy		Washington, DC		USA		USA		China		Ariana, Tunisia		Iran		Turkey		Turkey	
Groups	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control	Cases	Control
Source of selection	Pediatric allergy clinic	Primary healthcare centers	Hospital	Hospital	Outpatients	Healthy subjects	With asthma	Without asthma	NA	NA	Puerto Rican children	NA	NA	NA	From department	From pediatric emergency	Motahari clinic	Healthy control	Asthmatic children from clinic	Children without allergic diseases	Asthmatic children from clinic	Healthy children from social clinic
Number of subjects	483	483	62	24	45	59	92	21	263	284	287	273	30	40	39	30	50	50	120	74	85	85
Age mean (±SD) (years)	7.0 (3.8)	8.4 (3.6)	11.5 (9.5-14)*	10.5 (9-13)*	NA	NA	11.1 (SE 0.4)	7 (0.3) *P*<0.001	Range 2-19 years	Range 2-19 years	Range 6-14 years	6-14 years	NA	NA	Median 9.8 (6-16)	9.2	9.31±2.67	10.91±3.28	4.4±1.2	4.6±1.5	6.2±2.4	6.2±2.4
Male/female	247/236	247/236	32/30	15/9	27/18	36/23	58/34	8/13 *P*=0.05	NA	NA	NA	NA	NA	NA	27/12	20/10	31/19	31/19	73/47	38/36	NA	NA
Vitamin D levels mean (±SD) ng/ml	17.2 (11.0)	26.8 (9.9) *P*<0.05	11.2 (8.8-15.2)*	22.6 (18-26.8)* *P*=0.001	19.7 (15.2-23)*	21.6 (16.3-25.7) *P*=0.268	18.5 (11.3-25.1)*	40.4 (34.6-49.5)* *P*=0.002	28.64±10.09	28.42±11.47 *P*=1.0	NA	NA	18±3	43±3 *P*<0.01	20.89±7.51	23.30±4.57 *P*=0.12	49.29±21.44	66.82±28.76 *P*=0.001	21.49±7.74	23.94±8.97 *P*=0.094	16.6±8.5	28.2±19.5 *P*=<0.001
Number of Vitamin D status#																						
Suff.	65/483	84/483	NA	NA	5/45	7/59	NA	NA	NA	NA	NA	NA	NA	NA	6/39	24/30	42/50	48/50	11/120	7/74	8/85	30/85
Insuff.	89/483	225/483	59/62	20/24	17/45	27/59	73/85	NA	NA	126/287	128/273	NA	NA	NA	16/39	6/30	6/50	1/50	57/120	43/74	20/85	25/85
Def.	329/483	174/483	48/62	8/24	23/45	25/59	46/85	NA	NA	NA	NA	NA	NA	NA	17/39	0/30	2/50	1/50 *P*=0.094	52/120	24/74 *P*=0.302	57/85	30/85 *P*<0.001
Controls matched for	Age, sex, ethnicity		NA		NA		Locality, enrollmentsiteandobesity		Age		NA		NA		Age and sex		NA		NA		Epidemiological characters	
Relation between FEV_1 and Vitamin D levels	NA		NA		NA		NA		NA		NA		NA		No correlation (r=0.319; *P*=0.0507		Significant correlations; R^2=0.318; *P*=0.024		NA		NA	
Quality of study (NOS)	Selection**** Comparability** Exposure***		Selection*** Comparability* Exposure***		Selection*** Comparability* Exposure***		Selection*** Comparability* Exposure***		Quality not assessed as only abstract was available				Quality not assessed as only abstract was available		Selection*** Comparability** Exposure***		Selection*** Comparability** Exposure***		Selection*** Comparability** Exposure***		Selection*** Comparability* Exposure***	

*Median (IQR), NOS: Newcastle–Ottawa Scale, NA: Data not available, SE: Standard error, #Vitamin D status - Suff.: Sufficient (>30 ng/ml), Insuff.: Insufficient (20-30 ng/ml), Def.: Deficient (<20 ng/ml), IQR: Interquartile range, SD: Standard deviation, FEV_1: Forced expiratory volume in 1 s, *P* value <0.05 is significant. Quality of study: Increasing number of stars (*) indicate good quality of study. There are maximum four, two and three stars for Selection, Comparability, and Exposure respectively

