

Correlation between vitamin D serum levels and passive smoking exposure in children with asthma

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ABSTRACT

Objective: To establish the relationship between vitamin D serum levels, pulmonary function, asthma control, and passive smoking exposure in children with asthma.

Methods: We studied the relationship between 25-hydroxy cholecalciferol (25[OH]D) concentrations and baseline spirometry and levels of asthma control, and the effect of parental tobacco smoke exposure in 152 white children (84 boys [55.3%]) with a mean age $\pm$ standard deviation of 9.9 ± 2.0 years (range 5–15 years) in a cross-sectional study carried out during the winter and early spring.

Results: Only 9.9% of our children had a sufficient serum 25(OH)D level (at least 30–40 ng/mL). A significant positive correlation was found between the force vital capacity % predicted, forced expiratory volume in the first second of expiration % predicted, and serum 25(OH)D level ($r = 0.36$, $p < 0.001$ for both). The subjects with controlled asthma had higher serum levels of 25(OH)D than children with partially controlled or noncontrolled asthma, both according to Global Initiative for Asthma parameters and the Test for the control of asthma in childhood ($p = 0.011$). Children with both nonsmoking parents presented significantly higher serum levels of 25(OH)D than children with both smoking parents (median, 20.5 ng/mL [interquartile range {IQR}, 16.6–24.0 ng/mL] versus median, 14.5 ng/mL [IQR, 11.1–19.1 ng/mL], respectively; $p < 0.001$), with intermediate values for children exposed to single maternal (median, 20.3 ng/mL [IQR, 13.0–23.2 ng/mL]) or to paternal smoking (median, 17.8 ng/mL [IQR, 14.7–22.1 ng/mL]).

Conclusion: Our results indicated that hypovitaminosis D was frequent in children with asthma who lived in a Mediterranean country. In these children, lower levels of vitamin D were associated with reduced asthma control and passive smoking exposure.

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Vitamin D deficiency and insufficiency are global health concerns that afflict >1 billion children and adults worldwide.¹ The consequences of vitamin D deficiency cannot be underestimated, particularly during the fetal life and in children. In a birth cohort study, maternal vitamin D deficiency during pregnancy was associated with impaired lung development in 6-year-old offspring, neurocognitive difficulties at age 10 years, increased risk of eating disorders in adolescents, and lower peak bone mass at 20 years, which clearly documents that vitamin D may have an important, multifaceted role in the development of fetal lungs, brain, and bone.²

Vitamin D deficiency, and its link with the immune mechanisms, was recently described as a risk factor for childhood allergic disease and asthma. More recently, it was demonstrated that 25-hydroxy cholecalciferol (25[OH]D) deficiency in early childhood is associated with the onset of asthma and allergic diseases^{3,4} and with an increased risk for persistent asthma, potentially through modulating susceptibility to early allergic sensitization, upper respiratory tract colonization with bacterial pathogens, or both.⁵ Furthermore, several studies found that low serum levels of vitamin D (<20 ng/mL) are associated with increased exacerbations, increased airway inflammation, remodeling induced by inflammatory mediators,⁶ decreased lung function, and poor prognosis in patients with asthma⁷; vitamin D supplementation⁸ has been suggested as one of the effective strategies to modify the natural history of asthma, which warrants increased investigation and implementation.⁹

Also, it is well documented that tobacco smoke and nicotine exposure during prenatal and postnatal life can impair lung development, alter the immune response to viral infections, and increase the prevalence and severity of wheezing during childhood.¹⁰ For these reasons, the aim of our study was to evaluate, in chil-

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dren with asthma, the correlations between disease control, lung function, serum vitamin D, and parental tobacco smoking exposure.

METHODS

Italian children with asthma, diagnosed according to the American Thoracic Society (ATS) guidelines,¹¹ who consecutively attended the outpatient clinic of the Department of Pediatrics at the University of Verona hospital between November 2016 and March 2017. The hospital ethics committee approved the study protocol (CE 1716), and the parents provided written informed consent to participate. A single measurement of the level of vitamin D (measured as 25-hydroxy cholecalciferol [25(OH)D]) was made in all the subjects by using a radioimmunoassay method. These values were used as continuous variables, and the vitamin D levels were also categorized, in descriptive analyses, as being desirable (or sufficient) when at least 30–40 ng/mL (75–100 nmol/L), insufficient when between 20 and 30 ng/mL (50 and 75 nmol/L), and deficient when <20 ng/mL.^{12,13}

