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Letters to the Editor

Association of phthalates with nasal patency and small airway dysfunction in first-grade elementary school children

Introduction

To the Editor,

Phthalates are widely used plasticizers to make plastics flexible and are common ingredients in polyvinyl chloride (PVC) products, medical devices, solvents, and toys.(1)Because of the widespread use of phthalates and the identification of possible adverse health effects,governments have restricted exposure levels and increased monitoring.(2)Phthalates may have harmful effects on the reproductive system by functioning as endocrine disruptors, are associated with allergic diseases such as eczema, urticaria, asthma, and rhinitis as well as airway inflammation and reduced lung function.(2-5)The route of exposure is usually *via* ingestion, inhalation, intravenous injection and skin absorption.(1) Particularly, children are more likely to have exposure to phthalates than adults through ingestion of dietary sources or inhalation of dust from phthalate containing

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products. Recent studies demonstrated that exposure to phthalates influences T helper 2 (Th2) cells, cytokines, and fractional exhaled nitric oxide (FeNO), a marker of type 2 airway inflammation.(1-7) However, the association of phthalates with functional parameters of allergic diseases, such as upper nasal airway patency or lower small airway dysfunction, is unknown. Therefore, we investigated the associations of urinary phthalate metabolites with whole airway dysfunction, from the upper nose to the lower small airways using acoustic rhinometry, spirometry, and an impulse oscillation system (IOS).

Methods

This cross-sectional study examined 149 randomly selected first-grade students at 11 elementary schools during from January to December of 2016 in Seongnam City, Korea. The study subjects were enrolled and asked to perform the tests, as described in a previous study.(3) The study protocol was approved by the Institutional Review Board of CHA University (2016-04-031). Written informed consent was obtained from the parents or caregivers of all children who participated.

Demographic data of the children, such as age, sex, height, and weight, were collected. Parents were asked to complete questionnaires that examined the history of wheezing and nasal symptoms, based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, during the past 12 months.(3) Spirometry (Jaeger MasterScreen device, Jaeger Co., Germany), IOS (Jaeger Co., Germany) and acoustic rhinometry (A1 Acoustic Rhinometer, GM Instruments Ltd, UK) tests were conducted in each child.(8) These functional studies were conducted between 9:00 AM and 11:00 AM from 27 June to 21 July, to minimize bias from daily and seasonal variations. First, IOS was performed, followed by spirometry, and finally acoustic rhinometry by technicians who were in charge of each examination. The nasal airway patency was defined by measuring nasal volume 15 min after administration of a topical alpha agonist (one puff of intranasal xylometazoline [1 mg/mL]) to each nostril.

We analyzed 3 metabolites of phthalates in urine: mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(iso-butyl) phthalate (MiBP). MEHHP and MEOHP are both secondary metabolites of di-ethylhexyl phthalate (DEHP), the most widely consumed high molecular weight (HMW) phthalate. HMW phthalates are used to impart flexibility to PVC and lower molecular weight (LMW) phthalates as solvents or

adhesives. DEHP is widely used in plastic products such as toys or food packages, and PVC floorings.(1,4-7) MiBP is a metabolite of diisobutyl phthalate (DiBP), a LMW phthalate that is used in ink for printing on paper, cosmetics, emollients, and medical devices.(1)A previous report found that the urinary levels of DEHP and DBP metabolites were higher in Korea than in the U.S., but other metabolites were much lower in Korea.(9)This is why we selected these specific metabolites. We used single spot urine samples that were collected between 9:00 AM to 11:00 AM from 27 June to 21 July to minimize bias from daily and seasonal variations. After sample collection, urine samples were immediately stored at -70 °C . These three compounds were measured in children's urine using gas chromatography/tandem mass spectroscopy. The urinary concentration of each compound is expressed as a fraction of urinary creatinine concentration. After measurements, we divided subjects into low and high concentration groups according to the median concentration of each metabolite (Fig. E1).

Statistical analysis was conducted using SPSS version 23.0 (IBM Co, Armonk, NY, USA). Student's *t*-test, chi-square test, and a generalized linear regression model, with the logit function for dichotomous variables and the gamma function for continuous variables, were used for data analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined by 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 gamma function. A *P*-value below 0.05 was considered statistically significant.

Results

Among 149 children who were in first grade at one of 11 elementary schools, 140 (94.0%) met the study criteria by completing the spirometry, IOS, and acoustic rhinometry testing. The mean age was 7.1 ± 0.3 years and 57.9% were males. A total of 7.9% of children had recent wheezing and 51.4% had recent rhinitis (Table E1). The generalized linear regression model was adjusted by parameters, including height, sex, body mass index (BMI) z score [obtained by the LMS method, full description of this method has been described elsewhere (10)], and second-hand smoke, which were significantly associated with at least one measure of airway dysfunction (Table E2).

However, there were no significant differences of phthalate metabolites according to allergic signs and/or symptoms (Table E3). Children with high levels of MEHHP and MiBP had

significantly greater resistance of the respiratory system at 5 Hz (Rrs5) and reactance area (AX), and significantly reduced nasal cavity volume (Vol 0-5cm and Vol 2-5cm; Fig.E2). However, none of the spirometric parameters (FEV₁, FVC, and FEF₂₅₋₇₅) were significantly associated with the levels of urinary phthalate metabolites (Table E4).