Table 2: Cohort studies for asthma and Vitamin D in children

Study ID	Wu *et al*., 2012[35]			Van Oeffelen *et al*., 2011[14]			Hollams *et al*., 2011[36]			Camargo *et al*., 2011[9]			Wawro *et al*., 2014[37]		
Study type (prospective/ retrospective)	Prospective			Prospective and cross sectional study			Prospective			Prospective			Retrospective		
Study site(s)	Multicentric USA			The Netherlands			Brisbane, Australia			New Zealand			Germany		
Vitamin D measured at age of	NA			NA			NA			Cord blood at birth			10 years		
Outcome assessed at age of	NA			NA			NA			5 years			Lifetime till 10 years of age		
Duration of follow-up	FEV_1 and BDR - 12 months, PC_{20}-8 months			Up to 2008, assessment at 4 years and 8 years			6 years, 14 years			5 years			10 years		
Total number of subjects/ Vitamin D levels available	1041/1024			700 (at 4 years=372, at 8 years=328)			At 6 years - 989, at 14 years - 1380			922/922			2815/2815		
Confounding factors controlled for	Age, sex, height, and baseline FEV_1			Season, sex, parental atopy and smoking			Sex, collection month			season			NA		
Mean (±SD) Vitamin D; ng/ml	37.8 (15.7)			NA			NA			Median IQR 17.6 (11.6-31.2)			29.7 (9.3)		
	Vitamin D status#			**Vitamin D status#**			**Vitamin D status# (at age 14)**			**Vitamin D status#**			**Vitamin D status#**		
	Suff.	**Insuff.**	**Def.**	**Suff.**	**Insuff.**	**Def.**	**Suff.**	**Insuff.**	**Def.**	**Suff. (≥30)**	**Insuff. (10-30)**	**Def. (<10 ng/ml)**	**Suff.**	**Insuff.**	**Def.**
Number of subjects as per Vitamin D status	663	260	101	NA	NA	NA	818	501	61	251/922	491/922	180/922	NA	NA	NA
Male/female	405/258	146/114	60/41	NA	NA	NA	Overall at age 6 years 554/435, at age 14 years 380/313			128/123	255/236	83/97	NA	NA	NA
Lost to follow-up	-	-	-				Total 296 in all group			Total 99 lost to follow-up at 5 years			NA	NA	NA
Incidence of asthma	NA	NA	NA	NA	NA	NA	NA			OR (95% CI)=1.19 (0.78-1.83) and 0.94 (0.53-1.64) for insuff. and def. to suff.			NA	NA	NA
Prevalence of asthma at outcome assessment	NA	NA	NA	4-year-old subgroup: Inverse associations; 8 years old sub-group: No association			At 14 years 79/793	At 14 years 61/542	NA	NA	NA	NA	No association with Vitamin D		
FEV_1 mean (±SD) L/s at outcome assessment	Only for ICS group 1.93 (0.73)	2.01 (0.65)	1.97 (0.43) *P*=0.08	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
Change in FEV_1 mean (±SD) L/s	0.30 (0.023)	0.033 (0.031)	0.14 (0.057) *P*=0.0072	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
Asthma exacerbations	OR (insuff. and def./suff.) 1.76 (95% CI 1.01-3.09)			NA			NA	NA	NA	NA	NA	NA	NA		
Linear relationship between Vitamin D level and lung function	No linear relationship between Vitamin D levels and FEV_1, BDR and PC_{20}							NA	NA	NA	NA	NA	NA		
Quality of study (NOS)	Selection**** Comparability** Outcome***			Selection*** Comparability* Outcome*			Selection*** Comparability* Outcome*			Selection**** Comparability** Outcome*			Selection**** Comparability* Outcome**		

NOS: Newcastle–Ottawa Scale, OR: Odds ratio, NA: Data not available, #Vitamin D status - Suff.: Sufficient (>30 ng/ml), Insuff.: Insufficient (20-30 ng/ml), Def.: Deficient (<20 ng/ml), BDR: Bronchodilator response, SD: Standard deviation, FEV_1: Forced expiratory volume in 1 s, OR: Odds ratio, CI: Confidence interval, ICS: Inhaled corticosteroid, IQR: Interquartile range, *P* value <0.05 is significant. Quality of study: Increasing number of stars (*) indicate good quality of study. There are maximum four, two and three stars for Selection, Comparability, and Outcome respectively

