



Associations between phthalic acid esters in household dust and childhood asthma in Shanghai, China

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ABSTRACT

Phthalic acid esters (PAEs) have a negative impact on human health and are widely distributed in China. As part of the China, Children, Home, Health (CCHH) study, we investigated the associations between childhood asthmatic symptoms and PAEs in settled house dust in Shanghai, China.

We found that di-2-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and diisobutyl phthalate (DiBP) were abundant in the indoor environment. A total of 27 % of children suffered from diagnosed asthma. The Mann-Whitney *U* test and multiple logistic regression were used to obtain the associations between PAEs and childhood asthmatic symptoms. Stratification analysis was performed to reveal the influence of gender on the associations between PAE exposure and target symptoms. Compared with low concentrations of PAEs, high concentrations of high molecular weight PAEs (HMW-PAEs) were significantly associated with childhood diagnosed asthma (adjusted odds ratios (AORs) > 1, *P* < 0.05). Moreover, significantly negative associations were found between high concentrations of DiBP and current cough (AORs < 1, *P* < 0.05). All significantly positive associations were observed among girls, and most of the associations of dimethyl phthalate (DMP) and diethyl phthalate (DEP) exposure with the studied symptoms among girls were higher than those among boys. Exposure to PAEs may be a risk factor for asthmatic symptoms in children, especially in girls.

1. Introduction

PAEs are a group of environmental endocrine-disrupting chemicals, whose health risks, including mutagenesis, carcinogenesis, teratogenicity, and reproductive toxicity, have attracted widespread attention (Bamai et al., 2014a; Wang et al., 2016; Jurewicz and Hanke, 2011; Bu et al., 2018). With the economic development and improvement in human living standards in China, material manufacturing has expanded. PAEs have wide applications as plasticizers to make products more flexible in toys, personal care products, food packaging, and electronic or medical equipment. Due to their wide range of use, PAEs have been widely detected in many kinds of environmental media, such as soil, groundwater, air, and dust (Dietz and Singley, 1994; Fromme et al., 2013; Wei et al., 2020). The routes by which people are exposed to PAEs include inhalation, skin absorption, and ingestion (Bekö et al., 2013; Bu et al., 2016). Metabolites of PAEs have been detected in serum, urine, breast milk, and other biological media (Specht et al., 2014; Casas et al., 2011; Hines et al., 2009).

Several studies in recent decades have suggested that the prevalence

of asthma and other allergies among children has increased in China and Western countries (Ellwood et al., 2005; De et al., 2012; Huang et al., 2015; Zhang et al., 2013; Duksal et al., 2013). In addition to genetic factors, adverse environmental factors are likewise significantly related to childhood allergies. People spend more than 80 % of their time indoors, and indoor environments are critical to human health. A review study has concluded that indoor environmental factors aggravate asthma and other allergies (Kanchongkittiphon et al., 2014). People have always been exposed to indoor pollutants such as formaldehyde (Costa et al., 2019), volatile organic compounds (VOCs) (Guo et al., 2004), and particulate matter (PM) 2.5 (Quintana-Belmares et al., 2018) which are generated by smoking, cooking, household renovation, and adding new furniture (Mendell, 2010). PAEs exist in indoor air and dust due to their release from polyvinyl chloride (PVC) building materials. Therefore, human exposure to PAEs is extensive and inevitable (Pei et al., 2013).

Studies have demonstrated that PAEs are harmful to human reproductive health. Duty and Hauser analysed the associations between metabolites of PAEs in urine and reproductive indices and found

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negative dose-response relationships between mono-n-butyl phthalate (MnBP: the urinary metabolites of DBP) and low sperm activity. High concentrations of monobenzyl phthalate (MBzP: the urinary metabolites of BBP) have also been shown to be associated with low sperm concentrations (Duty et al., 2003; Hauser et al., 2006). In a cross-sectional study in Shanghai, China, positive associations were observed between the concentrations of PAE metabolites in sperm and the liquefied duration of sperm, and metabolites of DEHP was associated with the malformation rates of sperm (Zhang et al., 2006).

Exposure to PAEs also appear to cause other adverse health outcomes. Philippat analysed the relationships between PAEs and childhood autism spectrum disorder, as well as developmental delay, and found that although there were no significant associations between PAEs in household dust and childhood autism spectrum disorder, higher concentrations of DEP and DBP were associated with greater hyperactivity-impulsivity and inattention (Philippat et al., 2015). Colón's study suggested possible associations between PAE exposure and premature breast development among female (Colón et al., 2000).