Next, we analyzed associations of urinary phthalate metabolites with airway function parameters using generalized linear regression model with adjustment for confounding variables (Table 1). The results indicated significant associations of several urinary phthalate metabolites with IOS parameters and nasal cavity volume (Table 1), but no significant associations with spirometric parameters. In particular, Rrs5 and AX were positively associated with MEHHP and MiBP, and negatively associated with nasal volume (Vol 0-5cm and Vol 2-5cm). These findings indicated that higher exposure to phthalates was associated with increased airway resistance and decreased nasal patency, characteristic findings of asthma and rhinitis (Fig.1).

Discussions and conclusion

In the present study, we used objective measurement tools (acoustic rhinometry and IOS) to demonstrate that the levels of urinary phthalate metabolites were associated with nasal patency and lower small airway function. To the best of our knowledge, this is the first study to investigate the upper and lower airway simultaneously using specific measurements to evaluate the impact of phthalates on airway dysfunction. IOS is widely used to assess small airway dysfunction, and acoustic rhinometry provides reliable measurements of nasal volume, representing nasal patency. We found that the airway resistance and reactance were greater in the high phthalate group and in those with decreased nasal volume. These findings implicate phthalates, well-known and widely used endocrine disruptors, as possible contributors to airway inflammation from the nose to the distal small airways, thus reflecting the concept of a united airway disease (UAD). The UAD concept posits a connection of upper and lower airway inflammation in rhinitis and asthma, and that these should be treated as one disease with the same pathogenesis (11).

The main strength of our study is that we performed all measurements under the same conditions, in that all samples and data were collected at about the same time and by the same physicians/technicians. Also, we adopted multiple functional tests, such as spirometry, IOS and acoustic rhinometry for measurements. However, the current study is limited in that we examined

a relatively small number of total subjects using a cross-sectional study design. Consequently, a relative small number of study subjects had allergic symptoms. This may be why phthalate metabolites had no significant associations with allergic symptoms or diseases, but did have a significant association with functional measurements. Further laboratory studies are needed to delineate the mechanisms by which phthalate metabolites contribute to the development of allergic inflammation in the upper and lower airways.

In conclusion, the levels of urinary phthalate metabolites in children were significantly associated with upper and lower airway dysfunction. Thus, interventions that reduce the exposure to phthalates in children could help to prevent airway dysfunctions from the nose to the distal small airways.

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Conflicts of interest

The authors declare that they have no competing interests related to the submitted work.

Running title

Association of phthalates with airway inflammation

Keywords

Phthalate, urinary metabolites, small airway, nasal cavity area, lung function

Author contributions

Mi-Ae Kim and Man Young Han contributed to conception and design; Hye Mi Jee and Man Young Han acquired the data; Man Young Han, Mi-Ae Kim, Ju Hee Kim, Jisoo Park, Myungsoon Seong analyzed and interpreted the data; Mi-Ae Kim drafted the article; Dong Keon Yon, Seung Won Lee, and Youn Ho Shin critically revised the article and provided important intellectual content; and all authors approved the final version to be published.

Figure legends

Fig.1. Schematic summary of the association of phthalates with airway dysfunction

Fig.E1. Urinary concentrations of three phthalate metabolites in 140 children (red line: medians)

Fig.E2. Resistance at 5 Hz (A to C), reactance at 5 Hz (D to F), and nasal cavity volume at 0 to 5 cm (G to I), and nasal cavity volume at 2 to 5 cm (J to L) among children with high and low levels of three phthalate metabolites

* *P* values are from Student's *t*-test. † *P* values are from a generalized linear regression with adjustment for height, sex, and BMI z score.

Table 1. Association of urine phthalate metabolites with lung function parameters from IOS and nasal volume

		Rrs5 (hPa/L/s)		AX (hPa/L/s)		Vol 0-5 cm (cm ³)		Vol 2-5 cm (cm ³)	
		a β (SE)	P value	a β (SE)	P value	a β (SE)	P value	a β (SE)	P value
MEHHP	Low	ref		ref		ref		ref	
	High	0.082 (0.0280)	0.003	0.147 (0.0570)	0.010	-0.094 (0.0459)	0.041	-0.110 (0.0510)	0.032
MEOHP	Low	ref		ref		ref		ref	
	High	0.040 (0.0286)	0.161	0.048 (0.0582)	0.414	0.010 (0.0466)	0.837	0.011 (0.0519)	0.838
MiBP	Low	ref		ref		ref		ref	
	High	0.070 (0.0282)	0.013	0.156 (0.0569)	0.006	-0.094 (0.0459)	0.042	-0.102 (0.0512)	0.047

Rrs5, resistance of respiratory system at 5 Hz; AX, reactance area; Vol 0-5 cm, nasal volume (cm³) at 0 to 5 cm behind the nostril opening; Vol 2-5 cm, nasal volume (cm³) at 2 to 5 cm behind the nostril opening; SE, standard error; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MiBP, mono-isobutyl phthalate.

Data were analyzed using generalized linear regression with gamma function adjustment for height, sex, BMI z score, and second-hand smoke.

