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Serum vitamin D level mitigates fractional exhaled nitric oxide linked to bisphenol-A in school-aged children

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Abstract. – OBJECTIVE: Previous studies on the relationship of bisphenol-A (BPA) with fractional exhaled nitric oxide (FeNO) had conflicting results, suggesting that other factors may modulate this relationship. Thus, we investigated the modulating effect of vitamin D on the relationship of BPA with FeNO in children.

PATIENTS AND METHODS: This study recruited 432 children (10 to 12 years old) from the general pediatric population of Korea between June and July 2017. We conducted measurements of urinary BPA, serum vitamin D, specific serum IgE, FeNO, and data from impulse oscillometry (reactance area [AX], airway resistance at 5 Hz [Rrs5] and 20 Hz [Rrs10], and the difference of Rrs5 and Rrs20 [Rrs5-20]).

RESULTS: Serum vitamin D (adjusted β =-0.014, *p*=0.002) and urinary BPA (β = 0.006, *p*<0.001) level was significantly associated with FeNO. Urinary BPA level was significantly associated with FeNO in children with low vitamin D levels (≤23 ng/mL; αβ = 0.006, *p* < 0.001), but not in children with high vitamin D levels (>23 ng/mL). The interaction of vitamin D and BPA had a significant effect on FeNO (pint = 0.005). There was no relationship with the airway lung function (Rrs5, AX, and Rrs5-20) to serum vitamin D and urinary BPA level. Vitamin D ameliorated the BPA-mediated increase of FeNO in children.

CONCLUSIONS: These results suggest that children with low vitamin D levels may be more susceptible to airway inflammation due to BPA.

Key Words:
Vitamin D, Bisphenol-A, Fraction of exhaled nitric oxide, Impulse oscillometry.

Abbreviations

BPA: bisphenol-A; FeNO: fractional exhaled nitric oxide; IOS: impulse oscillometry system; 25-(OH)D3 : 25-hydroxyvitamin D3; ppb: parts per billion; AD: atopic dermatitis; AR: allergic rhinitis; ISAAC: International Study of Asthma and Allergies in Childhood; BMI: body mass index; WHO: world Health Organization; GM: geometric mean; CIs: confidence intervals; IQR: interquartile range; ORs: Odds ratios; SE: standard error; AX: Reactance area; Rrs5: airway resistance at 5 Hz; Rrs20: airway resistance at 20 Hz ; Rrs5-20: the difference between Rrs5 and Rrs20.

Introduction

Bisphenol-A (BPA) is a synthetic compound present in many plastics that can disrupt the endocrine system[1]. BPA may affect the immune system, and animal studies indicated it reduced the levels of regulatory T cells, IL-10, and IFN-γ, and increased the levels of IL-4 and antigen-specific IgE[2-4]. BPA is also a risk factor for childhood asthma, aggravation of airway inflammation, and decreased lung function[5-7]. Recent investigations[8,9] suggested that BPA level is strongly associated with an increased level of fractional exhaled nitric oxide (FeNO) (an indicator of asthma), but this relationship is controversial. Thus, further studies are needed to confirm the association between BPA and FeNO.

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Vitamin D modulates diverse immunologic pathways that function in airway dysfunction and inflammation, regulates lymphocytes and structural cells, and reduces excessive inflammatory responses[10,11]. Vitamin D deficiency or insufficiency may be a pivotal risk factor for type 2 airway inflammation in children with asthma[12]. This suggests that vitamin D potentially affects the association between BPA and FeNO. Children are more likely to be exposed to BPA and phthalates than adults due to their greater consumption of foods from containers lined with BPA-containing plastics[13]. Therefore, studies are needed to identify the immuno-modulating effects of vitamin D on BPA exposure and lung function and FeNO in children.

To our knowledge, no previous studies examined whether vitamin D affected FeNO and small airway function in schoolchildren from the general population who were exposed to BPA. Thus, we investigated the effect of vitamin D in modulating the relationship of BPA with FeNO and small airway lung function.

