ANALYSIS

24(103), May - June, 2020

ISSN 2321–7359 EISSN 2321–7367

Medical Science

Vitamin D status and viral-induced wheeze in children under three years of age

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Article History
Received: 26 March 2020
Reviewed: 27/March/2020 *to* 23/April/2020
Accepted: 24 April 2020
E-publication: 30 April 2020
P-Publication: May - June 2020

Citation
Yurii Bolbot, Kateryna Hodiatska, Olha Shvaratska, Tina Bordii, Svitlana Alifanova. Vitamin D status and viral-induced wheeze in children under three years of age. *Medical Science*, 2020, 24(103), 1764-1772

ABSTRACT

The study *aimed* to investigate the frequency of wheezing episodes in relation to vitamin D status in young children. Also, we explored factors associated with vitamin D deficiency and recurrent viral-induced wheeze episodes. *Methods and Materials:* The study enrolled 60 patients with episodic wheezing, 60 patients with recurrent wheezing, and 30 healthy individuals, all aged 6 months to 3 years. Serum vitamin D concentrations were measured in all study participants using electrochemiluminescence

immunoassay. *Results:* Vitamin D deficiency was detected in 75% of recurrent wheezers and in 6.6% of children with episodic wheeze (P <.001). We registered an inverse relationship between the number of wheezing episodes and serum vitamin D concentrations. Children without vitamin D supplementation had substantially elevated odds of being found vitamin D deficient or recurrent wheezers. Other significant factors linked to recurrent wheezing were family history of allergy, maternal anemia during pregnancy, maternal active smoking currently. *Conclusion:* vitamin D deficiency and failed vitamin D supplementation are associated with the increased odds of recurrent wheezing in children of the first three years of life.

Keywords: Young children, vitamin D, deficiency, wheezing

1. INTRODUCTION

Viral respiratory tract infections (RTIs) significantly contribute to morbidity rates in children of the first three years of life (Esposito and Lelii, 2015) and perform as a trigger in the majority of wheezing episodes. A number of studies show that approximately one out of three children experience at least a single episode of virus-induced wheeze before they reach the age of three and half of them develop recurrent episodes, which are not associated with asthma development in the future (Beigelman and Bacharier, 2014). Miscellaneous factors are considered to increase the risk of such a recurrence, ranging from maternal smoking to atopic dermatitis in a child (Burke et al., 2012; Bessa et al., 2014; Bercedo-Sanz et al., 2015). However, these predictors may be absent in a large number of wheezers. Therefore, it necessitates further search for more specific prognostic criteria for early childhood recurrent wheezing.

A growing body of research exploring a role of vitamin D (VD) in the pathogenesis of childhood disorders and illnesses has emerged in the recent years. Going far beyond the scope of calcium and phosphorus regulation, VD has been linked to numerous biological processes in the human body including cell proliferation, differentiation, apoptosis, immune regulation, and antiviral defense (Bhatt et al., 2019; Pulvirenti et al., 2019). Globally, the prevalence of hypovitaminosis D in pediatric population was reported as 29 to 100 per cent depending on the geographical location of the country (Cashman et al., 2016). Regarding Ukraine, about 80 per cent of healthy children aged from 1 month to 3 years may be at risk of having depleted VD levels, however, available data are limited to several local studies only (Kvashnina, 2017). Abnormal serum VD level has been linked to an elevated risk of recurrent and severe RTIs in children (Esposito and Lelii, 2015; Zhang et al., 2020). Albeit, the interrelation between VD status and the development of recurrent wheezing in young children has not been comprehensively investigated yet.

Considering all the aforementioned, the first objective of this study was to assess VD status and estimate the prevalence of VD deficiency or insufficiency in young children with viral-induced wheeze in comparison with healthy non-wheezing peers. The second objective was to explore retrospectively factors potentially associated with low VD levels as well as factors linked to recurrent viral wheeze episodes, including VD status in particular, in wheezers.