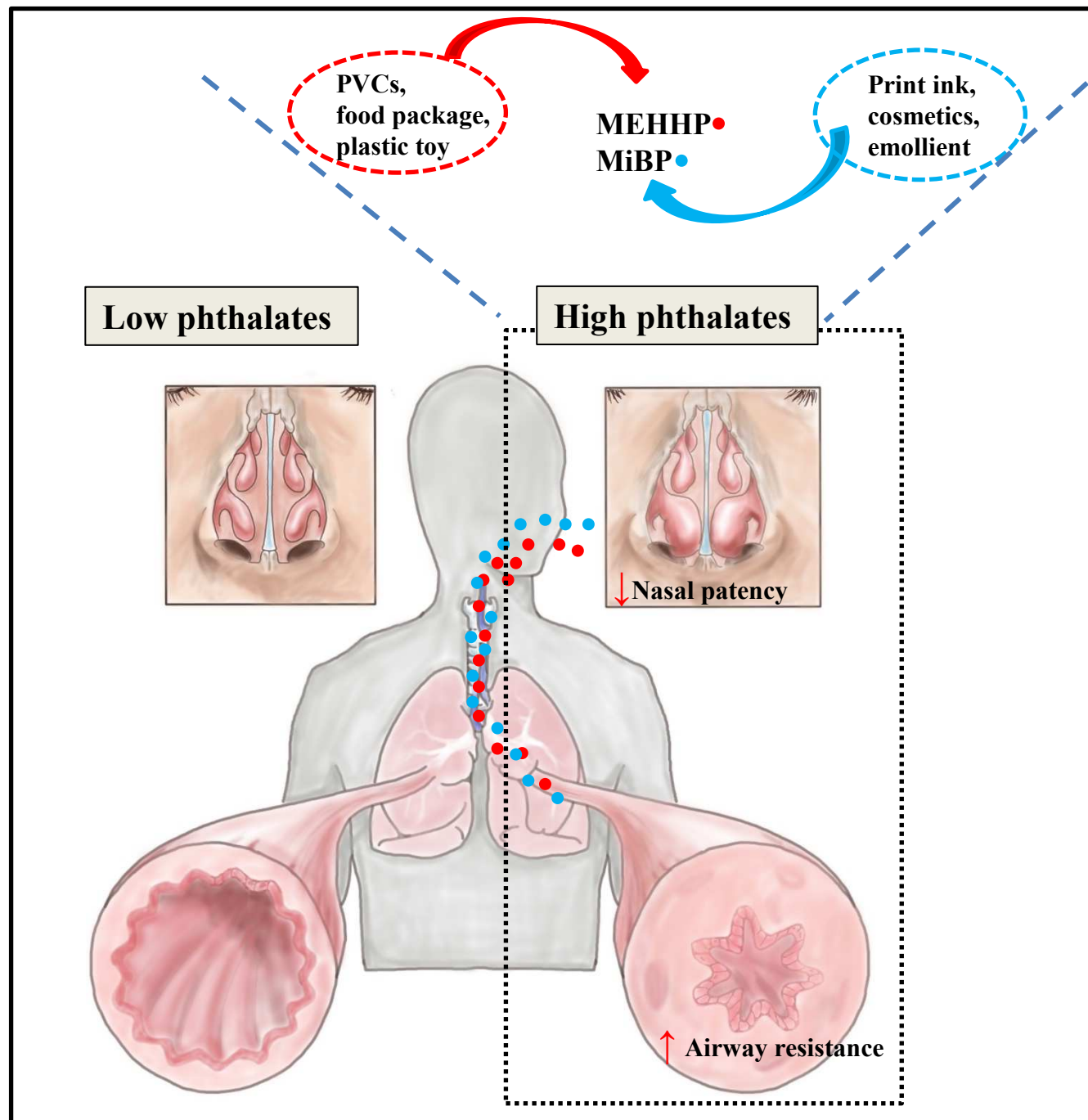


Fig. 1.