Patients and Methods

Study Design

This general population-based cross-sectional study of children who were 10 to 12 years of age and from elementary schools in Seongnam City (South Korea) was conducted between June and July 2017. A total of 432 children had parents who returned completed questionnaires and agreed to supply samples of blood and urine and measurements of FeNO and from an impulse oscillometry system (IOS). The parents were asked to respond to the questionnaires prior to the physical examination. Pediatricians and well-trained pediatric technicians performed the physical examinations, which included measurements of weight, height, FeNO, and collection of blood and urine samples.

Measurement of Urinary BPA, Serum 25-(OH)D_3, and Specific Serum IgEs

To minimize bias from daily and seasonal variations in BPA, urine BPA levels were determined from single spot urine samples that were collected between 9:00 am to 11:00 am during June and July. After sample collection, samples were immediately stored at -70°C. BPA was measured using gas chromatography/tandem mass spectroscopy (GC/MS/MS). The urinary concentration was expressed as a fraction of urinary creatinine concentration[14].

Serum 25-hydroxyvitamin D_3 [25-(OH)D_3] level was determined using an enzyme-linked immunoassay (ELISA) kit (Immunodiagnostic Systems, COBAS 6000 Roche, Manheim Germany) after extraction with acetonitrile. For statistical analysis, the serum 25-(OH)D_3 level was considered deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), or normal (≥30 ng/mL)[15]. Blood samples from all participants were analyzed for serum specific IgE against the six major aeroallergens in South Korea (*Dermatophagoides farinae*, birch, Japanese hop, cat, dog, and *Alternaria*) using the ImmunoCAP system (Phadia AB, Uppsala, Sweden). A subject was considered allergic if there was one or more positive reaction (>0.35 U/L). Children were categorized as non-sensitized, mono-sensitized (positive result for a single antigen), or poly-sensitized (positive results for multiple antigens)[16].

Measurement of FeNO and Small Airway Functions

FeNO was measured using an online technique with a portable device (NIOX MINO® Airway Inflammation Monitor, Aerocrine, Solna, Sweden) in accordance with international guidelines[17], and expressed as parts per billion (ppb). This procedure was performed with the subject seated in a comfortable position, and taking full inhalation followed by exhalation at a constant flow rate. Lung function measurements were performed using the Jaeger MasterScreen IOS (Jaeger Company, Wurzburg, Germany) as described previously[18]. Reactance area (AX), airway resistance at 5 Hz (Rrs5), and airway resistance at 20 Hz (Rrs20) were recorded, and the difference between Rrs5 and Rrs20 (Rrs5-20) was calculated.

Questionnaires and Demographic Data

The diagnosis of allergic disease (atopic dermatitis [AD], allergic rhinitis [AR], and asthma) was based on the Korean version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, a standardized method of evaluating allergic diseases in epidemiologic studies in Korea[19]. The diagnosis of current allergic disease was based on relevant symptoms during the previous 12 months. This questionnaire also recorded general information about the children, including gender, birth date, height, weight, and family history of allergic

disease. Body mass index (BMI) z-scores were calculated based on age- and sex standardized measures of adiposity in children from World Health Organization (WHO) growth standards.

Statistical Analysis

All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and R Packages (version 3.5.0; R Foundation, Vienna, Austria). Each value was reported as a geometric mean (GM) and 95% confidence interval (CIs) or as a median (interquartile range [IQR]), unless otherwise stated. Student's *t*-test and the chi-square test were used for comparisons. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using a generalized linear regression model with the logit function. Beta (β) and standard error (SE) were obtained from a generalized linear regression model with the identity function. The interactions between the levels of urinary BPA and serum 23-(OH)D_3 in relation to FeNO and IOS parameters were tested using a logistic regression model that considered all 3 main effects and all 3 two-way interactions. A *p*-value below 0.05 was considered significant.

Ethical Considerations

The study protocol was approved by the Institutional Review Board of the CHA Bundang Medical Center (IRB No. 2017-04-049). Written informed consent was obtained from the parents or guardians of all participants following a detailed explanation of the study.