2. MATERIALS AND METHODS

Participants and study design

The two-stage non-interventional study of a mixed design was conducted in Dnipro Children's City Clinical Hospital №6, one of the secondary healthcare level municipal children hospitals in Dnipro, Ukraine, in the period from January 2016 to April 2018. We obtained a written informed consent from the parents or legal representatives of all study subjects. Principles of the World Medical Association Declaration of Helsinki (ethical principles for medical research involving human subjects) were applied in the research.

We hypothesized that lowered VD status may be associated with the development of viral-induced wheeze in children, and with the development of recurrent wheezing episodes in particular. Both parts of the study were observational in nature. In accordance with the first aim of the study, on the first stage we performed a cross-sectional non-differentiated assessment of the serum VD levels in wheezing patients. We used purposive sampling to identify children with viral-induced wheeze among all children hospitalized with RTIs during the study period.

To identify risk factors for recurrent viral wheezing and deficient VD status, the second part of the research instantly followed the first one. Here we performed a retrospective case-control study with an additional sub-setting of the study subjects enrolled at the previous stage into patients with episodic wheezing ("controls"), and patients with recurrent wheezing ("cases"). In accordance with the conventional approach in the clinical practice, wheezing was considered episodic in those having not more than two episodes in a preceding year, and recurrent in those patients who developed three and more episodes per year (Prasad et al., 2016). Such wise, a total of 120 patients aged six months to three years were consecutively enrolled into the study; numbered 60 per each group. A

parallel group of 30 healthy peers with negative history for wheezing were additionally enlisted as a second control group to obtain VD reference values.

Inclusion and exclusion criteria

All the recruited patients met the following inclusion criteria: Caucasian ethnicity; formal diagnosis of viral-induced wheeze at present verified in accordance with the national clinical recommendations and evidence-based medicine guidelines of the Finnish Medical Society Duodecim "Difficulty breathing in a child" (2017) and "The optimal treatment of young children with acute expiratory wheezing and asthma exacerbations" (2018) acknowledged by the Ministry of Health of Ukraine.

All the study subjects were screened for the criteria of exclusion: chronic broncho pulmonary diseases or disorders, primary and secondary immunodeficiency, gastroesophageal reflux disease, prematurity, and a history of corticosteroid or anticonvulsant medications use. None of the participants had a verified diagnosis of asthma on inclusion and none of them were diagnosed with asthma during the study period.

Assessment of serum vitamin D

In the cross-sectional part of the study quantitative determination of serum 25-hydroxyvitamin D (25(OH)D) was performed in all study participants by using electrochemiluminescence immunoassay (ECLIA) on the Cobas e411 auto analyzer (Roche Diagnostics GmbH, Germany). Serum 25(OH)D concentration is a major circulation form of VD; nowadays, it is considered to reflect VD status in individuals more precisely than other VD metabolites (Jukic et al., 2018). Based on the conventional recommendations (Holick, 2011), we categorized VD status in the study subjects into sufficiency, or optimum (≥30 ng/ml), insufficiency, or potential deficiency (20-29 ng/ml), and deficiency (<20 ng/ml).

Data collection

In the retrospective part of the study we recorded a detailed history in each study subject using a semi-structured questionnaire and interviews. The written questionnaire comprised standardized questions recommended by European Vitamin D Association Scientific Society (2013) and Endocrine Practice Guidelines Committee (2011) (Holick et al., 2011) regarding feeding practices in the first year of life, outdoor activity, the child's daily duration of sun exposure, and VD supplementation at the time of interview. According to Ukrainian national recommendations, administration of vitamin D_3(cholecalciferol) at a minimum prophylactic daily dose of 500 IU should be applied to all children aged one month to three years. We did not consider maternal VD supplementation during pregnancy as any benefit granted by antenatal maternal VD supplementation does not extend beyond 6 months (Fink et al., 2019), and our youngest participant was 6 month old. Hence, the questionnaire covered common major risk factors for VD deficiency in pediatric population (Holick et al., 2011)

Only the time of regular sun exposure between the day hours of 10:00 and 15:00 was taken into consideration. Insolation for less than 15 minutes twice a week was regarded as a low level of sun exposure, from 15 min to 30 min – as a moderate level and for more than 30 min – as a high level of exposure to sunlight (Almeida et al., 2018).