Measurements of pulmonary function were performed according to ATS criteria,¹⁴ by considering the best of three efforts, starting with full force vital capacity (FVC) maneuvers with an electronic spirometer (Master Screen IOS; Jaeger, Hochberg, Germany). The spirometer was calibrated for each subject by using a 3-L syringe (Cardinal Health, Dublin, OH). The FVC maneuvers were carried out with the child standing and wearing a nose clip. The subjects were instructed to avoid the use of short-acting bronchodilators for at least 6 hours before testing. Fractional exhaled nitric oxide was measured by using the NIOX system (Aerocrine, Stockholm, Sweden) by using of a single-breath online method according to European Respiratory Society/ATS guidelines.¹⁵ Briefly, the children inhaled NO-free air to total lung capacity and exhaled through a dynamic flow restrictor, with a target flow of 50 mL/s for at least 6 to 7 seconds. No nose clip was used. The NIOX system was calibrated according to the manufacturer's instructions.

Serum total immunoglobulin E (IgE) was determined by high-sensitivity nephelometry (BN II System; Siemens Health Care Diagnostics, Deerfield, IL) and expressed as kIU/L. Peripheral blood eosinophil count was measured by automatic flow cytometer (Advia 2120 Hematology System; Siemens Health Care Diagnostics) and expressed as cells/mm³. Skin testing was done by following standard methods.¹⁶ In addition to histamine and saline solution controls, the following antigens were applied to the volar surface of the forearm: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat dander, dog dander, mixed grass pollen, mixed tree pollen, *Parietaria officinalis*, and *Alternaria*

tenuis. A test result was considered positive if the maximal diameter of the wheal was ≥ 3 mm after subtracting the maximal diameter of the negative control. Mean wheal dimensions were calculated by measuring the greater diameter plus its perpendicular diameter and by dividing by two. All the mean wheal diameters were measured and added together to obtain a total allergy score, expressed in mm, as previously described.¹⁷

Asthma control was categorized as controlled, partly controlled, or uncontrolled in agreement with the Global Initiative for Asthma (GINA) guidelines.¹⁸ In particular, levels of asthma control were defined by depending on the presence or absence of daytime symptoms, limitations of activities, nocturnal symptoms or awakening, the need for reliever or rescue treatment, and forced expiratory volume in the first second of expiration (FEV₁) results. Furthermore, the children were asked to complete the Childhood Asthma Control Test (C-ACT) questionnaire¹⁹ before their clinical evaluation. C-ACT is a self-administered questionnaire with seven questions on asthma symptoms and the effects of asthma on daily functioning. The first four questions were answered by the children and the last three were answered by their parents. Each question had four response options for children, from 0 (worse) to 3 (best), and had six response options for parents, from 0 (worse) to 5 (best). The lowest and highest possible scores thus were 0 (totally uncontrolled asthma) to 27 (total asthma control); a score of ≤ 19 was an indication of poorly controlled asthma. In the statistical analysis, C-ACT was considered as a numerical variable that ranged from 0 to 27. Permission was obtained to use the C-ACT questionnaire. Information on parental tobacco smoke exposure was evaluated by using a standardized and validated questionnaire.²⁰

I. Chinellato conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and approved the final manuscript as submitted. M. Piazza designed the data collection instruments, coordinated and supervised data collection, performed statistical analysis, critically reviewed the manuscript, and approved the final manuscript as submitted. M. Sandri designed the data collection instruments, coordinated and supervised data collection, performed statistical analysis, critically reviewed the manuscript, and approved the final manuscript as submitted. G. Paiola coordinated and supervised data collection, reviewed and revised the manuscript, and approved the final manuscript as submitted. G. Tezza coordinated and supervised data collection, reviewed and revised the manuscript, and approved the final manuscript as submitted. A.L. Boner conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Table 1 Investigated parameters stratified according to deficient, insufficient, and sufficient vitamin D serum levels