Table 3: Cross-sectional studies for asthma and Vitamin D in children

Study ID	Chinellato *et al*., 2011[38]	Searing *et al*., 2010[39]	Brehm *et al*., 2009[15]	Niruban *et al*., 2012[40] (conference abstract)	Krobtrakulchai 2012[41] (conference abstract)	Neagu 2012[42] (conference abstract)	Elnady *et al*., 2012[43] (conference abstract)
Country	Verona, Italy	Denver	Costa Rica	Canada	NA	Chicago, USA	Egypt
Study period	November 2008 to March 2009	NA	February 2001 to December 2006	2007-2009	NA	April-August 2011	NA
Number of patients	75	100	616	1213	90	72	185
Age mean±SD (range) years	9.6±1.7 (5-11)	Median IQR 7 (4-10) range 0-18	Median 8.7 (7.6-10.5) (range 6-14)	Range 5-12 years	11±3	Below 18 years	Range 5-12 years
Male/female	43/32	64/36	370/246	637/576	61/29	NA	105/80
Vitamin D mean±SD (ng/ml)	NA	Median 31	NA	NA	NA	24 (range 8-53)	NA
Vitamin D status							
Sufficiency (>30 ng/ml)	7/75	36/100	420/616	86/1213	NA	8/52	NA
Insufficiency (20-30)	28/75	47/100	175/616	50/1213	55/90	23/52	NA
Deficiency (<20)	40/75	17/100	21/616	138/1213	24/90	21/52 (Vitamin D level NA in 20)	65/185
Association between Vitamin D level and FEV_1	No correlation (r=0.16, 95% CI=−0.06-0.39, P=0.16)	Spearman rank correlation coefficient 0.34, P=0.004	No association; by multiple regression	NA	No association	No association	Significant positive correlation
Association between Vitamin D level and FEV_1/FVC	No correlation (r=−0.15, 95% CI=−0.35-0.05, P=0.14)	Spearman rank correlation 0.30, P=0.01	NA	NA	No association	NA	Significant positive correlation
Use of steroids and Vitamin D levels	NA	Inhaled, oral and total steroids significant inverse correlations	Inhaled steroids-yes; multiple	NA	No relation to inhaled steroid doses	NA	NA
Correlation between Vitamin D levels and asthma control	Significant correlation	NA	NA	NA	No association	No association	NA
Correlation between Vitamin D levels and hospitalizations for asthma	NA	NA	Yes; multiple regression 0.05 (0.004-0.71) (P=0.03)	NA	No association	No association	Significant inverse correlation

NA: Data not available, FEV_1: Forced expiratory volume 1 s, FVC: Forced vital capacity, SD: Standard deviation, CI: Confidence interval, IQR: Interquartile range

Table 4: Meta-analysis of Vitamin D levels in asthmatic and nonasthmatic children

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Mean 25(OH) D levels (ng/ml) in asthmatic and nonasthmatic children	10	2383	Mean difference (IV, random, 95% CI)	−9.41 (−16.57-−2.25)
Proportion of asthmatic and nonasthmatic children with 25(OH) D sufficiency (levels >30 ng/ml)	6	1603	Odds ratio (M-H, random, 95% CI)	0.35 (0.15-0.84)
Proportion of asthmatic and nonasthmatic children with 25(OH) D insufficiency (levels 20-30 ng/ml) and deficiency (levels <20 ng/ml)	9	4150	Odds ratio (M-H, random, 95% CI)	2.34 (1.23-4.43)
Vitamin D insufficiency (levels 20-30 ng/ml)	9	2355	Odds ratio (M-H, random, 95% CI)	1.40 (0.67-2.91)
Vitamin D deficiency (levels <20 ng/ml)	8	1795	Odds ratio (M-H, random, 95% CI)	3.41 (2.04-5.69)

IV: Inverse variance, M-H: Mantel–Haenszel, CI: Confidence interval, 25(OH)D: 25-hydroxyvitamin D