We also collected a set of additional anamnestic data, such as a family history of allergic diseases, history of prenatal and postnatal maternal smoking and maternal anemia during pregnancy, patient's history of atopic dermatitis, antibiotic use and daycare attendance.

Data analysis

All data were collated in Microsoft Excel-2010 (Microsoft Office 2016 Professional Plus, Open License 67528927) and exported to Statisticav.6.1 software (serial number AGAR909 E415822FA) for analysis. All patients contributed with complete data and all results were taken into consideration. Shapiro-Wilks and Lilliefors tests for normality were run to evaluate the probability distribution of variables.

Quantitative data were represented with medians (Me) and the inter-quartile range ((IQR, [Q25; Q75]) as the normality assumption was violated. Comparisons of characteristics among wheezing children and healthy controls were performed using nonparametric univariable Mann-Whitney U-test and Pearson chi-square test for quantitative (continuous) and qualitative (categorical) variables, respectively; the aforementioned tests were also run to ensure that the case-control data were adequately matched. Spearman's rank-order correlation R was used to evaluate the association between the parameters studied. Measures of probability were based on odds ratio (OR) with 95 per cent confidence interval (95% CI), and P-value. The boundary for statistical significance was defined as a P value of .05 or less; Bonferroni and Holm's multiple-comparison corrections were applied where relevant.

Ethical committee approval

Ethical approval for the research protocol was granted by the Biomedical Ethics Committee of Dnipropetrovsk Medical Academy of Health Ministry of Ukraine (Protocol No. 3 dated 04.03.2015).

3. RESULTS

Sixty children with recurrent pattern of viral-induced wheeze showed an uneven gender distribution with male sex predominance (N=40, 66.7%). The median age in this sample was 20.0 months (IQR, 15.0-26.5; range, 6-36 months). The first control group was case-matched accurately to the recurrent wheeze cases and consisted of 60 patients with episodic viral-induced wheezing. Seventy per cent (N=42) of this episodic wheezers were males and the median age in this sample was 17.5 months (IQR, 13.0-22.0; range, 6-35 months). The median age of healthy controls was 21.0 months (IQR, 7.0-29.0; range, 6-36 months), 30 per cent of them were females. Thereby, no significant differences in terms of gender or age were present, according to Mann-Whitney U-test used (P > .05).

Table 1 shows characteristics of VD status in a total sample of children with viral-induced wheeze versus those in healthy non-wheezing controls and thus represents the results of a cross-sectional part of the study. Children with viral-induced wheeze demonstrated significantly lower median levels of VD over the controls' values. The proportion of individuals with optimal levels of VD among wheezy children was depleted compared to the healthy controls. In each two out of five wheezing patients VD deficiency was registered while none of the controls had serum 25(OH)D levels below 19.9 ng/ml.

Table 1 Characteristics of vitamin D status in the study participants (N=150)

	Children with viral-induced wheeze (N=120)	Healthy controls (N=30)	P-value
Serum 25(OH)D concentration (ng/ml), median (Q25; Q75)	24.23 (14.18; 33.13)	37.96 (26.47; 43.52)	< .001*
VD status categories, N(%)			
Optimal level (≥ 30ng/ml)	41 (34)	21 (70)	< .001**
Insufficiency (20-29 ng/ml)	30 (25)	9 (30)	.577**
Deficiency (≤ 19.9 ng/ml)	49 (41)	0 (0)	< .001**

* P-value is derived from the Mann-Whitney U-test;

** P-value is referred to the Pearson's chi-square test

With the Spearman's rank correlation test we elicited a significant negative relationship between the number of wheezing episodes and serum VD concentrations in the wheezing sample (R=−0.27, p =.002). The aforementioned provided a basis for subsequent sub-setting of children with viral-induced wheeze in accordance with the frequency of wheezing episodes per year for the following case-control part of the study. Indeed, a further subset analysis within the wheezing sample revealed that the median serum 25(OH)D concentrations in episodic wheezers significantly exceeded those in children with recurrent wheezing episodes: 33.0 (28.19; 41.97)ng/ml versus13.68 (7.96; 19.51) ng/ml, respectively, p<.001 by Mann-Whitney U-test.

