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Association Between Vitamin D Deficiency and Recurrent Wheezing in Children

Ayesha Naseem, Sohail Ashraf, Shiza Safdar, Yumna Zafar, Hajra Iqbal Alvi

Department of Pediatrics, POF Hospital Wah Cantt, Pakistan.

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Corresponding Author: Ayesha Naseem
Department of Pediatrics, POF Hospital Wah Cantt, Pakistan.
Email: naseemayesha25@gmail.com

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ABSTRACT

Background: Vitamin D plays a crucial role in immune regulation and respiratory health, with its deficiency being implicated in recurrent wheezing among children. Given the high prevalence of vitamin D deficiency in pediatric populations, understanding its association with recurrent wheezing can guide preventive and therapeutic strategies. **Objective:** The objective of the study was to determine the frequency of vitamin D deficiency among the children with recurrent wheezing. **Study Design:** Cross-sectional study. **Duration and Place of Study:** The study was conducted between March 2024 to September 2024 in the Pediatrics Department of POF Hospital Wah Cantt. **Methodology:** A total of 95 children aged 2–5 years, with a history of at least three wheezing episodes in the past year, were included. Children with clinical rickets, prior vitamin D supplementation, or chronic illnesses affecting vitamin D metabolism were excluded. Serum 25(OH)D levels were measured using an ELISA kit and categorized as sufficient (>30 ng/mL), insufficient (21–29 ng/mL), or deficient (<20 ng/mL). **Results:** The mean age of participants was 3.49 ± 1.09 years, and the mean serum vitamin D level was 26.93 ± 9.36 ng/mL. Among the children, 56.8% were male, and 43.2% were female. Vitamin D deficiency was found in 27.4% of children, while 30.5% had insufficient levels, and 42.1% had sufficient levels. Younger children (2–3 years) exhibited a higher deficiency rate (35.4%) than older children (4–5 years) (p=0.003). **Conclusion:** Vitamin D deficiency is prevalent among children with recurrent wheezing and is significantly associated with younger age, female gender, and lower socioeconomic status.

INTRODUCTION

Wheezing in children is an acute breathing symptom described by whistling during breathing, most commonly occurring while exhaling.[1] Wheezing is most commonly produced by an obstruction or narrowing in respiratory passages and can be attributed to various diseases including mild viral infections to life-long diseases such as asthma.[2] Wheezing in children is most commonly caused by viral infections in children in the form of colds, but wheezing can be caused by environmental factors in the form of allergies to substances in the environment, smoking by parents, or atmospheric pollution.[3] Repeated wheezing over time is referred to as recurrent wheezing and is most concerning since wheezing can be an indicator of developing asthma or other life-long breathing disorders in children. It is necessary to identify the underlying factors causing wheezing to treat wheezing appropriately and avoid future wheezing episodes.[4]

Recurrent wheezing in children has been attributed to an interplay among genetic factors, environmental factors, and immune factors.[5] Heredity has an increased role in wheezing in children in families with allergy or asthma, which suggests an innate predisposition.[6] Allergens (such as dust mites, cat dander, and pollen) in the environment, irritants (such as secondhand smoking), and indoor pollutants induce wheezing by inflaming and hyperreactivity of tissues in the airway.[7] Low birth weight, prematurity, and infections in early life during infancy have been confirmed to be risk factors causing repeated wheezing.[8] RSV infection and infection by certain rhinovirus have been strongly implicated in wheezing in early childhood.[9] Abnormalities in immune system performance in the form of increased inflammatory responses or in immune regulation can also cause repeated wheezing in children. All these etiological factors with multiple factors have to be treated by an comprehensive process in the form of evaluation by physicians, changes in physical environment, and in certain patients pharmacological therapy.[10] Recent findings point towards an emerging connection between wheezing in children and vitamin D deficiency, calling attention to ensuring appropriate amounts of this nutrient to maintain healthy breathing.[11] Vitamin D plays an essential role in modulating immune responses to prevent over-inflammation in respiratory

passages and to promote healthier pulmonary status.[12] Findings have revealed that children who possess inadequate amounts of this nutrient have frequent occurrences of wheezing and an increased risk of developing asthma.[13] The link can be attributed to this nutrient's ability to modulate immune responses to avoid over-inflammation in respiratory passages and to induce healthier pulmonary function. Furthermore, pregnant women who have deficiencies in this nutrient have been revealed to have increased wheezing incidence in children born to these women, calling attention to ensuring appropriate amounts before conception.[14] Maintaining appropriate amounts through sunlight exposure, diet, or supplements can be an effective preventive measure to avoid wheezing in children. However, further studies should be carried out to validate causal associations and establish optimal amounts of this nutrient in children to achieve healthy breathing.[15]