Epidemiological studies have found relationships between exposure to PAEs and hypersensitivity and confirmed significant associations between high concentrations of PAEs in household dust and childhood allergies such as asthma (Kolarik et al., 2008b; Bamai et al., 2014b; Bekö et al., 2015). Although the adverse impact of urinary metabolites of PAEs on childhood asthmatic symptoms has also been analysed (Bekö et al., 2015; Shi et al., 2018), findings have been inconsistent. Bamai and Bekö found a significant association for DBP but not for DEHP and childhood asthma. In contrast, Kolarik reported a significant association between DEHP and wheezing for children in the preceding 12-months. Bekö found a significant relationship between mono (2-ethyl-5-carboxy-pentyl) phthalate (MECPP: urinary metabolite of DEHP) and childhood asthma, but Shi found the opposite result (Shi et al., 2018).

Dust samples have been collected from floors in most studies. However, Bamai reported a concentration difference between dust-phase PAEs on floors and other sites (Bamai et al., 2014a).

To the best of our knowledge, there have been no studies on the associations between PAEs in household dust and childhood asthma in Shanghai. The specific aims of the present study are to investigate the concentration distributions of PAEs in household dust within different asthmatic groups, to characterize the associations between PAEs and childhood asthmatic symptoms in Shanghai, and to analyse a possible effect of gender on the associations between PAEs and target symptoms.

2. Methods and materials

2.1. Study design and on-site inspection

The CCHH study was conducted to investigate indoor risk factors for childhood asthma, rhinitis, eczema and other allergic diseases in Chinese cities (Zhang et al., 2013). In Shanghai, the CCHH study has consisted of two phases. From April 2011 to April 2012, more than 15,000 families of pre-school children were randomly selected and agreed to join in Phase 1 (i.e. cross-sectional survey). Phase 2 was conducted from March 2013 to December 2014. Based on the history of diagnosed asthma among preschool children and household renovation in Phase 1, 454 families were selected and agreed to join the case-control study. Approval for the study was obtained from the ethical committee of the School of Public Health, Fudan University in Shanghai, China and informed consent was obtained from all individual participants in the study. The CCHH study group performed on-site inspections of indoor environments in 454 dwellings in Shanghai to explore associations between indoor air quality and children's health. Dust samples from doors and window frames which were cleaned relatively infrequently were gathered during the on-site inspections. Frequent cleaning results in smaller dust samples with small quantities of PAEs that may underestimate the pollution levels of indoor PAEs. Of 454 dust samples, 36 dust samples were excluded because of insufficient mass. Of the remaining

418 samples, 152 dust samples were excluded because of difficulties with the precision of the gas chromatography-mass spectrometer (GC-MS). Finally, 266 dust samples in children's bedrooms were accepted as valid for further analyses. Except for the distribution frequency of children's ages and prevalence of lifetime wheeze, covariate distribution frequencies and prevalences of studied allergies did not differ significantly between the 266 accepted samples and 152 rejected samples (testing by Pearson's chi-squared test, p -values > 0.05 were obtained). Detailed data were shown in Table S1.1 and S1.2 in supplementary materials. Therefore, we believed that 266 samples well represent the total samples ($N = 454$). The dust samples were collected with a vacuum cleaner and stored at -40°C . DMP, DEP, diallyl phthalate (DAP), DiBP, DBP, dihexyl phthalate (DHXP), butyl benzyl phthalate (BBP), DEHP, dioctyl phthalate (DNOP), and dinonyl phthalate (DNP) were included in the study. "Low molecular weight PAEs (LMW-PAEs)" is the sum of DMP, DEP, DiBP, and DBP. "High molecular weight PAEs (HMW-PAEs)" is the sum of BBP, DEHP, DNOP, and DNP. "Total PAEs" is the sum of all studied PAEs except DAP and DHXP.

2.2. Health outcomes

Allergic diseases or symptoms were reported by the children's parents in questionnaires. We used the questions from the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 1995). When the responder chose "Yes", we accepted that children experienced the corresponding disease or symptom. We included four symptoms or diseases.

Lifetime wheeze was defined as a "Yes" response to the question in the questionnaire, "Has your child ever had wheezing or whistling in the chest at any time in the past (Yes or No)";

Current wheeze was defined as a "Yes" response to the question questionnaire "Has your child wheezed or whistled in the chest in the last 12 months? (Yes or No)";

Current cough was defined as a "Yes" response to the question in the questionnaire "Has your child suffered a dry cough (not caused by a cold or lung infection were excluded) at night for more than two weeks? (Yes or No)";

Diagnosed asthma was defined as a "Yes" response to the question in the questionnaire "Has your child ever been diagnosed with asthma by a doctor? (Yes or No)".