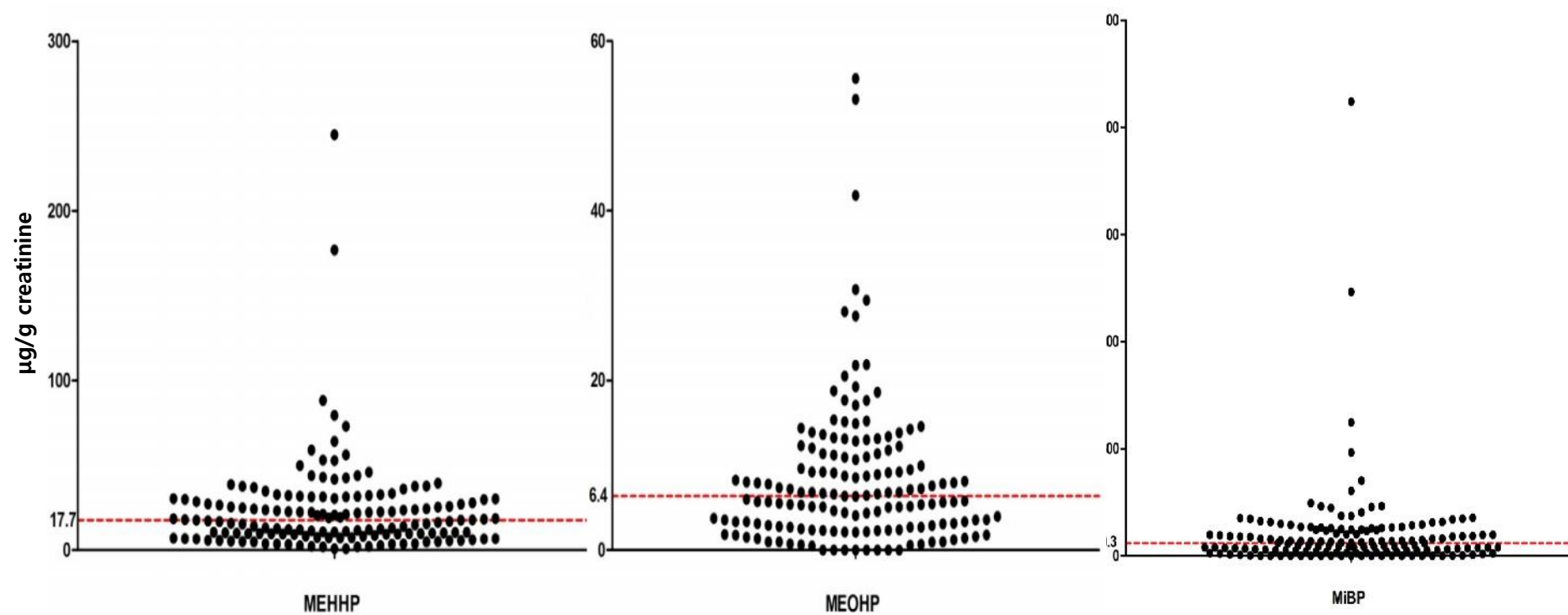


Fig. E1.

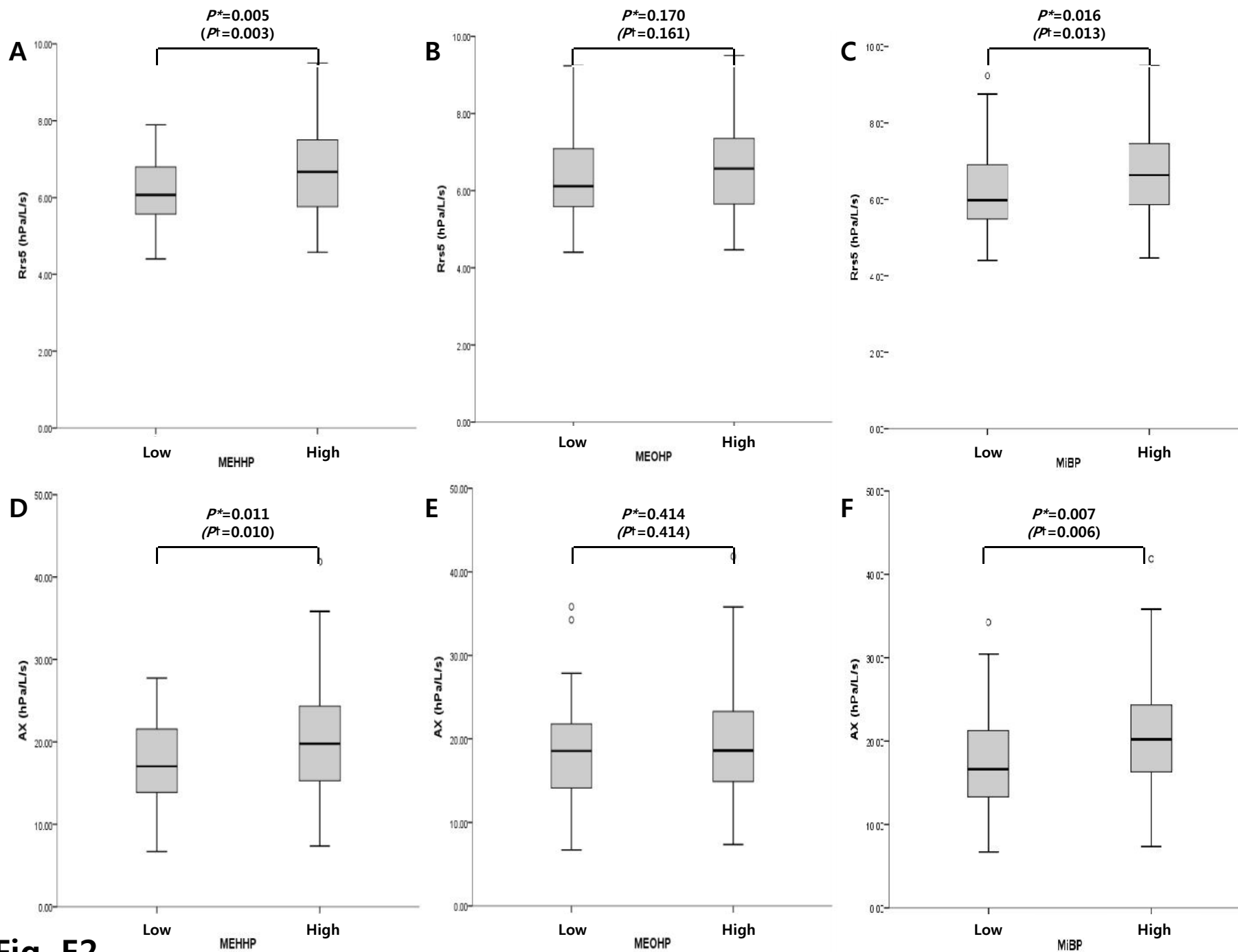


Fig. E2.