A cross-sectional study was conducted to assess the prevalence of vitamin D deficiency and its association with recurrent wheezing in children. Using a semi-structured questionnaire, trained interviewers collected data from the legal guardians of the participants. The study found that 57.3% of children with recurrent wheezing had vitamin D deficiency or insufficiency.[16]

The current study is necessary because repeated wheezing in children is increasingly prevalent and is most commonly related to diseases including asthma. Lack of vitamin D has been shown to be an etiological determinant in breathing difficulty, but little is understood about its significance in wheezing. Through an evaluation of this link, this study can gain meaningful information that can inform preventive interventions and improved management of wheezing in children in populations where this condition is endemic.

METHODOLOGY

The study was conducted between March 2024 to September 2024 in Pediatrics Department in POF Hospital Wah Cantt. Ninety-five children aged between 2 to 5 years of both genders, diagnosed with recurrent wheezing of having three or more episodes of wheezing in the past 12 months, as reported by their parents was included in this sample. The sample size was calculated using the WHO sample size calculator, with an expected prevalence of vitamin D deficiency of 57.3%,[16] an absolute precision of 10%, and a 95% confidence level.

Exclusion criteria were children with clinical rickets who had received previous administration of vitamin D in the previous half-year, congenitally malformed children, or children with concomitant diseases including cardiac disease, cystic fibrosis, pneumonia, pulmonary tuberculosis, or immunodeficiencies among others.

After obtaining approval form hospital ethics committee, informed written consent was obtained from parents of children fulfilling the eligibility criteria. Demographics such as gender, age, and family history of atopy were collected in addition to drawing blood samples (2 mL) to analyze in serum. Serum was centrifuged in hospital laboratory and stored at -4°C to analyze later to determine 25(OH)D status by an ELISA kit. Status was categorized in three categories: sufficient (>30 ng/mL), insufficient (21–29 ng/mL), or deficient (<20 ng/mL). Data was analyzed in SPSS version 23.0. Quantitative variables such as serum concentration of vitamin D and age had mean and standard deviation calculated. Frequency and percentage was calculated in the case of categorical variables such as gender, family history of atopy, vitamin D status, socioeconomic status, education and residence. Stratification was carried out to adjust for potential confounding factors by taking factors such as gender, family history of atopy, residence, socio-economic status, and education into consideration. Post-stratification was carried out by chi-square testing where p-value of <0.05 was considered to determine significance.

RESULTS

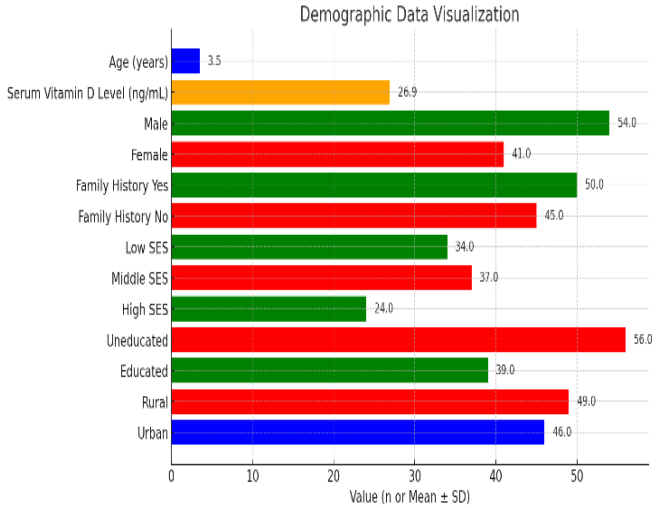
The mean age of the participants was 3.49±1.09 years, and the mean serum vitamin D level was 26.93±9.36 ng/mL. Among the 95 children included, 54 (56.8%) were male, and 41 (43.2%) were female. A family history of atopy was reported in 50 (52.6%) children, while 45 (47.4%) had no such history. Socioeconomic status distribution showed that 34 (35.8%) children belonged to the low-income group, 37 (38.9%) to the middle-income group, and 24 (25.3%) to the high-income group. Regarding education levels, 56 (58.9%) of the children had guardians who were uneducated, whereas 39 (41.1%) had guardians with formal education. The residential distribution was nearly equal, with 49 (51.6%) of children residing in rural areas and 46 (48.4%) in urban areas (as shown in Table-1).