Results

We first analyzed the characteristics of all 432 participating children (Table I). There were 233 males (53.9%) and the mean age was 11.0 years (95% CI: 10.9 to 11.1). Among the 270 children with one or more allergic diseases, 245 (57.1%) had AR, 65 (15.4%) had AD, and 9 (2.1%) had asthma. Among the 289 children with sensitization to aeroallergens, 147 (34.0%) had mono-sensitization and 142 (32.9%) had poly-sensitization. The median urinary BPA level was 2.75 ng/mL (IQR: 1.41 to 5.75) and the median serum 25-(OH)D_3 level was 21.1 ng/mL (IQR: 17.4 to 25.4). The serum 25-(OH)D_3 level was normal in 34 children (7.9%), insufficient in 214 children (49.5%), and deficient in 184 children (42.6%). The median FeNO was 16.0 ppb (IQR: 11.0 to 22.0). IOS measurements indicated the median Rrs5 was 4.89 hPa/L/sec (IQR: 4.32 to 5.59), the median AX was 1.75 hPa/L/sec (IQR: 1.33 to 2.29), and the median Rrs5-20 was 11.0 hPa/L/sec (IQR: 7.87 to 15.1).

Associations Between 25-(OH)D_3 and BPA with Indicators of Small Airway Function

We examined the relationships of serum 25-(OH)D_3, urinary BPA, and indicators of small airway function- total airways (Rrs5), small airways (Rrs5-20), and FeNO (Table II). The unadjusted and adjusted analyses indicated that serum 25-(OH)D_3 level was significantly associated with FeNO (adjusted β = −0.014, 95% CI: −0.023 to −0.005, p = 0.002). The unadjusted analysis indicated that serum 25-(OH)D_3 level was significantly associated with Rrs5 (β = 0.006, 95% CI: 0.003 to 0.009), AX (β = 0.016, 95% CI: 0.008 to 0.024), and Rrs5-20 (β = 0.014, 95% CI: 0.007 to 0.020), but these relationships were not significant after adjustment for confounding. Urinary BPA level was associated with FeNO in unadjusted and adjusted analyses (β = 0.006, 95% CI: 0.003 to 0.009, p < 0.001), but was not significantly associated with IOS parameters in either analysis (all comparisons, p > 0.05).

We also examined the effect of 25-(OH)D_3 in modulating the impact of BPA on FeNO and IOS parameters (Table II). The results indicated that serum 25-(OH)D_3 ameliorated the effect of BPA on FeNO in unadjusted analysis (p_{int} = 0.001) and in adjusted analysis (p_{int} = 0.005). However, 25-(OH)D_3 had no other modulating effects in unadjusted and adjusted analyses (all comparisons, p_{int} > 0.05).

Marginal Effect of Serum 25-(OH)D_3 on FeNO and IOS Parameters

A "marginal effect" is the amount of change in a dependent variable (in this case FeNO and IOS parameters) when there are changes in an independent variable [in this case 25-(OH)D_3][20]. The results indicated that the marginal effect of serum 25-(OH)D_3 level was 23 ng/mL (Figure 1). Thus, we divided all subjects into two groups based on serum 25-(OH)D_3 level (≤23 ng/mL and >23 ng/mL). The results indicated that these two groups had significant differences in age (p = 0.001) and gender (p < 0.001), but no differences in BMI, allergic diseases, sensitization to aeroallergens, and levels of urinary BPA and FeNO (all comparisons, p > 0.05; **Supplementary Table I**).

Table I. Study group characteristics (n = 432).

Characteristic	Mean (95% CI or IQR) or n (%)
Demographic	
Gender, boy, n (%)	233 (53.9)
Age, years (95% CI)	11.0 (10.9 to 11.1)
BMI z score (95% CI)	-0.02 (-0.12 to 0.09)
Height, cm (95% CI)	49.6 (148.9 to 150.3)
Allergic disease, n (%)*	431 (99.8)
≥ 1 allergic disease (AR or AD or asthma)	270 (62.6)
AR	245 (57.1)
AD	65 (15.4)
Asthma	9 (2.1)
Sensitization, n (%)**	432 (100)
None	143 (33.1)
Mono-sensitization	147 (34.0)
Poly-sensitization	142 (32.9)
Sensitization to aeroallergen, n (%)	
Dermatophagoides farina	256 (59.3)
Birch	103 (23.8)
Cat dander	75 (17.4)
Dog dander	65 (15.0)
Japanese hop	43 (10.0)
Alternaria	37 (8.6)
Laboratory fiding	
Bisphenol (IQR), ng/mL	2.75 (1.41 to 5.75)
25-(OH)D3(IQR), ng/mL	21.1 (17.4 to 25.4)
Normal (≥30 ng/mL), n (%)	34 (7.9)
Insufficiency (20-29.9 ng/mL), n (%)	214 (49.5)
Deficiency (<20 ng/mL), n (%)	184 (42.6)
FeNO (IQR), ppb	16.0 (11.0 to 22.0)
20 ppb, n (%)	297 (68.8)
20-34 ppb, n (%)	104 (24.1)
≥ 35 ppb, n (%)	31 (7.2)
IOS	
Rrs5(IQR), hPa/L/sec	4.89 (4.32 to 5.59)
AX(IQR), hPa/L/sec	1.75 (1.33 to 2.29)
Rrs5-20(IQR), hPa/L/sec*	11.0 (7.87 to 15.1)