2.3. Chemical pretreatment and quality control of dust samples

The settled dust samples (50 mg) were extracted in precleaned 5-ml glass vials with hexane:acetone (4:1) and were ultrasonically treated for 30 min and then centrifuged at 2500 rpm. This procedure was repeated, and the two extractants were combined in one glass vial. After concentration to a 0.5 ml volume using flowing nitrogen, the vials were transferred to 2-ml autosampler vials. A GC-MS was used to obtain the concentrations of different PAEs. The initial GC temperature was 100°C and was held for 1 min, then increased by $10^{\circ}\text{C}/\text{min}$ to 200°C and held for 3 min, then increased to 240°C at $10^{\circ}\text{C}/\text{min}$ and held for 5 min, and finally increased to 300°C at $15^{\circ}\text{C}/\text{min}$ and held for 5 min, while the temperature of the transfer line and detector were set at 300°C . Selective ion mode (SIM) was used in the GC-MS analysis. There were three blank samples per 20 dust samples. Information about quality control, including regression coefficients of the standard curves, relative standard deviation (RSD), method detection limit (MDL), and spiked recoveries, is shown in Table 1. The standard curve method was applied in the concentration calculations of PAEs. The regression coefficients of the related equations were all higher than 0.99, and the MDL was defined as triple the RSD value that was calculated in the experiments with blank samples. The spiked recovery rates ranged from 87.51 % to 111.44 %, and the RSDs ranged from 0.95 % to 4.59 %. These indices all met the requirements of the analytical methodology.

Table 1
Related information about quality control of studied PAEs.

PAEs	Regression equation	Regression Coefficient	MDL ($\mu\text{g/g}$)	Spiked Recoveries	RSD
DMP	$y = 4 \text{ E}+06\text{x}+42833$	0.9992	0.015	87.51 %	1.03 %
DEP	$y = 4 \text{ E}+06\text{x}+45531$	0.9982	0.020	90.76 %	1.37 %
DAP	$y = 1 \text{ E}+06\text{x}+3195.1$	0.9992	0.031	111.44 %	2.05 %
DiBP	$y = 4 \text{ E}+06\text{x}+73869$	0.9999	0.031	106.52 %	2.10 %
DBP	$y = 5 \text{ E}+06\text{x}+2779.3$	0.9996	0.065	107.23 %	4.33 %
DHXP	$y = 5 \text{ E}+06\text{x}-53846$	0.9991	0.017	100.16 %	1.10 %
BBP	$y = 2 \text{ E}+06\text{x}-23377$	0.9991	0.014	108.95 %	0.95 %
DEHP	$y = 4 \text{ E}+06\text{x}-26335$	0.9981	0.069	96.17 %	4.59 %
DNOP	$y = 5 \text{ E}+06\text{x}-66547$	0.9989	0.034	94.08 %	2.27 %
DNP	$y = 5 \text{ E}+06\text{x}-66855$	0.9984	0.021	89.41 %	1.43 %

2.4. Covariates and statistical analysis

In the present study, according to previous epidemiological studies, the adjusted covariates in the multiple logistic regression model include children's gender (boy or girl) (Almqvist et al., 2010), age (<7 or ≥ 7) (De et al., 2000), family atopic history (yes or no) (Postma et al., 1995), family members' smoking behaviour (Tamim et al., 2003), early renovation status (yes or no) (Deng et al., 2015a), residence location (urban or suburban) (Nicolaou et al., 2005), and indoor dampness (yes or no) (Sahakian et al., 2008). The independence of the covariates is indicated by the calculated correlations (Table S2 in supplementary materials), and multicollinearity issues could be avoided in the logistic regression model. Among these covariates, family atopic history was defined as "Have parents or other family members experienced asthma or other allergic diseases/symptoms?" The family members' smoking behaviour was defined by whether there were smokers in the families. Indoor dampness was defined as any report of at least one of the following dampness-related indicators: mould spots, damp stains, damp condensation on windows, and mouldy odour in the children's bedrooms.

Statistical Product and Service Solutions (SPSS) 17.0 was used to perform statistical analysis. We obtained Spearman correlations among the studied PAEs in household dust. We used Pearson's chi-squared test to compare the prevalences of different asthmatic symptoms among children in the different subgroups stratified by the covariates. The Shapiro-Wilk test told us that the PAE concentrations in dust samples were not normally distributed ($P < 0.05$), so we used the Mann-Whitney U test to determine whether the concentration differences of the PAEs in children with and without asthmatic symptoms were statistically significant. A multiple logistic regression model was used to evaluate the adjusted associations of PAE concentrations with childhood asthmatic symptoms. The associations were indicated by the odds ratios (ORs) and AORs with 95 % confidence intervals (CIs) in the univariate and multiple regression analysis, respectively. The logistic regression model was adjusted for gender, age, family atopic history, family members' smoking behaviour, early renovation status, residence location, and indoor dampness. We accepted a p -value < 0.05 as significant.

Association analysis stratified by gender was conducted to explore its possible effect on the associations between PAE exposure and childhood asthmatic symptoms. Due to missing data for various items, the number of children with different symptoms or different exposures in the subgroups are not equal to the total numbers. The PAEs were divided into two levels according to the values of their median concentrations, and the low concentration level was used as the reference in the logistic

regression model. Dust sample concentrations that were lower than the MDL were replaced by MDL/2 in the statistical analysis.