Table 1

Patient Demographics n=95

Demographics		Mean ± SD
Age (years)		3.494±1.09
Serum Vitamin D Level (ng/mL)		26.926±9.36
Gender	Male n (%)	54 (56.8%)
	Female n (%)	41 (43.2%)
Family History of Atopy	Yes n (%)	50 (52.6%)
	No n (%)	45 (47.4%)
Social economic Status	Low n (%)	34 (35.8%)
	Middle n (%)	37 (38.9%)
	High n (%)	24 (25.3%)
Education	Uneducated n (%)	56 (58.9%)
	Educated n (%)	39 (41.1%)
Residence	Rural n (%)	49 (51.6%)
	Urban n (%)	46 (48.4%)

Figure 1



The vitamin D status assessment indicated that 40 (42.1%) children had sufficient vitamin D levels, 29 (30.5%) had insufficient levels, and 26 (27.4%) were deficient, highlighting a considerable proportion of children with suboptimal vitamin D levels (as shown in Table-2).

Table 2

Vitamin D Status in children with recurrent wheezing

Vitamin D Status	Frequency	% age
Sufficient	40	42.1%
Insufficient	29	30.5%
Deficient	26	27.4%
Total	95	100%

Age was a significant factor, with children aged 2-3 years showing a higher proportion of vitamin D deficiency (35.4%) compared to older children aged 4-5 years, who had a significantly higher proportion of sufficient vitamin D levels (59.6%) (p=0.003). Gender differences were also observed, with males showing a higher proportion of sufficient vitamin D levels (51.9%), whereas females had a greater proportion of vitamin D insufficiency (46.3%) (p=0.011).

A strong association was observed between socioeconomic status and vitamin D levels (p<0.001). Children from low-income families had the highest vitamin D deficiency rate (55.9%), while those from high-income families had predominantly sufficient vitamin D levels (87.5%). In contrast, the middle-income group showed a more balanced distribution, with 40.5% having sufficient, 43.2% having insufficient, and 16.2% having deficient vitamin D levels. While education levels showed some variation, with children of educated guardians having a higher proportion of sufficient vitamin D levels (51.3%) compared to those with uneducated guardians (35.7%), this difference was not statistically significant (p=0.173). Similarly, the family history of atopy (p=0.445) and residential status (rural vs. urban, p=0.402) did not show significant associations with vitamin D status. These findings emphasize the role of socioeconomic factors, age, and gender in influencing vitamin D levels among children with recurrent wheezing, while education, residence, and family history of atopy did not demonstrate significant associations (as shown in Table 3).