Abbreviations: BMI, body mass index; AR, allergic rhinitis; AD, allergic dermatitis; IQR, Interquartile range; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; 25-(OH)D_3, 25-hydrovitamin D_3. *Missing data on 1 individual **Inhalant allergen-specific IgE > 0.35 kU/L for at least 1 of 6 aeroallergens (Alternaria, birch, cat dander, dog dander, Dermatophagoides farina, and Japanese hop).

We then determined the relationship of FeNO with other parameters in the two 25-(OH)D_3 groups (Table III). For children with serum 25-(OH)D_3 levels of 23 ng/mL or less and after adjustment for confounding, FeNO was associated with serum 25-(OH)D_3 (αβ: −0.029; 95% CI: −0.049 to −0.009; $p = 0.005$), urinary BPA (αβ: 0.006; 95% CI: 0.003 to 0.009; $p < 0.001$), Rrs5 (αβ: −0089; 95% CI: −0.153 to −0.025; $p = 0.06$), allergic disease (αβ: 0.244; 95% CI: 0.106 to 0.383; $p = 0.001$), mono-sensitization (αβ: 0.419; 95% CI: 0.261 to 0.577; $p < 0.001$), and poly-sensitization (αβ: 0.411; 95% CI: 0.251 to 0.570; $p < 0.001$). However, for children with serum levels of 25-(OH)D_3 above 23 ng/mL and after adjustment for confounding, FeNO value was only associated with mono-sensitization (αβ: 0.318; 95% CI: 0.139 to 0.498; $p = 0.001$) and poly-sensitization (αβ: 0.501; 95% CI: 0.312 to 0.690; $p < 0.001$).

Discussion

Our study of a general population of children indicated that urinary BPA and serum 25-(OH)D_3 levels were significantly associated with FeNO in those with serum 25-(OH)D_3 levels of 23 ng/mL or less but had no association with FeNO value in those with serum 25-(OH)D_3 levels above 23 ng/mL. Additionally, FeNO appeared

Table II. Associations between 25-(OH)D_3 and BPA with indicators of small airway function†.

FeNO (ppb)	Unadjuste β	95% CI	*p*-value	p_{int}**	Adjusted* β	95% CI	*p*-value	p_{int}**
25-(OH)D_3	-0.010	-0.019 to -0.002	0.021	0.001	-0.014	-0.023 to -0.005	0.002	0.005
Bisphenol	0.006	0.003 to 0.009	< 0.001		0.006	0.003 to 0.009	< 0.001	
Rrs5 (hPa/L/sec)	**Unadjuste β**	**95% CI**	***p*-value**	**p_{int}****	**Adjusted* β**	**95% CI**	***p*-value**	**p_{int}****
25-(OH)D_3	0.006	0.003 to 0.009	< 0.001	0.923	0.004	-0.002 to 0.010	0.224	0.969
Bisphenol	-0.001	-0.002 to 0.001	0.297	0.000	-0.002 to 0.002	0.759		
AX (hPa/L/sec)								
25-(OH)D3	0.016	0.008 to 0.024	< 0.001	0.530	0.003	-0.005 to 0.010	0.480	0.785
Bisphenol	-0.001	-0.004 to 0.001	0.296		-0.001	-0.003 to 0.001	0.358	
Rrs5-20 (hPa/L/sec)								
25-(OH)D_3	0.014	0.007 to 0.020	< 0.001	0.699	0.004	-0.002 to 0.010	0.224	0.969
Bisphenol	0.000	-0.003 to 0.0020	0.704		0.000	-0.002 to 0.002	0.759	