Relation between Vitamin D levels and control of asthma in children

A few studies reported correlation of Vitamin D levels with asthma control. A positive relationship was found between 25(OH)D level and childhood asthma control in the study by Gupta *et al*.[26] (r = 0.6, P = 0.001), Chinellato *et al*.,[38] and Uysalol *et al*.[34] No association between Vitamin D levels and asthma control was reported in study by Menon *et al*.,[28] Krobtrakulchai,[41] and Neagu.[42] Daily doses of inhaled steroids were inversely related to serum Vitamin D levels in the study by Brehm *et al*.,[15] Gupta *et al*.,[26] and Searing *et al*.,[39] but there was no association between Vitamin D levels and inhaled steroid doses in the study by Krobtrakulchai[41] Brehm *et al*.,[32] Gupta *et al*.,[26] and Wu *et al*.[35] Uysalol *et al*.[34] reported association between increased acute asthma exacerbations and lower serum 25(OH)D levels, but again no association between Vitamin D levels and asthma exacerbation in the study by Krobtrakulchai[41] and Neagu.[42] No associations were reported between Vitamin D level and eosinophil counts, duration of disease, and the number of hospitalization or unscheduled visits in a year ($P > 0.05$) by Alyasin *et al*.[31] Four studies[25,26,29,43] evaluated association between Vitamin D levels and total IgE in asthmatic children and found inverse correlation.

DISCUSSION

This systematic review of 23 observational studies found that mean Vitamin D levels were significantly lower in

asthmatic children compared to nonasthmatic children, but correlation between Vitamin D levels with incidence/prevalence of asthma, lung functions, and control of asthma was not uniform among the studies. Wide range of Vitamin D deficiency may be explained by variation in nutritional status, difference in sun exposure, fortification of food items, use of supplements, geographical location of country, and many other factors in different countries. Vitamin D deficiency and asthma may be linked by reverse causation because Vitamin D is synthesized by sun exposure and it is likely that asthmatic children may spend less time outdoor due to sickness by asthma. Brehm *et al*.[32] evaluated correlation between Vitamin D levels and asthma exacerbations in children after adjusting for time spent outdoors and racial ancestry and found that there was still a strong association between Vitamin D deficiency and asthma exacerbations after adjusting these factors. Therefore, this reverse causation seems to be less plausible. A recent review of observational studies by Cassim *et al*.[44] included both children and adult patients and identified 23 studies (12 cohort, 9 cross-sectional, and 2 case–control studies) and reported that higher Vitamin D levels were associated with decreased risk of acute exacerbations of asthma. Similar to our review, they also reported mixed results for association of Vitamin D levels with prevalence, incidence, and severity of asthma.[44] This review also included studies where Vitamin D levels were measured during pregnancy.[44] We excluded such studies, therefore number of cohort studies were less in our review. Yadav and Mittal[45] conducted a randomized controlled trial of oral Vitamin D3 (cholecalciferol) supplementation of 60,000 IU per month for 6 months in children and reported better peak expiratory flow rate improvement, better asthma control, and reduced need of emergency visit and oral steroids use in Vitamin D group compared to placebo group. However, the Vitamin D levels were not measured in the study.[45] In another pediatric RCT, 500 units of Vitamin D supplementation daily for 6 months showed decreased asthma exacerbation in Vitamin D group though Vitamin D levels did not change before and after supplementation and lung function improved significantly in both arms.[46] The Vitamin D assessment (VIDA) trial randomized 408 adults with poorly controlled asthma to supplement with high-dose Vitamin D or placebo.[47] Vitamin D supplementation did not alter the rate of first treatment failure during 28 weeks. In a subgroup analysis, subjects with a rise in Vitamin D levels >30 ng/ml had decreased rate of treatment failure and acute asthma exacerbations compared to placebo.[47] These trials suggest that Vitamin D supplementation will not be of help in all asthmatic children but in certain group of children.

Strength of the review includes broad search strategy, rigorous data extraction, and analysis. There are some limitations of review. First, we could not find full text of seven included studies (three case–control and four cross-sectional studies). Second, there was significant heterogeneity among included studies. Vitamin D levels were measured by different methods in different studies, e.g., radioimmunoassay method in Brehm *et al*.,[15] Chinellato *et al*.,[16] Bener *et al*.,[25] Maalmi *et al*.,[30] Alyasin *et al*.,[31] and Wu *et al*.;[35] enzyme-linked immunosorbent assay in van Oeffelen *et al*.,[14] Freishtat *et al*.,[27] and Hollams *et al*.;[36] high-performance liquid chromatography system–tandem mass spectrometry in Gupta *et al*. 2011;[26] and chemiluminescence immunoassay by Camargo *et al*.,[9] Chinellato *et al*.,[38] and Searing *et al*.[39] Finally, VIDA levels at different ages, diagnosis of asthma at variable ages, and partial control for confounders in some studies make results of the review difficult to rely upon. Large randomized clinical trials of Vitamin D supplementation with emphasis on timing and dosage are needed before recommending Vitamin D to children with asthma. It may be possible that Vitamin D supplementation may be beneficial in selected children who are Vitamin D deficient and dosages are sufficient enough to raise Vitamin D levels to normal range. It would be helpful if could identify asthmatic children who will benefit from Vitamin D supplementation in a particular dose for a particular duration.