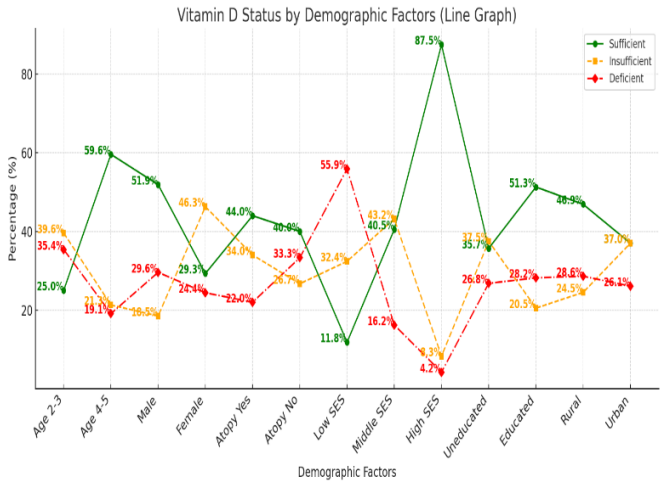
Table 3

Association of Vitamin D Status with Demographic Factors

Demographic Factors		Vitamin D Status			p-value
		Sufficient n (%)	Insufficient n (%)	Deficient n (%)	
Age (years)	2-3	12 (25%)	19 (39.6%)	17 (35.4%)	0.003
	4-5	28 (59.6%)	10 (21.3%)	9 (19.1%)	
Gender	Male	28 (51.9%)	10 (18.5%)	16 (29.6%)	0.011
	Female	12 (29.3%)	19 (46.3%)	10 (24.4%)	
Family History of Atopy	Yes	22 (44%)	17 (34%)	11 (22%)	0.445
	No	18 (40%)	12 (26.7%)	15 (33.3%)	
Socioeconomic Status	Low	4 (11.8%)	11 (32.4%)	19 (55.9%)	<0.001 *
	Middle	15 (40.5%)	16 (43.2%)	6 (16.2%)	
	High	21 (87.5%)	2 (8.3%)	1 (4.2%)	
Education	Un-educated	20 (35.7%)	21 (37.5%)	15 (26.8%)	0.173
	Educated	20 (51.3%)	8 (20.5%)	11 (28.2%)	
Residence	Rural	23 (46.9%)	12 (24.5%)	14 (28.6%)	0.402
	Urban	17 (37%)	17 (37%)	12 (26.1%)	

*Fischer Exact Test

Figure: 2



DISCUSSION

Vitamin D plays an essential role in immune modulation and pulmonary health while its deficiency has been implicated in wheezing pathogenesis in children. This present work established both an increased prevalence of both vitamin D deficiency and insufficiency in wheezing children with 27.4% being deficient while 30.5% was insufficient. This is most likely accounted for by increased playing outdoors and sunlight exposure in children who are older in order to yield greater

production of vitamin D. This gender variation where males had an increased percentage with sufficient amounts of vitamin D while women had an increased percentage who were insufficient can be attributed to variation in playing outdoors, clothing, and sunlight exposure. Socioeconomic status was an independent determinant of status in vitamin D where children in poorer families had highest rates of deficiency due to insufficient dietary intake, minimal sunlight exposure, and compromised accessibility to healthcare.

Our findings showed an average Vitamin D concentration by 26.93±9.36 ng/mL with 27.4% being deficient, 30.5% insufficient, and 42.1% being sufficient. This agrees with Peçanha et al.'s [16] observation that children who wheeze have an increased prevalence (57.3%) of vitamin D deficiency/insufficiency. Khan et al. [17] also observed wheezing children to have insufficient (73.8%) status of vitamin D with an average concentration of 16.87±4.9 ng/mL significantly lower than in controls (27.23±3.1 ng/mL, $p<0.001$). Prasad et al. [18] observed greater severity in wheezing children in vitamin D deficiency in that only 23% children had below 5 ng/mL while none was over 30 ng/mL. This can be attributed to differences in locations/geographic regions, sunlight exposure, dietary patterns, and differences in populations in metabolizing vitamin D. Unlike in this work where 42.1% children had an appropriate concentration of vitamin D, Peçanha et al. [16] and Prasad et al. [18] seen fewer rates in non-wheezing children. This can be attributed to differences in thresholds used to define deficiency in these studies and by differences in methods used to calculate concentration.

Age discrepancies in vitamin D status have been observed in this work as well where children who were younger (2-3 years) had a higher proportion (35.4%) in comparison to children who were older (4-5 years) who had higher amounts (59.6%) ($p=0.003$). Hodiatska et al. [19] have indicated that children who were younger (age range: between 6 months to 3 years) had increased prevalence (75%) of vitamin D deficiency which was correlated with increased (fourfold) recurrence of wheezing (OR = 4.35; 95% CI: 2.75-6.86, $p<0.001$). This suggests that children who are younger have increased vulnerability due to reduced dietary consumption, fewer outdoor visits during this period, increased hospital-related infections to which children in this age range have increased vulnerability, thus reduced sunlight exposure.