Abbreviations: FeNO, fractional exhaled nitric oxide; ppb, parts per billion; 25-(OH)D_3, 25-hydrovitamin D3;CI, confidence interval. †Generalized linear regression with gamma function. *Adjusted for age, gender, BMI z score, allergic disease (none, one, or two), residency floor (continuous variable), and aeroallergen sensitization (no *vs.* yes) **pint: *p* for interaction between vitamin D and BPA for FeNO. ***Adjusted for height, gender, BMI z score, allergic disease (none, one, or two), prematurity and/or low birth weight, and aeroallergen sensitization (no *vs.* yes).

to have a different relationship with exposure to BPA depending on vitamin D status and on the presence of allergic diseases, such as asthma and AR. These findings indicated that increased exposure to BPA and low vitamin D level were associated with increased airway inflammation and elevated FeNO.

It was well-known that vitamin D is an essential component of calcium metabolism, immune function, and anti-inflammatory activities[21]. Meanwhile, vitamin D levels for airway inflammation showed inconsistent results. According to a recent study[22], vitamin D supplementation in asthmatic children with vitamin D deficiency did not improve asthma control. However, another study[23] reported that vitamin D supplements led to a more significant decrease of the FeNO in children with AR and pollen than in controls. Meanwhile, one study[9] reported that BPA exposure was associated with a modest decrease in forced expiratory flow 25-75% (FEF25-75) and percent forced expiratory volume in 1 s (FEV1)/ forced vital capacity (FVC), but not with FeNO in children. Also, a recent study did not observe consistent associations with lung inflammation and lung function among US Black children with severe asthma[24]. Another prospective birth cohort study[8] reported that urinary BPA concentration at the age of 7 was associated with asthma and FeNO (β = 0.1; 95% CI: 0.02 to 0.2; p = 0.02). These reports showing no association of BPA and vitamin D with FeNO may suggest that the mechanism by which BPA and vitamin D affect pulmonary function is developed by a pathway

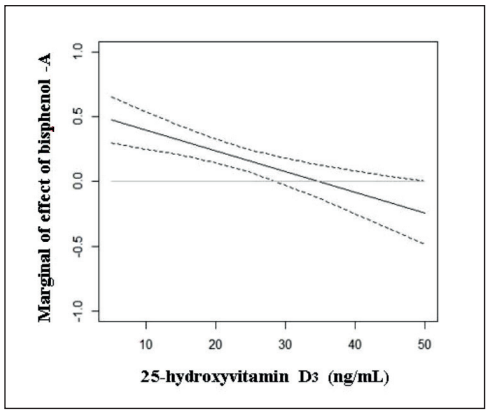

Figure 1. A marginal effect of serum 25-(OH)D_3 on BPA. A marginal effect is the amount of change in FeNO and IOS parameters when there are changes in a serum 25-(OH)D_3, and the marginal effect of serum 25-(OH)D_3 level was 23 ng/mL in this study. Abbreviations: 25-(OH)D_3, 25-hydroxyvitamin D_3; BPA, bisphenol A; FeNO, fractional exhaled nitric oxide; IOS, impulse oscillometry system.

Table III. Associations between FeNO and other parameters in children with high or low serum 25-(OH)D_3 levels†.