CONCLUSIONS

Prevalence of Vitamin D deficiency varied from country to country. Asthmatic children had significantly lower Vitamin D levels as compared to nonasthmatic children. Correlation between Vitamin D levels and incidence of asthma, lung functions, and control of asthma had mixed results. There is need of large well-conducted randomized trials of Vitamin D supplementation with different doses and different duration of supplementation to assess the efficacy of Vitamin D on lung function and asthma control in children.

Note

The abstract was presented at the International Congress of Pediatrics 2013 (ICP), the 27th Congress of International Pediatric Association, held at Melbourne, Australia, from 24-29 August 2013.

Acknowledgment

We would like to acknowledge Dr. S.K. Kabra and Dr. Rakesh Lodha (both from Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India) for their intellectual input in the final manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, *et al*. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;94:1-8.
2. Holick MF. Vitamin D deficiency in 2010: Health benefits of Vitamin D and sunlight: A D-bate. Nat Rev Endocrinol 2011;7:73-5.

3. Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, *et al*. Prevalence of Vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med 2008;162:505-12.
4. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics 2009;124:e362-70.
5. Damera G, Fogle HW, Lim P, Goncharova EA, Zhao H, Banerjee A, *et al*. Vitamin D inhibits growth of human airway smooth muscle cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1. Br J Pharmacol 2009;158:1429-41.
6. Adams JS, Hewison M. Unexpected actions of Vitamin D: New perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab 2008;4:80-90.
7. Raby BA, Lazarus R, Silverman EK, Lake S, Lange C, Wjst M, *et al*. Association of Vitamin D receptor gene polymorphisms with childhood and adult asthma. Am J Respir Crit Care Med 2004;170:1057-65.
8. Litonjua AA, Weiss ST. Is Vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 2007;120:1031-5.
9. Camargo CA Jr., Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ, *et al*. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics 2011;127:e180-7.
10. Camargo CA Jr., Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, *et al*. Maternal intake of sitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr 2007;85:788-95.
11. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, *et al*. Maternal Vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr 2007;85:853-9.
12. Camargo CA Jr, Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ, *et al*. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics 2011;127:e180-7.
13. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, *et al*. Maternal Vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr 2008;62:68-77.
14. van Oeffelen AA, Bekkers MB, Smit HA, Kerkhof M, Koppelman GH, Haveman-Nies A, *et al*. Serum micronutrient concentrations and childhood asthma: The PIAMA birth cohort study. Pediatr Allergy Immunol 2011;22:784-93.
15. Brehm JM, Celedón JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, *et al*. Serum Vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 2009;179:765-71.
16. Chinellato I, Piazza M, Sandri M, Peroni DG, Cardinale F, Piacentini GL, *et al*. Serum Vitamin D levels and exercise-induced bronchoconstriction in children with asthma. Eur Respir J 2011;37:1366-70.
17. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, *et al*. Serum Vitamin D levels and severe asthma exacerbations in the childhood asthma management program study. J Allergy Clin Immunol 2010;126:52-8.e5.
18. Hyppönen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, *et al*. Infant Vitamin D supplementation and allergic conditions in adulthood: Northern Finland birth cohort 1966. Ann N Y Acad Sci 2004;1037:84-95.
19. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
20. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, *et al*. Hypovitaminosis D in medical inpatients. N Engl J Med 1998;338:777-83.
21. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 2003;22:142-6.
22. Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, *et al*. The urgent need to recommend an intake of Vitamin D that is effective. Am J Clin Nutr 2007;85:649-50.
23. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. [Last accessed on 2015 Sep 17].