With the more detailed analysis, we found that the median levels of serum 25(OH)D in children with one wheezing episode in the preceding year were 38.25 (30.68; 46.05) ng/ml, two episodes– 31.35 (26.42; 34.53) ng/ml, three episodes– 21.03 (17.08; 24.04) ng/ml, four episodes– 13.68 (11.15; 24.47) ng/ml, five or more episodes – 10.77 (6.34; 14.78) ng/ml. With Bonferroni correction restricting the boundary of statistical significance to the meaning of P-value less than .005 here, the differences were significant between subgroups having experienced one or two wheezing episodes versus three or four or five episodes, and three versus four episodes.

Figure 1 illustrates the distribution of VD status categories among the study subjects based on serum 25(OH)D concentrations (ng/ml). Among the children who had recurrent wheezing episodes the majority, three quarters, revealed VD deficiency while episodic wheezers, alike healthy controls, mainly possessed optimal serum 25(OH)D levels.

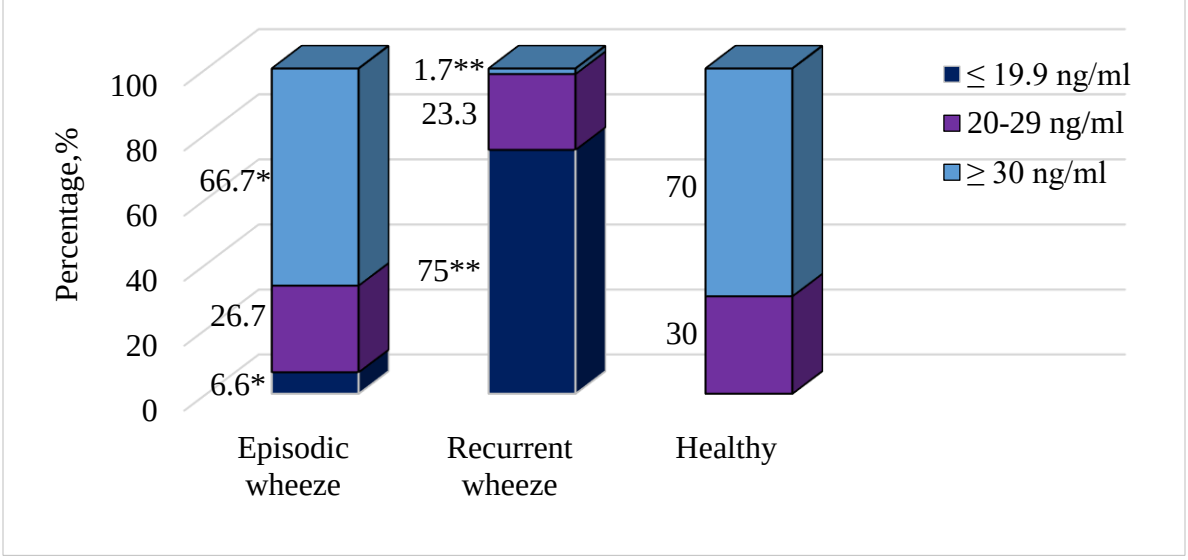

Figure 1 Categories of vitamin D status in study participants, %

* Asterisk indicates a P-value of <.05 derived from the pair wise chi-square test with Holm's correction for multiple comparisons performed between episodic versus recurrent wheeze subgroups;

** Two asterisks indicate a P-value of <.05 derived from the pairwise chi-square test with Holm's correction for multiple comparisons performed between episodic wheeze subgroup versus healthy individuals and recurrent wheeze subgroup versus healthy individuals.

Table 2 represents the prevalence of factors potentially influencing VD status in children with episodic and recurrent viral-induced wheeze. While there were no statistically significant differences between the two subgroups in distribution of feeding types or exposure to sunlight, the proportion of those currently receiving VD supplementation was significantly lower among recurrent versus episodic wheezers.