Investigated Parameters	Vitamin D Serum Levels			(p value)*
	Deficient (<20 ng/mL)	Insufficient ($20\text{--}30$ ng/mL)	Sufficient (≥ 30 ng/mL)	
Absolute and relative frequency distribution, no. (%)	80 (52.6)	57 (37.5)	15 (9.9)	
Total IgE, median (IQR), IU/mL	198.3 (102.0–480.0)	389.0 (97.0–788.0)	300.0 (124.0–475.0)	0.03 (0.749)
Eosinophil count, median (IQR), (cells/mm ³)	6.7 (3.5–9.7)	5.0 (4.0–9.0)	3.8 (3.2–7.6)	–0.09 (0.250)
C-ACT total score, median (IQR)	21 (17–23)	24 (22–25)	25 (22–26)	0.49 (<0.001)
Mean total allergy score, median (IQR), mm	23.0 (10.0–40.8)	24.0 (13.0–39.0)	12.0 (10.0–35.5)	–0.07 (0.383)
FVC value, median (IQR), %	100.0 (93.5–109.9)	103.5 (100.3–114.0)	110.0 (97.2–120.0)	0.36 (<0.001)
FEV ₁ , median (IQR), %	99.0 (90.2–105.7)	105.0 (97.0–113.0)	107.9 (99.8–110.1)	0.36 (<0.001)
FeNO, median (IQR), ppb	21.0 (10.5–30.6)	22.4 (12.0–42.0)	20.0 (12.5–22.8)	0.03 (0.804)

IgE = Immunoglobulin E; IQR = interquartile range (1st quartile to 3rd quartile); C-ACT = Childhood Asthma Control Test; FVC = force vital capacity; FEV₁ = forced expiratory volume in the first second of expiration; FeNO = fractional exhaled nitric oxide.

*Spearman's rank correlation r with p -value of the statistical independence test ($r = 0$).

Statistical Analysis

The degrees of association between vitamin D and baseline FVC% predicted, FEV₁% predicted, and C-ACT were estimated by use of partial correlation, that is, a linear correlation after adjusting for the effects of other variables and confounders (treatment, season in which levels were obtained, sex, and age).²¹ The strength of the pairwise associations between these variables and vitamin D serum levels was measured by use of the Spearman rank correlation. The median and interquartile range (IQR) of the vitamin D serum levels in the children were grouped according to treatment and GINA classification of control. The differences between the subgroup medians were tested by using the nonparametric Kruskal-Wallis one-way analysis of variance. The p value of <0.05 was considered statistically significant. All the calculations were performed with the Stata 13.0 statistical package (StataCorp, L.L.C., College Station, TX).

RESULTS

A total of 152 white children (84 boys [55.3%]) with a mean age $\pm$ standard deviation of 9.9 ± 2.0 years (range, 5–15 years) were included into the study. Eighty-five patients (55.9%) had intermittent asthma and received, only when needed, treatment with an albuterol and fluticasone propionate (FP) metered dose inhaler with a spacer. Of the other 67 children with persistent asthma, 44 (65.7%) received FP μ g 100 twice a day (b.i.d.) and 23 received salmeterol plus FP 25/50

μ g two puffs twice a day (b.i.d.) and montelukast 5 mg/die (S/FP+M). Only five patients had a clinical history of emergency department visits and oral prednisone treatment within the previous 6 months. All those children were in the group of not-controlled asthma.

The results of assessing vitamin D serum levels and their relationships with the different study parameters are reported in Table 1. As can be seen, only 9.9% of the children presented with sufficient (≥ 30 ng/mL) levels of vitamin D. Vitamin D serum levels showed a significant, positive, and moderate association with asthma control according to C-ACT results ($r = 0.49$ [95% confidence interval {CI}, 0.36–0.62]; $p < 0.001$), with FVC % predicted ($r = 0.36$ [95% CI, 0.22–0.50]; $p < 0.001$), and with FEV₁ % predicted ($r = 0.36$ [95% CI, 0.23–0.50]; $p < 0.001$). The relationships between vitamin D serum levels and treatment as well as asthma control, according to GINA guidelines, are reported in Table 2.

There was a trend toward higher levels of vitamin D in children with intermittent asthma versus those with persistent asthma and regular treatment ($p = 0.068$) and significantly higher levels of vitamin D in patients with asthma with well-controlled versus partially controlled or noncontrolled asthma ($p < 0.001$) according to the GINA guidelines. The serum levels of vitamin D with regard to different parental smoking exposure are depicted in Fig. 1. As can be seen, children with both nonsmoking parents, they presented significantly

Table 2 Median (IQR) and *p* values of the nonparametric k-sample test on the equality of medians for the investigated parameters, grouped by treatment and level of disease control