3. Results

Table 2 shows the concentration distribution of different kinds of PAEs in household dust, including the geometric mean, quartile, and detection rate. DiBP, DBP, and DEHP are detected in 100 % of samples. DEHP has the highest median concentration followed by DiBP and DBP. Due to their high volatility and low molecular weight, most DMP and DEP partition to indoor air, rather than dust (Li et al., 2016), and are detected in only 63 % and 68 % of the samples, respectively. On the other hand, BBP and DNOP are found in 75 % and 90 % of the samples, respectively. Compared with the other PAEs, DAP and DHXP have lower concentrations and detection rates, and are not included in the next statistical analysis.

Table 3 shows the Spearman correlations between the PAEs in household dust. Most of the correlations between PAEs are significant and positive ($p < 0.05$), except for those between DNP and DMP, DNP and DiBP, DiBP and DEHP, and DiBP and HMW-PAEs.

Table 4 shows demographic information and household environmental exposure for the children who participated in the on-site inspections. A total of 51 % of the participants are boys, and 78 % of the children are older than 7 years. Thirty-three percent of the participants have a family atopic history. A total of 51 % of the children are exposed to family members who smoke, and 56 % live in urban areas. Exposure to early home renovation is reported by the parents in 47 % of families. More than 60 % of families experience indoor dampness.

The prevalence of childhood asthmatic symptoms associated with different stratified factors is shown in Table 4. Boys are more likely to experience current wheeze. Children who are not exposed to household renovation have a significantly higher prevalence of current cough. Children with a family atopic history have a significantly higher prevalence of lifetime wheeze, current wheeze, and diagnosed asthma than those without a family atopic history. Children who are exposed to smoking by family members exhibit notably higher prevalences of lifetime wheeze. A significantly higher prevalence of lifetime wheeze is found in children who live in urban areas.

Table 5 compares the PAE concentrations for positive and negative asthma and childhood asthmatic symptoms. The DNOP concentration in the positive group with current wheeze is higher than that in the negative group at a nearly significant level ($p = 0.058$). Significantly higher concentrations of DiBP and LMW-PAEs are seen in the negative group of current coughs. The median concentrations and geometric mean concentrations of DEHP are higher in the positive group with studied asthmatic symptoms, but not significantly as determined by the Mann-Whitney U test.

The associations between PAEs and childhood asthmatic symptoms as calculated by multiple logistic regression analysis are shown in Table 6. In the adjusted model, the high concentration level of DNOP is significantly associated with lifetime wheeze and current wheeze ((AORs (95 % CI): 1.75 (1.00–3.11) and 2.14 (1.01–4.55), respectively). There are also significant positive associations between the high concentration level of HMW-PAEs and diagnosed asthma (1.80 (1.03–3.51)). When compared with the low concentration level, a high concentration level of DiBP is negatively associated with current cough (0.28 (0.13–0.62)).

Fig. 1 shows that most of the associations between exposure to DMP, DEP and childhood asthmatic symptoms are greater for girls than for boys. Detailed association data are shown in table S3. For girls, there are positive, significant associations between BBP and childhood lifetime wheeze (AORs (95 % CI): 2.28 (1.00–5.21)). The association between DNOP and current wheeze among girls is significant (7.87 (1.51–41.0)), and DEP exhibits significantly positive AORs for current cough (3.40 (1.03–11.2)). Moreover, DMP, DNOP and HMW-PAEs are positively and significantly associated with diagnosed asthma among girls (3.30

Table 2Concentrations of PAEs measured in 266 children's homes ($\mu\text{g/g}$).

PAEs	Geometric Mean	Min	Quartile			Max	Detected rate
			25 %	50 %	75 %		
DMP	0.21	<MDL ^a	<MDL	0.19	0.39	351.9	63 %
DEP	0.32	<MDL	<MDL	0.30	0.54	253.78	68 %
DAP	0.20	<MDL	<MDL	<MDL	<MDL	5.14	11 %
DiBP	22.50	0.34	10.45	20.53	40.00	2880.16	100 %
DBP	20.10	1.27	10.84	18.51	36.05	1209.73	100 %
LMW-PAEs ^b	50.20	3.2	26.55	42.50	83.73	2932.62	–
DHXP	0.12	<MDL	<MDL	<MDL	<MDL	1.23	12 %
BBP	0.49	<MDL	0.16	0.37	1.19	3532.59	75 %
DEHP	246.78	11.58	84.87	235.55	661.93	7322.73	100 %
DNOP	1.48	<MDL	0.69	1.37	2.60	102.57	90 %
DNP	0.38	<MDL	<MDL	0.28	0.66	59.7	59 %
HMW-PAEs ^b	258.08	12.90	87.84	252.50	672.06	7329.86	–
Total PAEs ^b	357.40	33.82	130.53	340.43	822.67	8094.97	–

^a MDL: Methods Detection limit.^b LMW-PAEs is the sum of DMP, DEP, DiBP; and DBP, HMW-PAEs is the sum of BBP, DEHP, DNOP, DNP; and Total PAEs is the sum of 8 studied PAEs excluding DAP and DHXP.**Table 3**

Spearman correlations of PAEs in the dust of children's bedroom.