Table 2 Prevalence of factors potentially linked to vitamin D deficiency among children with viral-induced wheeze

Characteristics	Children with episodic wheeze (N=60)	Children with recurrent wheeze (N=60)	P*
Type of feeding, N (%)			
Breastfeeding ≤ 6 months	28 (46.7)	19 (31.6)	.092
Breastfeeding> 6 months	26 (43.3)	34 (56.7)	.144
Formula feeding since birth	6 (10.0)	7 (11.7)	.769
Level of sun exposure, N (%)			
Low	38 (63.3)	44 (73.3)	.239
Moderate	16 (26.6)	13 (21.7)	.522
High	6 (10.0)	3 (5.0)	.488
VD supplementation at the time of the interview, N (%)			
Yes	36 (60.0)	3 (5.0)	<.001
No	24 (40.0)	57 (95.0)	<.001

* P-value is derived from the Pearson's chi-square test.

Furthermore, in the wheezing sample regardless of frequency of episodes the median serum 25(OH)D concentration in children currently receiving VD supplements in a minimum daily dosage of 500 IU/day (N = 39) doubled that of the patients with no VD supplementation (N = 81): 33.26 (30.61; 45.77) ng/ml versus 15.98 (10.96; 24.47) ng/ml (p<.001 by Mann-Whitney U-test). We found that the absence of VD supplementation demonstrated a strong positive association with an increased risk of VD deficiency

(OR=17.45; 95% CI 4.96 - 61.44; p<.001). Additionally, there was a significant inverse correlation between serum 25(OH)D level and the patient's age (R = – 0.38, p = .001).

Subsequently, the study analyzed a set of other characteristics presumably associated with wheeze recurrence in young children; results are displayed in Table 3.The two subgroups of the wheezing sample were conformable in terms of family history of asthma or urticaria, child's personal history of atopic dermatitis, or day care attendance (p>.05). Per contra, the prevalence of maternal anemia during pregnancy, maternal smoking during and after pregnancy, family history of allergic rhinitis as well as individual history of antibiotic use was significantly higher in recurrent wheeze subgroup than in episodic one. Table 4 summarizes the estimates for the association between recurrent wheezing and factors of personal and family history. Hereby, we identified the major predictors of recurrent wheezing in children less than three years of life.

Table 3 Prevalence of factors with potential impact on wheeze recurrence among study participants

Characteristics	Children with episodic wheeze (N=60)	Children with recurrent wheeze (N=60)	P*
Parental history of asthma			
Yes, N (%)	0 (0.0)	2 (3.3)	.476
No, N (%)	60 (100.0)	58 (96.7)	
Family history of allergic rhinitis			
Yes, N (%)	3 (5.0)	14 (23.3)	.009
No, N (%)	57 (95.0)	46 (76.7)	
Family history of urticaria			
Yes, N (%)	4 (6.7)	6 (10.0)	.742
No, N (%)	56 (93.3)	54 (90.0)	
Maternal smoking during pregnancy			
Yes, N (%)	16 (26.7)	6 (10.0)	.034
No, N (%)	44 (73.3)	54 (90.0)	
Maternal anemia during pregnancy			
Yes, N (%)	22 (36.7)	34 (60.0)	.028
No, N (%)	38 (63.3)	26 (40.0)	
Maternal active smoking currently			
Yes, N (%)	8 (13.3)	19 (31.6)	.016
No, N (%)	52 (86.7)	41 (68.4)	
History of antibiotic use			
Yes, N (%)	18 (30.0)	40 (66.7)	<.001
No, N (%)	42 (70.0)	20 (33.3)	
Daycare attendance			
Yes, N (%)	5 (8.3)	7 (11.7)	.543
No, N (%)	55 (91.7)	53 (88.3)	
Atopic dermatitis			
Yes, N (%)	10 (16.7)	9 (15.0)	.803
No, N (%)	50 (83.3)	51 (85.0)	

* P-value is derived from the Pearson's chi-square test.