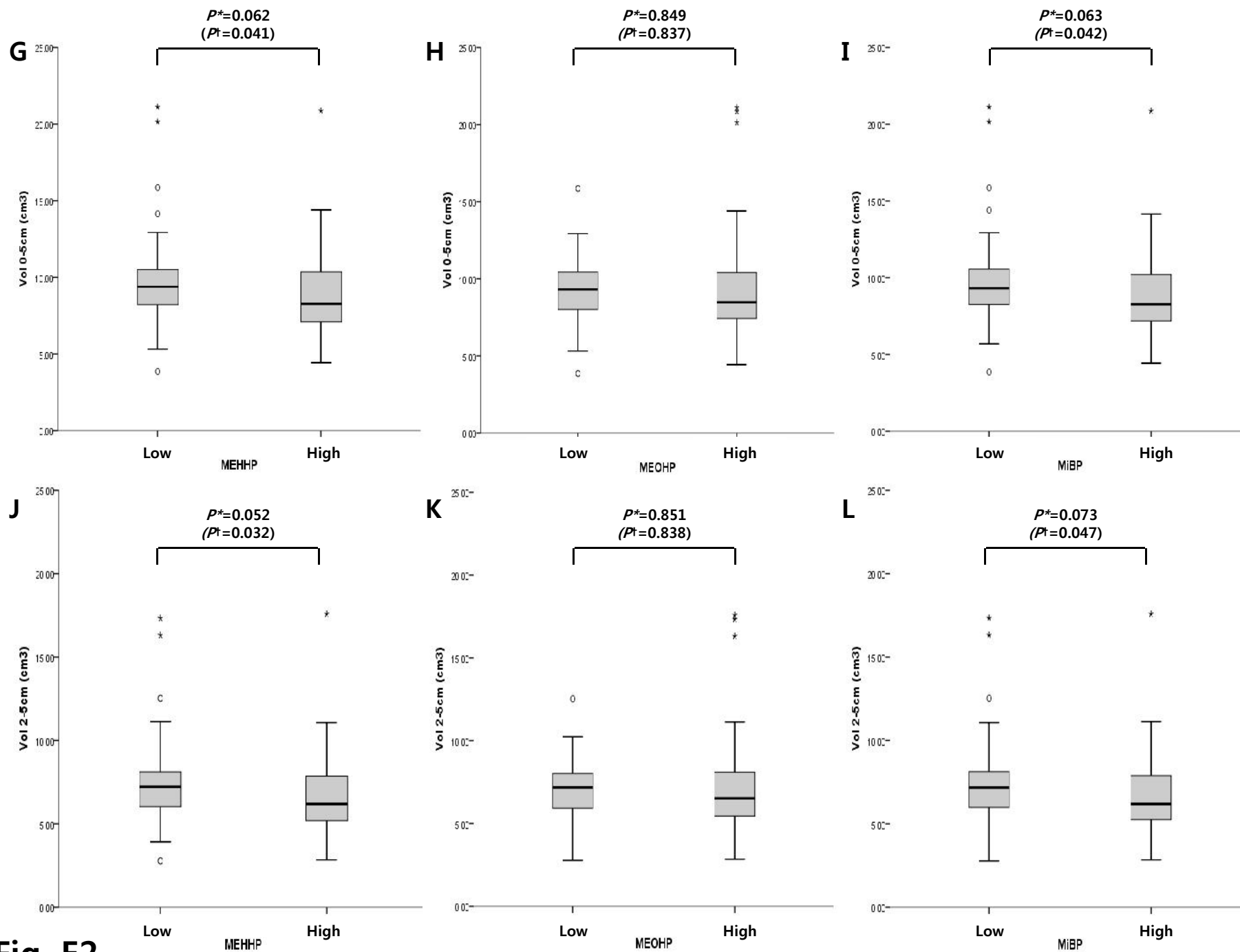


Fig. E2.

Table E1. Clinical characteristics of enrolled children (N = 140)