The gender differences in this study revealed that males had a greater percentage of adequate vitamin D status (51.9%), while females had greater rates of insufficiency (46.3%) ($p=0.011$). Khan et al. [17] also described an identical pattern where relatively better vitamin D status was observed in children who were males compared to children who were female, albeit not to a statistically significant degree. This difference can be explained by differences in sun exposure patterns between cultures, differences in clothing patterns, and possibly differences in biological variation in vitamin-D metabolism.

The socioeconomic status was a key determinant in this study in respect to vitamin D status since children in families with low economic status had the highest prevalence (55.9%), while children in families with high economic status had predominantly appropriate vitamin D status (87.5%) ($p<0.001$). This is in accordance with Peçanha et al. [16] who indicated that vitamin D deficiency was significantly correlated with environmental contamination and poorer socioeconomic status. Additionally, Prasad et al. [18] stressed that exclusive breastfeeding beyond six months and delayed introduction to complementary feeding beyond six months predicted vitamin D deficiency and increased wheezing risk indirectly. Low dietary intake of vitamin D-containing foods and limited accessibility to healthcare in families with low economic status can be used to explain these results.

Our findings indicated no significant relationship between family history of atopy ($p=0.445$) or residence ($p=0.402$) with vitamin D status. Peçanha et al. [16] however, established an increased relationship between patients with atopic dermatitis and vitamin D deficiency (OR = 1.8, $p=0.02$), where vitamin D was implicated in modulating immune responses in individuals with atopy. Similarly, Feketea et al. [20] described that children who wheezed repeatedly had lower amounts of vitamin D that were related to immune marker alterations in the form of IL-10 and IL-31. This variation in outcomes can be explained by sample sizes, genes, or variation in factors in the environment.

In terms of interventions, Hodiatska et al. [19] established that wheezing was significantly reduced by taking 1000 IU of vitamin D3 every day over 12 months ($p<0.001$) but was not sufficient to reverse completely the deficiency in vitamin D because 54.5% of initially deficient children still stayed in this condition. This highlights that in deficient children increased dosing should be employed. Feketea et al. [21] established that while decreased rates of asthma exacerbations and infections in the respiratory system can be achieved by taking vitamin D supplements, excessive dosing does not confer additional benefits.

Together, these findings indicate the key role played by vitamin D in wheezing status in children. Repeated observation in these studies between wheezing and vitamin D deficiency suggests that maintaining optimum status in vitamin D can prove beneficial in reducing wheezing attacks and in optimizing respiratory status. However, these differences in prevalence rates in deficiencies, responses to supplements, and demographic factors between populations indicate that interventions should be personalized to consider

regional, dietary, and socio-economic factors. Future directions should be towards developing universal recommendations about vitamin D supplements in children with wheezing recurrences and examining benefits to children with optimum status in vitamin D in the long term.

The following limitations apply to this current study. First it was carried out in a single centre, which can adversely affect generalizability to populations outside this centre. Secondarily, the sample was fairly small in number, which can have an effect upon power to detect certain associations. As this was not an interventional or cohort study, inferences between wheezing recurrence and status in respect to vitamin D cannot be derived by this cross-sectional design. Consumption in diet, sunlight exposure, and genes affecting status in respect to vitamin D have not been controlled in this analysis. Larger sample-size multicenter trials with follow-ups over time should be done to replicate these results and determine the role in wheezing in children.

CONCLUSION

Our study has confirmed that vitamin D deficiency is prevalent among children who have recurrent wheezing and is significantly correlated with gender, socioeconomic status, and age. Young children, females, and children in poorer families bore highest increased risk. Evidence is in favor of the importance of vitamin D in respiratory illness with wheezing exacerbations caused by insufficient amounts. No association was confirmed with family allergy status or residence status, but the strong link to socioeconomic factors highlights targeted dietary and public health interventions. Routine screening and targeted programs in children who have increased risk of repeated wheezing should be implemented to prevent future respiratory complications.

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** **Authors' Roles**

Each author has played a significant part in shaping this manuscript, as outlined below:

- Dr. Ayesha Naseem spearheaded the study's design, compiled hospital records, and played a key role in drafting the article.
- Dr. Sohail Ashraf was actively involved in refining the manuscript, contributing to study design, and analyzing and interpreting the data.

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