Table 4 Estimates for the association between recurrent wheezing and factors of personal and family history

	Episodic, N (%)	Recurrent, N (%)	OR, 95 % CI, P
VD deficiency	4 (6.6)	45 (75)	4.35, 2.75 - 6.86, <.001
Family history of allergic diseases	7 (11.7)	22 (36.7)	4.38, 1.70 - 11.30, .002
Maternal anemia during pregnancy	22 (36.7)	34 (60.0)	2.25, 1.09 - 4.69, .029
Maternal active smoking currently	8 (13.3)	19 (31.6)	1.47, 1.10 - 2.65, .041
No VD supplements currently	24 (40)	57 (95)	28.50, 7.99 - 101.55, <.001

Children with VD deficiency had four times the odds of developing recurrent wheezing episodes overall compared to those with optimal serum VD concentrations; individuals having family history of allergy were at similarly increased odds of recurrent wheeze. There was also weak evidence that current active maternal smoking half increased the odds of recurrent wheeze in a child as well as good evidence that maternal anemia during pregnancy was linked to twice the odds of wheeze recurrence in the descendant. Children receiving no VD supplements at the time of the study were substantially more likely to appear recurrent wheezers.

4. DISCUSSION

A substantial role of VD in pediatric respiratory physiology has been illustrated in previous research (Esposito and Lelii, 2015). Our study addressed the relationship between the serum VD concentrations and viral-induced wheeze in immunocompetent pediatric population aged three years and younger in Ukraine. Our main finding is that in the given cohort of children VD deficiency is tied to a fourfold increased odds of developing recurrent episodes of wheeze compared to non-deficient peers. It is also notable that a drop of serum VD levels is linked to a spike of number of wheezing episodes per year, and VD supplementation appears to be a crucial component for maintaining optimal VD levels in children, particularly, between the age of one and three years of life.

In this study we observed VD deficiency in each three out of four children with recurrent wheezing while only 6.6% of episodic wheezers had VD levels below 19.9 ng/ml. Likewise, Prasad et al. (2016) found VD deficiency in 73.8% patients with recurrent wheezing in the same age group in India. However, other similar study conducted among young children in Turkey detected only 12% infant wheezers as VD deficient (Durmaz et al., 2013). We speculate that these dramatic differences in results could be related to the geographical location of the subjects and varied conventional practice of VD supplementation. Therefore, VD deficiency was highly prevalent in young children who had three or more episodes of wheezing per year. Furthermore, we detected a significant negative correlation between serum VD concentrations and the number of wheeze episodes. The mechanisms underlying this association remain unclear. There is some evidence that VD influences immune system development in the early life and therefore VD deficiency, combined with other detrimental factors, could increase a risk of wheeze recurrence (Bivona et al., 2017; Bercedo-Sanz et al., 2015). It is also possible that the reverse is true: early exposure to respiratory viruses and contracting multiple wheeze episodes require extended amount and frequency of treatment which may alter the daily practice VD supplementation and lead to poor or irregular intake of VD resulting in low VD status.

Accounting the fact that the vast majority of the children with recurrent wheezing had VD deficiency, it was beneficial to study other factors affecting VD status. Our research has the acknowledged limitation of being a retrospective case-control study able only to document association not causality. But our findings are similar to those obtained in some population-based studies in other geographical regions and we also added an essential analysis regarding local practices of VD supplementation.

Our study focused on the duration of regular sun exposure to assess its impact on development of subsequent VD deficiency and recurrent wheeze in infants. Our results highlights that the majority of enrolled patients had low ultraviolet B exposure regardless of the number of wheezing episodes; also, we found no association of the level of ultraviolet B exposure and VD status. Such results could be partly explained by the season when the study was conducted: the predominant massive of data was obtained in winter and early spring when sunlight level is low in Ukraine. Albeit, sun exposure from 10 AM to 15 PM for at least 30 minutes just twice a week is considered to be sufficient for adequate production of VD in the skin, and such duration is quite attainable for Ukraine. We speculate that conventional community practice of outdoor time limitation in winter may also be responsible for the results obtained. In contrast to our findings, Ando et al. (2018) found that the background ultraviolet B radiation level was significantly associated with serum 25(OH)D levels in preschool children.