PAEs	DMP	DEP	DiBP	DBP	LMW-PAEs	BBP	DEHP	DNOP	DNP	HMW-PAEs	Total PAEs
DMP	1	0.402**	0.320**	0.260**	0.353**	0.124*	0.180#	0.144*	0.085	0.180**	0.230**
DEP		1	0.369**	0.378**	0.412**	0.172#	0.147*	0.167#	0.224**	0.152**	0.212**
DiBP			1	0.458**	0.866**	0.164#	0.111	0.240**	0.100	0.117	0.288**
DBP				1	0.783**	0.161#	0.290**	0.187#	0.226**	0.291**	0.401**
LMW-PAEs					1	0.157#	0.209**	0.236**	0.158#	0.214**	0.390**
BBP						1	0.145*	0.228**	0.318**	0.165**	0.179**
DEHP							1	0.260**	0.267**	0.999**	0.955**
DNOP								1	0.336**	0.272**	0.285**
DNP									1	0.281**	0.259**
HMW-PAEs										1	0.956**
Total PAEs											1

*: $p < 0.05$, #: $p < 0.01$, **: $p < 0.001$. Figures in bold indicate p -values < 0.05 .**Table 4**

Prevalence of asthma and asthmatic symptoms with different household environmental exposure.

Items	Sample sizes	Lifetime wheeze		Current wheeze		Current cough		Diagnosed asthma	
		n (prevalence)	<i>P</i>	n (prevalence)	<i>p</i>	n (prevalence)	<i>p</i>	n (prevalence)	<i>p</i>
Total	266 (100 %)	138 (55 %)		51 (21 %)		47 (19 %)		65 (27 %)	
Gender									
Girl	130 (49 %)	64 (52 %)	0.323	17 (14 %)	0.010	26 (22 %)	0.382	31 (25 %)	0.692
Boy	136 (51 %)	74 (58 %)		34 (28 %)		21 (17 %)		34 (28 %)	
Age									
<7	59 (22 %)	30 (55 %)	0.971	15 (28 %)	0.165	15 (28 %)	0.072	14 (27 %)	0.942
≥ 7	207 (78 %)	108 (55 %)		36 (19 %)		32 (17 %)		51 (26 %)	
Family atopic history									
Yes	86 (33 %)	55 (66 %)	0.006	23 (30 %)	0.012	17 (21 %)	0.577	34 (42 %)	<0.001
No	174 (67 %)	79 (47 %)		25 (16 %)		29 (18 %)		29 (18 %)	
Family members' smoking behaviour									
Yes	133 (51 %)	79 (61 %)	0.025	24 (20 %)	0.582	19 (17 %)	0.318	28 (24 %)	0.392
No	128 (49 %)	57 (47 %)		26 (22 %)		27 (22 %)		36 (29 %)	
Residence location									
Urban	138 (56 %)	80 (60 %)	0.038	30 (23 %)	0.630	22 (17 %)	0.397	36 (27 %)	0.591
Sub-urban	109 (44 %)	48 (47 %)		20 (20 %)		22 (22 %)		25 (24 %)	
Early renovation status									
Yes	116 (47 %)	57 (51 %)	0.402	28 (24 %)	0.286	13 (12 %)	0.019	25 (24 %)	0.353
No	131 (53 %)	71 (57 %)		19 (18 %)		30 (25 %)		36 (29 %)	
Indoor dampness									
Yes	178 (67 %)	98 (57 %)	0.342	37 (22 %)	0.501	34 (21 %)	0.602	46 (27 %)	0.756
No	88 (33 %)	40 (50 %)		14 (18 %)		13 (17 %)		19 (25 %)	

Figures in bold indicate p -values < 0.05 . The sums of the number of children in the subgroups are not equal to the total numbers due to missing data on various items.

(1.24–8.77), 3.11 (1.14–8.49), and 2.64 (1.00–7.01), respectively). BBP concentration is negatively and significantly associated with current wheeze among boys (0.33 (0.12–0.89)), and DiBP is negatively and significantly associated with current cough among girls (0.23

(0.08–0.69)).

AORs were adjusted for children's gender, age, family atopic history, family members' smoking behaviour, residence location, early renovation status, and indoor dampness. (Reference: Low concentration level of

Table 5Median (geometric mean) concentrations of PAEs for positive and negative groups of childhood asthmatic symptoms ($\mu\text{g/g}$).