	Treatment			<i>p</i> Value
	When Needed	FP	FP/S+M	
Vitamin D serum levels, median (IQR), ng/mL	20.3 (16.3–23.0)	16.7 (12.2–21.1)	17.9 (13.5–24.3)	0.068
	Levels of Asthma Control (GINA guidelines)			
	Uncontrolled	Partly Controlled	Controlled	
Vitamin D serum levels, median (IQR), ng/mL	13.5 (10.1–18.1)	17.8 (12.6–22.0)	22.4 (18.2–26.0)	<0.001

IQR = Interquartile range (1st quartile to 3rd quartile); FP = fluticasone propionate; FP/S+M, fluticasone propionate-salmeterol plus montelukast; GINA = Global Initiative for Asthma.

higher levels than children with both smoking parents (median, 20.5 ng/mL [IQR, 16.6–24.0 ng/mL] versus 14.5 ng/mL [IQR, 11.1–19.1 ng/mL], respectively; *p* < 0.001), with intermediate values for children exposed to single maternal (median, 20.3 ng/mL [IQR, 13.0–23.2 ng/mL]) or paternal smoking (median, 17.8 ng/mL [IQR, 14.7–22.1 ng/mL]). This association remained substantially unchanged after adjustment for sex, age, treatment, and season in which vitamin D levels were obtained.

DISCUSSION

Statement of Principal Findings

The current study confirmed that vitamin D insufficiency and deficiency were highly prevalent in children who lived in our region, at a latitude of 45°43'N.²² Our results also confirmed previous findings of improved lung function^{23–25} and better asthma control in children with asthma and with sufficient levels of vitamin D.^{26,27} These findings have biologic explanations because vitamin D-regulated genes are markedly over-represented in developing lung transcriptomes both in mouse and human embryonic lung tissue.²⁸ Moreover, in animal models, *in utero* vitamin D deficiency leads to decreased lung volumes, altered lung structure, and inflammation.^{29–31}

Although outcomes in human studies are not uniform, recent findings showed that vitamin D deficiency at 18 weeks gestation is associated with compromised lung function in 6-year-old children² and that vitamin D insufficiency was a determinant of reduced lung growth pattern from childhood into adulthood in a cohort of children with mild-to-moderate asthma.³² A novel finding of our study was the association between passive smoking exposure and vitamin D serum levels. It was previously documented that maternal exposure to cigarette smoking during pregnancy modestly reduces 25-hydroxyvitamin D, possibly because of re-

duced capacity of the placenta in women who smoke to transport the vitamin D.³³ In addition, smoking in adults is associated with low bone mass and reduced concentrations of serum 25(OH)D and parathyroid hormone (PTH),^{34,35} but, to our knowledge, no study evaluated the effect of passive smoking exposure on vitamin D serum levels.

Strengths and Weaknesses of the Study

The strengths of the study were represented by the relatively large number of patients, by the homogeneity of the sample, and by the simultaneous evaluations of different parameters. The main weakness of the study was the cross-sectional nature of the association; thus, no inference of causation can be made. Although vitamin D insufficiency can lead to increased symptoms of asthma and lower lung function, and, even if passive smoking exposure can cause decreased levels of vitamin D, the cross-sectional nature of this analysis cannot exclude the possibility that the reverse is true, that more symptoms and lower lung function led to less outdoor activity and lower vitamin D status. The same may be true for passive smoking exposure in relation to smokers' unhealthy life style with less outdoors activity.^{36–38}

Cigarette smoke exposure was collected by parental report and may be subject to response bias.³⁹ The questionnaire on smoking was mainly collected from mothers, and we could not exclude that some women might have preferred not to report their smoking status,⁴⁰ and this could explain the unexpectedly larger negative effect on the vitamin D serum level of isolated father smoking exposure compared with unique smoking mother's contact. Urinary cotinine level measurements could have solved this problem and could also have disclosed a dose-response relationship between the number of cigarettes per day and the investigated parameter.