Previous studies conducted by Rueter et al. (2019) have linked VD intake to VD status. Ukrainian national regulations recommend daily prophylactic intake of 500-1000 IU of VD to all children aged from 1 month to 3 years of age. Our results showed that only 32.5% of the studied wheezing sample had adequate supplementation of VD. Similarly, Zaharova et al. (2016) reported that in neighboring Russia each one out of three healthy infants received no VD supplements in their first year of life. It is also essential that VD supplementation rate was found to be significantly lower in children with recurrent wheeze than in patients who had one or two wheezing attacks per year. The study findings are significant for a strong positive association between serum 25(OH)D concentrations and regular prophylactic VD use. Similar results were published by Pludowski et al. (2011) and Carroll et al. (2014) demonstrating a positive correlation between VD supplementation and serum 25(OH)D levels in pediatric populations of different age in European region.Instead, a more recent study from Brazil (Almeida et al., 2018) failed to show an association between deficient serum 25(OH)D concentrations and use of VD supplements. Thus, it remains to be determined if daily VD supplementation would play a crucial role in VD deficiency prevention in young children in case of inadequate sun exposure.

Our results display that serum 25(OH)D levels decreases significantly with age. This tendency could be explained by discontinuation of VD supplements after the child's first birthday. Parents in Ukraine hardly accept the necessity for continuing VD supplementation after 12 months of ages VD is traditionally associated with the rickets prevention only. The other example of the given trend has been provided by the Turkish study (Durmaz et al., 2013). However, some other studies do not support these findings: for instance, Wójcik et al. (2018) have shown no significant correlation between the age of the infants and toddlers enrolled and serum 25(OH)D concentration. Postnatal maternal smoking is another factor closely tied to recurrent pediatric wheeze, according to our results. Similarly, Jones et al. (2011) and Bessa et al. (2014) reported that passive smoke exposure twice increased the odds of recurrent lower respiratory infections in the first years of life. Significant impact of maternal smoking on the wheeze recurrence is conventionally explained by the time which children under three years of life traditionally spend with their mothers and which substantially exceed time spent with other family members.

It is also notable that recurrent wheezers had higher rate of antibiotic use compared to peers with episodic viral-induced wheeze in our study. We doubt that antibiotic use is an independent risk factor for development of recurrent wheeze pattern; vice versa, the former is rather a consequence of the latter: children with recurrent RTIs are just at higher risk of antibiotic administration than those who contract respiratory infections rarely. In our study, recurrent wheezing in a child was linked to maternal anemia in pregnancy. Recently it has been plausibly suggested that prenatal iron deficiency could influence respiratory outcomes by causing minor changes in airway development (Shaheen et al., 2017). However, potential impact of low maternal iron status in pregnancy on early childhood wheezing still remains unclear. Bessa et al. (2014) and Bercedo-Sanz et al. (2015) demonstrated that family history of allergic rhinitis contributed to the risk of recurrent wheezing, and our data are consistent with their findings.

5. CONCLUSION

Summarizing the aforementioned, VD deficiency is associated with the fourfold higher odds for viral-induced wheeze recurrence in young children. Also, family history of allergy, maternal anemia during pregnancy, passive smoking appears to be additional predictors of recurrent wheezing. Consequently, these factors should be evaluated to identify children at increased risk of viral induced wheeze recurrence during first three years of life; also, correction of modifiable risk factors should be considered. Furthermore, it may be reasonable to determine serum 25(OH)D levels in all young patients with recurrent wheezing in the absence of VD supplementation, especially in children over 12 months of age. Further investigations are required to determine whether VD supplementation can be beneficial to reduce the number of wheezing episodes in the given cohort of patients.

Author's contributions

Yurii, Bolbot - Principle Investigator: idea and design of the study
Kateryna, Hodiatska - Study design, data collection and analysis, draft manuscript preparation
Olha, Shvaratska - Data analysis, draft manuscript preparation, final editing of the manuscript
Tina, Bordii - Study and article design, final editing of the manuscript
Svitlana, Alifanova - Data collection, draft manuscript preparation

Potential conflict of interests

The authors have no conflicts of interest to declare.