Items	Lifetime wheeze			Current wheeze			Current cough			Diagnosed asthma		
	Negative ^a	Positive ^a	p	Negative	Positive	p	Negative	Positive	p	Negative	Positive	p
No.	114	138	/	192	51	/	197	47	/	180	65	/
DMP	0.19 (0.21)	0.18 (0.20)	0.752	0.18 (0.20)	0.19 (0.20)	0.843	0.18 (0.21)	0.17 (0.18)	0.349	0.18 (0.20)	0.20 (0.20)	0.685
DEP	0.27 (0.30)	0.31 (0.32)	0.466	0.29 (0.32)	0.32 (0.38)	0.280	0.30 (0.32)	0.33 (0.29)	0.653	0.29 (0.32)	0.31 (0.32)	0.759
DiBP	21.63 (23.38)	19.54 (21.11)	0.435	19.99 (22.67)	21.91 (21.09)	0.863	22.85 (26.43)	13.36 (12.34)	<0.001	21.97 (23.97)	20.00 (20.25)	0.470
DBP	18.17 (20.56)	18.56 (19.19)	0.954	18.41 (20.28)	18.50 (18.36)	0.759	18.90 (21.13)	16.73 (16.37)	0.157	18.56 (20.15)	20.24 (20.54)	0.797
LMW-PAEs	42.23 (50.60)	42.50 (48.76)	0.827	42.50 (50.22)	44.47 (49.46)	0.898	45.38 (56.49)	32.69 (32.70)	0.003	44.39 (51.76)	45.64 (49.56)	0.799
BBP	0.34 (0.42)	0.34 (0.44)	0.849	0.35 (0.45)	0.29 (0.34)	0.430	0.36 (0.47)	0.30 (0.35)	0.377	0.33 (0.43)	0.34 (0.40)	0.846
DEHP	209.26 (231.14)	275.35 (256.23)	0.435	209.26 (230.12)	318.42 (275.73)	0.262	213.04 (238.52)	401.78 (295.76)	0.275	206.55 (238.46)	333.55 (274.59)	0.355
DNOP	1.27 (1.30)	1.51 (1.43)	0.311	1.31 (1.31)	1.63 (1.81)	0.058	1.37 (1.39)	1.53 (1.54)	0.567	1.33 (1.33)	1.59 (1.58)	0.217
DNP	0.30 (0.34)	0.30 (0.34)	0.881	0.29 (0.33)	0.32 (0.41)	0.501	0.30 (0.32)	0.26 (0.43)	0.495	0.30 (0.33)	0.31 (0.39)	0.349
HMW-PAEs	218.14 (239.06)	282.29 (267.29)	0.426	224.02 (239.89)	319.70 (319.70)	0.277	239.18 (248.25)	412.35 (306.39)	0.266	218.14 (248.63)	338.23 (283.13)	0.372
Total PAEs	302.03 (339.32)	376.53 (364.09)	0.500	326.28 (339.33)	399.36 (380.74)	0.437	337.14 (355.23)	519.62 (383.41)	0.622	333.89 (352.14)	434.33 (376.84)	0.577

Figures in bold indicate p -values < 0.01 .^a Negative indicates that children did not have corresponding disease/symptoms, positive indicates that children did have corresponding disease/symptoms.**Table 6**

Associations between PAE exposure and childhood asthmatic symptoms.

Items	Lifetime wheeze		Current wheeze		Current cough		Diagnosed asthma	
	OR	AORs ^a (95 % CI)	OR	AORs ^a (95 % CI)	OR	AORs ^a (95 % CI)	OR	AORs ^a (95 % CI)
DMP	0.90	1.05 (0.60–1.85)	1.11	1.79 (0.86–3.69)	1.05	1.15 (0.56–2.39)	1.31	1.67 (0.86–3.26)
DEP	1.34	1.31 (0.73–2.34)	1.27	1.65 (0.79–3.42)	1.03	1.22 (0.58–2.57)	1.25	1.40 (0.71–2.75)
DiBP	0.91	1.15 (0.66–2.02)	1.27	1.74 (0.85–3.59)	0.37**	0.28 (0.13–0.62)**	0.89	0.92 (0.48–1.76)
DBP	1.10	1.15 (0.65–2.02)	0.96	1.32 (0.65–2.69)	0.61	0.62 (0.30–1.30)	1.01	1.12 (0.58–2.15)
LMW-PAEs	1.04	1.12 (0.64–1.95)	1.04	1.33 (0.65–2.69)	0.61	0.49 (0.23–1.02)	0.97	0.96 (0.50–1.84)
BBP	1.03	1.09 (0.61–1.92)	0.80	0.85 (0.41–1.76)	0.84	0.73 (0.35–1.51)	1.15	1.05 (0.54–2.04)
DEHP	1.29	1.58 (0.89–2.78)	1.32	1.44 (0.71–2.95)	1.40	1.52 (0.73–3.17)	1.68	1.78 (0.91–3.47)
DNOP	1.42	1.75 (1.00–3.11)*	1.83	2.14 (1.01–4.55)*	1.49	1.46 (0.69–3.06)	1.50	1.73 (0.88–3.40)
DNP	0.99	0.97 (0.55–1.70)	1.08	1.08 (0.53–2.20)	0.91	0.93 (0.45–1.91)	1.12	0.94 (0.49–1.80)
HMW-PAEs	1.29	1.59 (0.90–2.79)	1.32	1.44 (0.71–2.94)	1.42	1.49 (0.72–3.09)	1.68	1.80 (1.03–3.51)*
Total PAEs	1.21	1.51 (0.86–2.65)	1.17	1.24 (0.61–2.50)	1.25	1.32 (0.64–2.71)	1.19	1.28 (0.67–2.46)