	N (%) or mean $\pm$ SD (range)
Sex (Male)	81 (57.9)
Age, years	7.1 $\pm$ 0.3 (6.4 – 7.5)
Height, cm	121.7 $\pm$ 5.4 (105.0 – 132.0)
BMI	16.6 $\pm$ 2.4 (13.0 – 31.0)
BMI, z score	0.06 $\pm$ 1.02 (-2.49 – 3.09)
Delivery type (Cesarean section)	38 (27.1)
Prematurity (gestational age $\leq$ 36 weeks)	16 (11.4)
Low birth weight ($\leq$ 2.5 kg)	7 (5.0)
Breast-feeding 4 months or more	72 (51.4)
History of parental asthma	12 (8.6)
Exposure to second-hand smoke	72 (51.4)
Past medical history (BA/AR/AD)	14/56/52 (10.0/40.0/37.1)
Aero-allergen sensitization (N=138)	57 (40.8)
Recent wheeze within 1 year	11 (7.9)
Recent rhinitis within 1 year	72 (51.4)
Spirometry	
FEV ₁ (L)	1.37 $\pm$ 0.18 (1.03 – 1.87)
FVC (L)	1.57 $\pm$ 0.22 (1.10 – 2.20)
FEV ₁ /FVC	0.87 $\pm$ 0.06 (0.58-0.99)
FEF _{25-75%} (L)	1.64 $\pm$ 0.42 (0.71 – 2.86)
Impulse Oscillation System (IOS)	
Rrs5, hPa/L/s	6.42 $\pm$ 1.11 (4.40 – 9.50)
AX, hPa/L/s	18.91 $\pm$ 6.48 (6.71 – 41.85)
Acoustic rhinometry (nasal volume after intranasal decongestant, cm ³)	
Vol 0-5 cm	9.26 $\pm$ 2.69 (3.86 – 21.11)
Vol 2-5 cm	7.03 $\pm$ 2.29 (2.78 – 17.58)

SD, standard deviation; BMI, body mass index; BA, bronchial asthma; AR, allergic rhinitis; AD, atopic dermatitis; Aero-allergen sensitization, positive skin prick test to one or common inhalant allergen (D.p., D.f., cat, dog, cockroach, birch, oak, elm, orchard, Hop J, mugwort, ragweed, alternaria) defined by wheal size $\geq$ 3mm; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75%}, forced expiratory flow between 25% and 75% of functional vital capacity; Rrs5, resistance of respiratory system at 5 Hz; AX, reactance area; Vol 0-5 cm, nasal volume (cm³) at 0 to 5 cm behind the nostril opening; Vol 2-5 cm, nasal volume (cm³) at 2 to 5 cm behind the nostril opening

Table E2. Association of continuous and binary factors with lung function (A: spirometry, B: ISO), nasal volume (C: acoustic rhinometry), and clinical symptoms (D).

A.

Continuous variables*		FEV ₁ , L		FVC, L		FEF ₂₅₋₇₅	
		β (SE)	*P value	β (SE)	*P value	β (SE)	*P value
Age		0.074 (0.037)	0.047	0.111 (0.038)	0.004	0.169 (0.172)	0.325
Height		0.014 (0.002)	< 0.001	0.017 (0.002)	< 0.001	0.008 (0.010)	0.417
BMI z score		0.046 (0.010)	< 0.001	0.049 (0.011)	< 0.001	0.129 (0.050)	0.010
Birth weight		0.044 (0.024)	0.070	0.038 (0.025)	0.136	0.258 (0.106)	0.015
Binary variables†		FEV ₁ , L		FVC, L		FEF ₂₅₋₇₅	
		Mean (SD)	†P value	Mean (SD)	†P value	Mean (SD)	†P value
Sex	Male	1.409 (0.192)	0.001	1.620 (0.243)	0.001	2.164 (4.496)	0.328
	Female	1.311 (0.152)		1.499 (0.164)		1.588 (0.431)	
Second-hand smoke	Yes	1.395 (0.183)	0.071	1.611 (0.234)	0.021	1.669 (0.450)	0.374
	No	1.339 (0.180)		1.525 (0.199)		2.188 (4.910)	
Past history of BA	Yes	1.372 (0.151)	0.937	1.634 (0.183)	0.262	1.432 (0.357)	0.056
	No	1.368 (0.188)		1.563 (0.227)		1.660 (0.426)	
Past history of AR	Yes	1.394 (0.190)	0.141	1.593 (0.222)	0.310	1.647 (0.383)	0.628
	No	1.346 (0.178)		1.554 (0.222)		1.610 (0.453)	
Past history of AD	Yes	1.387 (0.165)	0.387	1.587 (0.191)	0.481	1.664 (0.423)	0.625
	No	1.359 (0.194)		1.560 (0.240)		1.627 (0.423)	
Aero-allergen sensitization	Yes	1.360 (0.195)	0.628	1.589 (0.242)	0.414	1.539 (0.373)	0.023
	No	1.375 (0.175)		1.558 (0.209)		1.705 (0.436)	
History of parental asthma	Yes	1.339 (0.168)	0.614	1.525 (0.217)	0.467	1.619 (0.327)	0.991
	No	1.367 (0.180)		1.573 (0.214)		1.621 (0.427)	
Prematurity or LBW	Yes	1.348 (0.139)	0.617	1.527 (0.176)	0.367	1.658 (0.422)	0.722
	No	1.371 (0.190)		1.576 (0.228)		1.963 (3.706)	

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow between 25% and 75% of

functional vital capacity; BMI, body mass index; LBW, low birth weight; SE, standard error; SD, standard deviation; BA, bronchial asthma; AR, allergic rhinitis; AD, atopic dermatitis; Aero-allergen sensitization, positive skin prick test to one or common inhalant allergen (D.p., D.f., cat, dog, cockroach, birch, oak, elm, orchard, Hop J, mugwort, ragweed, alternaria) defined by wheal size $\geq 3\text{mm}$
**P* values are from a generalized linear regression with gamma function. [†]*P* values are from Student's *t*-test.