Independent variables	FeNO (ppb)					
	Serum 25-(OH)D_3 ≤ 23			Serum 25-(OH)D_3 > 23		
	αβ	95% CI	*p*-value	αβ	95% CI	*p*-value
Age	-0.031	-0.121 to 0.059	0.505	-0.046	-0.111 to 0.019	0.16
Gender						
Girl	Ref	Ref	-	Ref	Ref	-
Boy	-0.032	-0.167 to 0.103	0.639	0.073	-0.084 to 0.230	0.361
BMI, z score	0.023	-0.040 to 0.086	0.466	-0.031	-0.104 to 0.041	0.397
Allergic disease						
No	Ref	Ref	-	Ref	Ref	-
Yes	0.244	0.106 to 0.383	0.001	0.165	-0.002 to 0.331	0.052
Sensitization to aeroallergen						
Non	Ref	Ref	-	Ref	Ref	-
Mono-	0.419	0.261 to 0.577	< 0.001	0.318	0.139 to 0.498	0.001
Poly-	0.411	0.251 to 0.570	< 0.001	0.501	0.312 to 0.690	< 0.001
25-(OH)D_3 (ng/mL)	-0.029	-0.049 to -0.009	0.005	-0.014	-0.035 to 0.007	0.187
Bisphenol (ng/mL)	0.006	0.003 to 0.009	< 0.001	0.004	0.002 to 0.009	0.173
Rrs5 (hPa/L/sec)	-0.089	-0.153 to -0.025	0.006	-0.017	-0.090 to 0.056	0.650
AX (hPa/L/sec)	-0.004	-0.016 to 0.008	0.523	0.000	-0.014 to 0.013	0.966
Rrs5-20 (hPa/L/sec)	-0.011	-0.104 to 0.083	0.822	-0.009	-0.115 to 0.096	0.861

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; 25-(OH)D_3, 25-hydrovitamin D3.; CI, confidence interval. †Generalized linear regression with gamma function with adjustment for age, gender, BMI z score, allergic disease (none, one, or two), residency floor (continuous variable), and aeroallergen sensitization (no vs. yes).

other than eosinophilic inflammation. This result may also explain why the relationship between BPA and FeNO has been controversial. Thus, when examining the relationship between BPA and FeNO, vitamin D level should also be considered as a crucial modulating factor that can also affect airway inflammation. Future mechanistic studies are needed to clarify the nature of this relationship.

Interestingly, we found that after adjustment for confounding factors, serum 25-(OH)D_3 level modified the effects of BPA on the risk of a high FeNO. A previous animal study[25] reported that administration of vitamin D to mother mice ameliorated the BPA-induced increase of IL-6 and IL-23 in their offspring. This may be because these vitamin D supplements attenuated the BPA-induced side effects on the immune system *via* a vitamin D receptor (VDR)-dependent regulation of transcription factors and cytokines[26]. Environmental exposure to BPA may alter the serum level of vitamin D in adult population[27]. These previous results and the results presented here suggest that vitamin D supplements may alleviate the adverse effects of BPA on the immune system.

However, the present study did not identify a modulating effect of vitamin D in the relationship between BPA and small airway function. Measurements from the IOS and FeNO are widely used to measure lung function in young children[28]. The IOS provides measurements of respiratory impedance (Zrs), which consists of respiratory resistance (Rrs) and respiratory reactance (Xrs)[29]. The IOS also provides measures of peripheral airway resistance (Rrs5-20) and AX, considered a sensitive indicator of reactive airflow limitation[29]. However, we found that 25-(OH)D_3 did not modify the effects of BPA on some IOS parameters (Rrs5, AX, and Rrs5-20). This result may be because FeNO is a marker of airway inflammation and is significantly correlated with FEV1/FVC, but IOS parameters are unrelated to FeNO because they reflect small airway obstruction[29].

The present study had some limitations. Because of the cross-sectional study design, we could only examine a few children with AR and moderate or severe asthma and had low generalizability of their results. One of the additional limitations of this study is not measuring lung function with spirometry. This study showed no effects of BPA on small airway function assessed with IOS, but we do not know if there are any effects of BPA on spirometry indices. Therefore,

further studies of children with severe AR and asthma are warranted to confirm the effects of BPA and vitamin D on airway function in children.

However, the present study has several strengths. First, we examined a large sample of schoolchildren from the general population. We performed all measurements under the same conditions in that all samples and data were collected at about the same time. Second, we used multiple objective measurement tools, such as specific serum IgE, FeNO, and the IOS, to demonstrate that the levels of urinary BPA and serum 25-(OH)D_3 were associated with lower small airway function.

Conclusions

High urinary BPA and low serum vitamin D levels were significantly associated with airway inflammation in children. Furthermore, serum 25-(OH)D_3 levels ameliorated the BPA-mediated increase of FeNO.

To the best of our knowledge, this study is the first to investigate lower airway function and also perform specific measurements that evaluate the impact of BPA and its relationship with vitamin D on airway dysfunction in a general pediatric population. Thus, reducing exposure to BPA and increasing vitamin D levels in children may help prevent airway dysfunction.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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