*: $p < 0.05$, **: $p < 0.01$. Figures in bold indicate p -values < 0.05 .^a AORs were adjusted for children's gender, age, family atopic history, family members' smoking behaviour, residence location, early renovation status, and indoor dampness. (Reference: Low concentration level of PAEs, AOR = 1.00). AOR, adjusted odds ratio; CI, confidence interval.

PAEs, AOR = 1.00); AOR, adjusted odds ratio; CI, confidence interval. Detailed AORs and their 95 % CIs are presented in [Table S3](#) in supplementary materials.

4. Discussion

4.1. Major findings

In the present study, DiBP, DBP, and DEHP are frequently detected in household dust. More than half of the participants are boys, live in urban areas, and are exposed to family members' smoking. A total of 55 %, 21 %, 19 %, and 27 % of participants are reported to have lifetime wheeze, current wheeze, current cough, and diagnosed asthma, respectively. DNOP is positively associated with lifetime wheeze and current wheeze. DiBP is also significantly associated with current wheeze. HMW-PAEs are positively and significantly associated with diagnosed childhood asthma. However, DiBP is negatively associated with current cough. Stronger associations between DMP and DEP are observed among girls, and significantly positive associations between PAEs and asthmatic symptoms are found only among girls.

4.2. Similar studies

The associations between PAE exposure and childhood asthmatic

symptoms have been analysed by epidemiological methods in numerous previous studies, but with inconsistent findings. Bornehag's nested case-control study showed a significant positive association between the DEHP levels in household dust and childhood asthma ([Bornehag et al., 2004](#)). While we found no association between DEHP and diagnosed childhood asthma, we did observe an association between HMW-PAEs and asthma. A cross-sectional study in Taiwan suggested that there were significant associations between BBP in settled dust and asthmatic children aged 3–9 years old ([Hsu et al., 2012](#)). A study in Denmark that examined associations between different PAE exposure pathways and allergic symptoms, reported significant associations between non-dietary exposures to DBP and BBP in the dust of day-care centres and childhood asthmatics ([Bekö et al., 2015](#)). BBP was not associated with the studied allergies in the present study as shown in [Table 6](#). A negative association between DiBP with current cough has not been reported in previous studies. Different sampling methods, sample sizes, studied populations, and statistical methods may explain the contradictions between the results of the previous studies and present study.

4.3. Animal experiments

Animal experiments have provided evidence that exposure to PAEs may be a risk factor for childhood asthma. In a case-control study of BALB/cJ mice conducted in Denmark, high concentrations of airborne