B.

Continuous variables*		Rrs5, hPa/L/sec		Ax	
		β (SE)	* <i>P</i> value	β (SE)	* <i>P</i> value
Age		-0.026 (0.049)	0.593	-0.145 (0.100)	0.147
Height		-0.011 (0.003)	< 0.001	-0.018 (0.005)	0.001
BMI z score		0.006 (0.014)	0.685	-0.020 (0.028)	0.474
Birth weight		-0.046 (0.032)	0.145	-0.037 (0.066)	0.573
Binary variables†		Rrs5, hPa/L/sec		Ax	
		Mean (SD)	† <i>P</i> value	Mean (SD)	† <i>P</i> value
Sex	Male	6.324 (1.065)	0.241	18.504 (5.902)	0.390
	Female	6.547 (1.164)		19.462 (7.213)	
Second-hand smoke	Yes	6.347 (1.108)	0.441	18.334 (6.751)	0.283
	No	6.493 (1.113)		19.514 (6.171)	
Past history of BA	Yes	6.590 (0.782)	0.540	20.267 (5.721)	0.396
	No	6.398 (1.141)		18.712 (6.546)	
Past history of AR	Yes	6.433 (1.014)	0.957	18.503 (6.260)	0.415
	No	6.444 (1.181)		19.438 (6.684)	
Past history of AD	Yes	6.406 (1.066)	0.963	17.954 (6.605)	0.213
	No	6.415 (1.149)		19.377 (6.398)	
Aero-allergen sensitization	Yes	6.475 (1.173)	0.529	19.654 (6.484)	0.253
	No	6.354 (1.059)		18.368 (6.390)	
History of parental asthma	Yes	6.296 (0.774)	0.597	18.718 (3.914)	0.777
	No	6.470 (1.100)		19.270 (6.574)	
Prematurity or LBW	Yes	6.452 (0.896)	0.866	18.534 (5.737)	0.809
	No	6.406 (1.144)		18.924 (6.620)	

Rrs5, resistance of respiratory system at 5 Hz; AX, reactance area; BMI, body mass index; LBW, low birth weight; SE, standard error; SD, standard deviation; BA, bronchial asthma; AR, allergic rhinitis; AD, atopic dermatitis; Aero-allergen sensitization, positive skin prick test to one or common inhalant allergen (D.p., D.f., cat, dog, cockroach, birch, oak, elm, orchard, Hop J, mugwort, ragweed,

alternaria) defined by wheal size $\geq 3\text{mm}$

* P values are from a generalized linear regression with gamma function. [†] P values are from student's t -test.

C.

Continuous variables*		Vol 0-5 cm		Vol 2-5 cm	
		β (SE)	*P value	β (SE)	*P value
Age		-0.023 (0.0784)	0.765	-0.026 (0.0871)	0.764
Height		0 (0.0045)	0.967	3.701E-5(0.0051)	0.994
BMI z score		-0.054 (0.0229)	0.018	-0.070 (0.0255)	0.006
Birth weight		-0.027 (0.0497)	0.588	-0.029 (0.0548)	0.600
Binary variables†		Vol 0-5 cm		Vol 2-5 cm	
		Mean (SD)	†P value	Mean (SD)	†P value
Sex	Male	9.119 (2.697)	0.484	6.936 (2.315)	0.564
	Female	9.452 (2.688)		7.170 (2.277)	
Second-hand smoke	Yes	9.170 (2.194)	0.705	6.921 (1.879)	0.562
	No	9.350 (3.150)		7.153 (2.680)	
Past history of BA	Yes	9.031 (1.954)	0.718	6.831 (1.583)	0.706
	No	9.310 (2.794)		7.079 (2.391)	
Past history of AR	Yes	9.339 (2.616)	0.952	7.076 (2.206)	0.881
	No	9.368 (2.733)		7.137 (2.356)	
Past history of AD	Yes	9.459 (3.168)	0.517	7.231 (2.739)	0.450
	No	9.143 (2.380)		6.917 (2.002)	
Aero-allergen sensitization	Yes	8.939 (2.657)	0.261	6.800 (2.267)	0.332
	No	9.481 (2.715)		7.199 (2.322)	
History of parental asthma	Yes	9.498 (3.956)	0.762	7.223 (3.542)	0.763
	No	9.244 (2.571)		7.006 (2.180)	
Prematurity or LBW	Yes	9.761 (3.340)	0.381	7.466 (2.887)	0.377
	No	9.172 (2.583)		6.959 (2.196)	

Vol 0-5 cm, nasal volume (cm3) at 0 to 5 cm behind the nostril opening; Vol 2-5 cm, nasal volume (cm3) at 2 to 5 cm behind the nostril opening; BMI, body mass index; LBW, low birth weight; SE, standard error; SD, standard deviation; BA, bronchial asthma; AR, allergic rhinitis; AD, atopic dermatitis; Aero-allergen sensitization, positive skin prick test to one or common inhalant allergen

(D.p., D.f., cat, dog, cockroach, birch, oak, elm, orchard, Hop J, mugwort, ragweed, alternaria) defined by wheal size $\geq 3\text{mm}$

* P values are from a generalized linear regression with gamma function. † P values are from student's t -test.