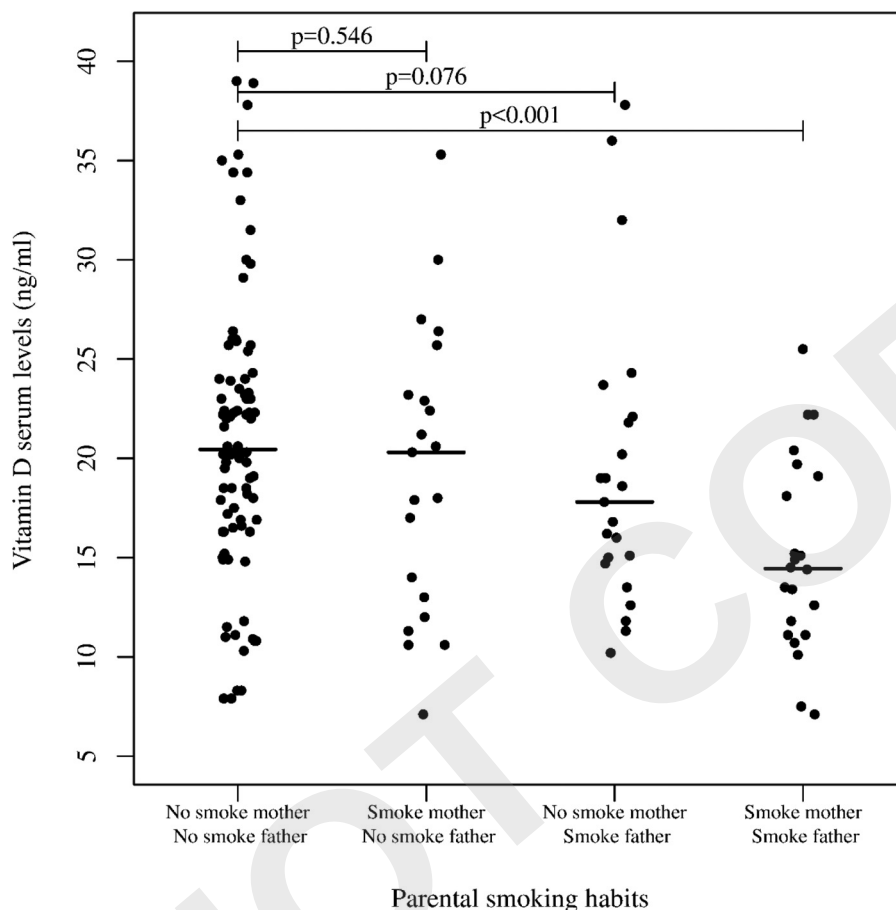


Figure 1. Vitamin D serum levels in groups of children with different parental habits: both nonsmoking parents, single maternal or paternal smoking, both smoking parents. p = p -value of the nonparametric Wilcoxon rank-sum test.

Furthermore, we did not study the vitamin D receptor gene and binding proteins, and no evaluation was done of circulating levels of PTH. For this reason, the reported association should be interpreted with caution. Despite this weakness, this study added to the accumulating data of an association between vitamin D insufficiency and symptomatic asthma and lower lung function, and added the suspicion that this might be aggravated by passive smoking or by factors associated with this lifestyle. Contrary to our finding in a previous study, male sex and cigarette smoke exposure were positively associated with 25(OH)D (all $p < 0.05$).⁴¹ Cigarette smoking is often accompanied by multiple high-risk health behaviors, including increased unprotected sun exposure,⁴² which, associated with higher levels of outdoor physical activity in boys, might explain the observed higher vitamin D serum concentrations.⁴³ However, the higher 25(OH)D concentrations seen among children exposed to cigarette smoke disagreed with the findings of adult studies, which found smoking to be associated with a low bone mass and reduced concentrations of serum 25(OH)D and PTH.^{34,35}

Meaning of the Study and Unanswered Questions

In adults, smoking is associated with bone mass loss and the risk of osteoporosis-related fractures, reduced calcium absorption, and reduced serum vitamin D levels.^{34,44,45} Although, the underlying mechanisms for this effect remain unclear, some speculative explanations are possible. Smokers may differ from nonsmokers in vitamin D intakes and physical exercise habits,⁴⁶ and the life style present in parents can affect children's diet and physical activity as well,⁴⁷ all of which can potentially confound an association between smoking and endogenous vitamin D. An altered hepatic metabolism of 25(OH)D is possible because smokers have enhanced hepatic degradation of another steroid, *viz.*, estrogen.⁴⁸ The results of earlier studies in adults indicate that the smoking-associated changes in the PTH-vitamin D system are reversible when smoking ceases.⁴⁵ At present, it is not well known whether children's exposure to smoke components may have long-term repercussions and whether it may reverse as a consequence of smoking exposure cessation.

CONCLUSION

Our results showed that low vitamin D levels were associated with a worse outcome in children with asthma and indicated that exposure to cigarette smoke might further aggravate vitamin D deficiency, although longitudinal studies are necessary to confirm our findings.

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