24. The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.
25. Bener A, Ehlayel MS, Tulic MK, Hamid Q. Vitamin D deficiency as a strong predictor of asthma in children. Int Arch Allergy Immunol 2012;157:168-75.
26. Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, *et al*. Relationship between serum Vitamin D, disease severity, and airway remodeling in children with asthma. Am J Respir Crit Care Med 2011;184:1342-9.
27. Freishtat RJ, Iqbal SF, Pillai DK, Klein CJ, Ryan LM, Benton AS, *et al*. High prevalence of Vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. J Pediatr 2010;156:948-52.
28. Menon J, Maranda L, Nwosu BU. Serum 25-hydroxyvitamin D levels do not correlate with asthma severity in a case-controlled study of children and adolescents. J Pediatr Endocrinol Metab 2012;25:673-9.
29. Ma XL, Zhen YF. Serum levels of 25-(OH)D (3) and total IgE in children with asthma. Zhongguo Dang Dai Er Ke Za Zhi 2011;13:551-3.
30. Maalmi H, Sassi FH, Berraies A, Ammar J, Hamzaoui K, Hamzaoui A. Association of Vitamin D receptor gene polymorphisms with susceptibility to asthma in Tunisian hildren: A case control study. J Asthma Allergy 2012;5:11-9.
31. Alyasin S, Momen T, Kashef S, Alipour A, Amin R. The relationship between serum 25 hydroxyvitamin D levels and asthma in children. Allergy Asthma Immunol Res 2011;3:251-5.
32. Brehm JM, Acosta-Pérez E, Klei L, Roeder K, Barmada M, Boutaoui N, *et al*. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. Am J Respir Crit Care Med 2012;186:140-6.
33. Dogru M, Kirmizibekmez H, Yesiltepe Mutlu RG, Aktas A, Ozturkmen S. Clinical effects of Vitamin D in children with asthma. Int Arch Allergy Immunol 2014;164:319-25.
34. Uysalol M, Mutlu LC, Saracoglu GV, Karasu E, Guzel S, Kayaoglu S, *et al*. Childhood asthma and Vitamin D deficiency in Turkey: Is there cause and effect relationship between them? Ital J Pediatr 2013;39:78.
35. Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A; Childhood Asthma Management Program Research Group. Effect of Vitamin D and inhaled corticosteroid treatment on lung function in children. Am J Respir Crit Care Med 2012;186:508-13.
36. Hollams EM, Hart PH, Holt BJ, Serralha M, Parsons F, de Klerk NH, *et al*. Vitamin D and atopy and asthma phenotypes in children: A longitudinal cohort study. Eur Respir J 2011;38:1320-7.
37. Wawro N, Heinrich J, Thiering E, Kratzsch J, Schaaf B, Hoffmann B, *et al*. Serum 25(OH) D concentrations and atopic diseases at age 10: Results from the GINIplus and LISAplus birth cohort studies. BMC Pediatr 2014;14:286.
38. Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL. Vitamin D serum levels and markers of asthma control in Italian children. J Pediatr 2011;158:437-41.
39. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum Vitamin D levels in children with asthma are associated with increased corticosteroid use. J Allergy Clin Immunol 2010;125:995-1000.
40. Niruban SJ, Alagiakrishnan K, Beach J, Senthilselvan A. Association of Vitamin D with current asthma and lung function in children: Results from the Canadian health measures survey. Am J Epidemiol 2012;176:1.
41. Krobtrakulchai W. The effect of Vitamin D status on pediatric asthma in a university hospital, Thailand. J Allergy Clin Immunol 2012;129 2 Suppl: 1.
42. Neagu F. Hypovitaminosis D is very frequent but not associated with asthmacontrol in a low-income pediatric population seen in an allergy and immunology clinic. J Allergy Clin Immunol 2012;129 2 Suppl: 1.
43. Elnady HG, Abdel Hameed E, Fouda E, Abdel Shaheed A, Refaat E, Badawy E. Serum Vitamin D levels and markers of childhood asthma severity in Greater Cairo. Intensive Care Med 2011;37 Suppl 2:S355-6.
44. Cassim R, Russell MA, Lodge CJ, Lowe AJ, Koplin JJ, Dharmage SC. The role of circulating 25 hydroxyvitamin D in asthma: A systematic review. Allergy 2015;70:339-54.
45. Yadav M, Mittal K. Effect of Vitamin D supplementation on moderate to severe bronchial asthma. Indian J Pediatr 2014;81:650-4.
46. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. J Allergy Clin Immunol 2011;127:1294-6.
47. Castro M, King TS, Kunselman SJ, Cabana MD, Denlinger L, Holguin F, *et al*. Effect of Vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower Vitamin D levels: The VIDA randomized clinical trial. JAMA 2014;311:2083-91.