Financial resources

None

REFERENCE

1. Almeida ACF, de Paula FJA, Monteiro JP, et al. Do all infants need vitamin D supplementation? PLoS ONE 2018;13:e0195368.
2. Ando E, Morisaki N, Asakura K, et al. Serum 25-hydroxyvitamin D levels showed strong seasonality but lacked association with vitamin D intake in 3-year-old Japanese children. Br J Nutr 2018;120:1034-44.
3. Beigelman A, Bacharier L. Infection-induced wheezing in young children. J Allergy ClinImmunol 2014;133:603-4.
4. Bercedo-Sanz A, Lastra-Martínez L, Pellegrini-Belinchón J, et al. Wheezing and risk factors in the first year of life in Cantabria, Spain. The EISL study. AllergolImmunopathol (Madr) 2015;43:543-52.
5. Bessa OA, Leite ÁJ, Solé D, Mallol J. Prevalence and risk factors associated with wheezing in the first year of life. J Pediatr (Rio J) 2014;90:190-6.
6. Bhatt N, Ali A, Waly MI. Non-Skeletal Benefits of Vitamin D. Canad J ClinNutr 2019;7:141-59.
7. Bivona G, Agnello L, Ciaccio M. Vitamin D and immunomodulation: is it time to change the reference values? Ann Clin Lab Sci 2017;47:508-10.
8. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: Systematic review and meta-analysis. Pediatrics 2012;129:735-44.
9. Carroll A, Onwuneme C, McKenna MJ, et al. Vitamin D status in Irish children and adolescents: value of fortification and supplementation. Clinical Pediatrics 2014;53:1345-51.
10. Cashman KD, Dowling KG, Škrabáková Z, et al. Vitamin D deficiency in Europe: Pandemic? Am J ClinNutr 2016;103:1033-44.
11. Durmaz C, Asilsoy S, GüçUsta B. Serum vitamin D levels among recurrently wheezy infants. TurkiyeKlinikleri J Med Sci 2013;33:1337-43.
12. Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC Infect Dis 2015;15:487.
13. Fink C, Peters RL, Koplin JJ, et al. Factors Affecting Vitamin D Status in Infants. Children (Basel) 2019;6:7.
14. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evolution, treatment and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011;96:1911-30.
15. Holick MF. Vitamin D: a D-lightful solution for health. J Investig Med 2011;59:872-80.
16. Jones LL, Hashim A, McKeever T, et al. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. Respir Res 2011;12:5.
17. Jukic AMZ, Hoofnagle AN, Lutsey PL. Measurement of vitamin D for epidemiologic and clinical research: shining light on a complex decision. Am J Epidemiol 2018;187:879-90.
18. Kvashnina LV. Vitamin D in different periods of childhood: what we know, what to remember and what we forgot. Health of Ukraine 2017:29-31.
19. Pludowski P, Socha P, Karczmarewicz E, et al. Vitamin D supplementation and status in infants: a prospective cohort observational study. J PediatrGastroenterolNutr 2011;53:93-9.
20. Prasad S, Rana RK, Sheth R, Mauskar AV. A hospital based study to establish the correlation between recurrent wheeze and vitamin D deficiency among children of age group less than 3 years in Indian scenario. J ClinDiagn Res 2016;10:18-21.
21. Pulvirenti G, Parisi GF, Manti S, et al. The Immunomodulatory role of vitamin D in respiratory diseases. CurrRespir Med Rev 2019; 15:238-45.
22. Rueter K, Jones AP, Siafarikas A, et al. Direct infant UV light exposure is associated with eczema and immune development. J Allergy ClinImmunol 2019;143:1012-20.
23. Shaheen SO, Macdonald-Wallis C, Lawlor DA, Henderson AJ. Haemoglobin concentrations in pregnancy and respiratory and allergic outcomes in childhood: Birth cohort study. ClinExp Allergy 2017;47:1615-24.
24. Wójcik M, Jaworski M, Pludowski P. 25(OH)D concentration in neonates, infants, and toddlers from Poland-evaluation of trends during years 1981-2011. Front Endocrinol (Lausanne) 2018;9:656.
25. Zaharova IN, Klimov LY, Kuryaninova VA, et al. The effectiveness of hypovitaminosis D prevention in infants: the role of feeding, dose and duration effect of cholecalciferol medications use. Pediatriya 2016;95:62-69.
26. Zhang X, Liu Z, Xia L, et al. Clinical features of vitamin D deficiency in children: A retrospective analysis. J Steroid Biochem MolBiol 2020;196:105491.