D.

Continuous variables*		Recent wheeze within 1 year		Recent rhinitis within 1 year	
		OR (95% CI)	*P value	OR (95% CI)	*P value
Age		0.535 (0.068-4.185)	0.551	0.965 (0.314-2.967)	0.950
Height		0.980 (0.875-1.098)	0.727	1.035 (0.972-1.102)	0.290
BMI z score		1.066 (0.575-1.973)	0.840	0.826 (0.593-1.149)	0.256
Birth weight		1.876 (0.479-7.349)	0.367	1.112 (0.540-2.291)	0.774
Binary variables†		Recent wheeze within 1 year		Recent rhinitis within 1 year	
		N (%)	†P value	N (%)	†P value
Sex	Male	8 (10)	0.289	42 (51.9)	0.907
	Female	3 (5.1)		30 (50.8)	
Second-hand smoke	Yes	5 (6.9)	0.661	35 (48.6)	0.492
	No	6 (9.0)		37 (54.4)	
Past history of BA	Yes	4 (30.8)	0.002	11 (78.6)	0.035
	No	7 (5.7)		60 (48.8)	
Past history of AR	Yes	5 (9.1)	0.578	44 (78.6)	<0.001
	No	5 (6.5)		24 (31.2)	
Past history of AD	Yes	6 (11.8)	0.215	33 (63.5)	0.028
	No	5 (5.8)		33 (44.2)	
Aero-allergen sensitization	Yes	7 (13.2)	0.076	33 (66.1)	0.092
	No	4 (4.8)		39 (46.4)	
History of parental asthma	Yes	3 (25)	0.027	10 (83.3)	0.015
	No	7 (6.4)		51 (46.4)	
Prematurity or LBW	Yes	0 (0)	0.181	12 (63.2)	0.286
	No	11 (9.2)		60 (50.0)	

BMI, body mass index; LBW, low birth weight; OR, odds ratio; CI, confidence interval; BA, bronchial asthma; AR, allergic rhinitis; AD, atopic dermatitis; Aero-allergen sensitization, positive skin prick test to one or common inhalant allergen (D.p., D.f., cat, dog, cockroach, birch, oak, elm, orchard, Hop J, mugwort, ragweed, alternaria) defined by wheal size ≥ 3 mm

* P values are from a generalized linear regression with logit function. † P values are from chi-square test.

Table E3. Association of urine phthalate metabolites with allergic symptoms

Continuous variables		Recent wheeze within 1 year		Recent rhinitis within 1 year	
		aOR (95% CI)	[*] <i>P</i> value	aOR (95% CI)	[†] <i>P</i> value
MEHHP		1.001 (0.977-1.025)	0.962	0.991 (0.976-1.007)	0.269
MEOHP		1.012 (0.949-1.080)	0.719	0.997 (0.937-1.018)	0.268
MiBP		0.999 (0.995-1.004)	0.763	1.001 (0.998-1.003)	0.503
Ordinary variables		aOR (95% CI)	[*] <i>P</i> value	aOR (95% CI)	[†] <i>P</i> value
MEHHP	Low	Ref		Ref	
	High	3.640 (0.761-17.422)	0.106	0.559 (0.263-1.189)	0.131
MEOHP	Low	Ref		Ref	
	High	3.260 (0.726-14.643)	0.123	0.942 (0.449-1.978)	0.875
MiBP	Low	Ref		Ref	
	High	3.352 (0.751-14.955)	0.113	0.770 (0.635-1.625)	0.493

aOR, adjusted odds ratio; CI, confidence interval. MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MiBP, mono-isobutyl phthalate.

^{*}*P* values are from a generalized linear regression with logit function after adjusting for history of parental asthma and aero-allergen sensitization. [†]*P* values are from a generalized linear regression with logit function after adjusting for history of parental asthma and aero-allergen sensitization.

Aero-allergen sensitization, positive skin prick test to one or common inhalant allergens (D.p., D.f., cat, dog, cockroach, birch, oak, elm, orchard, Hop J, mugwort, ragweed, alternaria) defined by wheal size ≥ 3 mm

Recent symptoms were defined by the presence of wheezing and rhinitis in the ISAAC questionnaire.

Table E4. Association of urine phthalate metabolites with lung function parameters from spirometry

		FEV ₁		FVC		FEF ₂₅₋₇₅	
		aβ (SE)	<i>P</i> value	aβ (SE)	<i>P</i> value	aβ (SE)	<i>P</i> value
MEHHP	Low	ref		ref		ref	
	High	-0.027 (0.0223)	0.232	-0.018 (0.0233)	0.439	-0.029 (0.0432)	0.497
MEOHP	Low	ref		ref		ref	
	High	-0.002 (0.0224)	0.929	-0.011 (0.0233)	0.628	0.019 (0.0432)	0.662
MiBP	Low	ref		ref		ref	
	High	-0.033 (0.0222)	0.133	-0.023 (0.0233)	0.313	-0.021 (0.0432)	0.628

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75%}, forced expiratory flow between 25% and 75% of functional vital capacity; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MiBP, mono-isobutyl phthalate; SE, standard error

Data were analyzed using generalized linear regression with gamma function after adjustment for sex, height, BMI z score, and second-hand smoke.