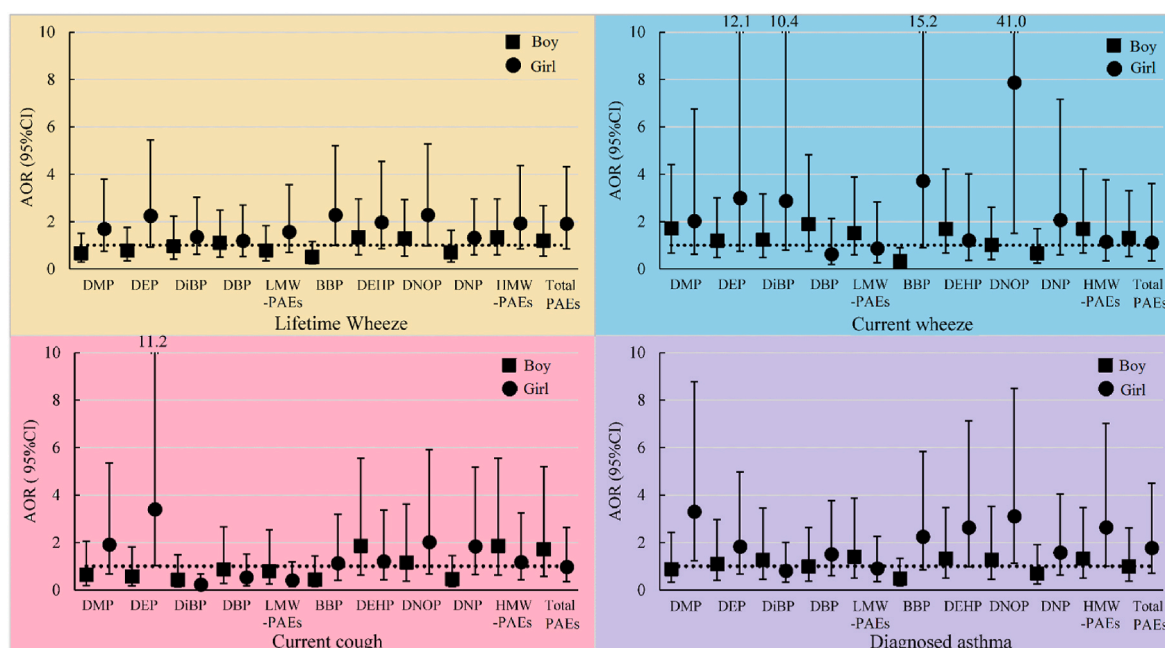


Fig. 1. Adjusted associations between exposure to PAEs and childhood asthmatic symptoms stratified by gender.

DEHP significantly increased lung inflammatory cell and serum immunoglobulin G1 (IgG1) levels, which were linked to asthma and related symptoms (Larsen et al., 2007). An animal experiment by Li et al. divided 30 BALB/c mice into 5 groups and treated them with different doses of DBP and saline. The results were that dermal exposure to DBP increased total immunoglobulin E and Th cytokine levels may have aggravated asthma in experimental subjects (Li et al., 2016). Parallel research has suggested that DEHP exposure also plays a critical role in asthma in mice (Yang et al., 2008). Findings in mice experiments may help to explain the association between PAE exposure and asthma among humans (Kimber and Dearman, 2010; North et al., 2014).

4.4. Impact of PAEs on asthma

Exposure to PAEs from household dust may play a critical role in total PAE exposure (Bekö et al., 2013). A study by Kolarik et al. reported significantly higher DEHP concentrations in a case group with childhood current wheeze (Kolarik et al., 2008a). In the present study, we found that high levels of DNOP were found to be associated with lifetime wheeze. Exposure to HMW-PAEs was a risk factor for diagnosed asthma. The negative association between DiBP and current cough disagrees with Jaakkola's findings (Jaakkola et al., 2000). Avoidance might explain our finding, but this requires further research. After entering the human body through different routes, the PAE metabolites that can have adverse health effects are generated by the action of enzymes (Shi et al., 2018). Shi et al. explored associations among urinary PAE metabolites and allergic symptoms among children in Shanghai, China and found that MnBP was associated with current childhood wheeze (Shi et al., 2018). Different health risks of PAEs with different molecular weights were found for the studied symptoms. From the perspective of physical chemistry, PAEs with different molecular weights possess distinct characteristics. Moreover, based on previous animal experiments (Larsen et al., 2001a, 2001b, 2002, 2003, 2001b), Larsen et al. concluded that different PAEs would produce different effects on mice as there are different PAE biotransformations and metabolic pathways. Kolarik et al. reported that different health outcomes were associated with different PAEs (Kolarik et al., 2008a).

4.5. Gender-based stratification analysis

Several studies have suggested that there are gender differences in asthma, with higher prevalence of asthmatic symptoms in boys, but higher prevalence in adult women (Almqvist et al., 2010; Postma, 2007). We stratified by gender and found that PAE exposure risks for childhood wheeze and diagnosed asthma were greatest among girls. The sample proportion of boys (51.5 %) is close to that of girls (48.5 %), and well represents the total gender proportion in China (male vs. female: 51.2 % vs. 48.8 %) and in Shanghai (male vs. female: 51.8 % vs. 48.2 %) (National Bureau of Statistics of China, 2021; Shanghai Municipal Statistics Bureau, 2021). Our gender difference results are credible and representative from the perspective of sample size. There are significant differences in asthma between boys and girls exposed to PAEs, a phenomenon that may be explained by environmental exposure differences and/or biological sex differences (Postma, 2007). Biological sex differences, such as the differences in sex hormones and different genetic sensitivities to environmental factors, could explain the sex differences due to internal causes. As a requirement for the development of allergic asthma, higher numbers of natural killer T cells were found in females (Sandberg and Ljunggren, 2005). Female hormones have been found to be a risk factor for asthma development. Hamano's study suggested that female hormones may enhance eosinophil function and promote allergic inflammation (Hamano et al., 1998). A cohort study in Norway indicated that smoking and overweight caused a higher risk of respiratory symptoms in girls than in boys (Tollefsen et al., 2006).

4.6. Concentrations of dust-phase PAEs in other countries

The concentrations of PAEs in household dust have been measured in many other countries, for example Germany, Sweden, the United States, and Japan (Becker et al., 2002; Rudel et al., 2003; Kolarik et al., 2008b; Langer et al., 2010; Kanazawa et al., 2010; Kubwabo et al., 2013; Gevaio et al., 2013; Orecchio et al., 2013; Mercier et al., 2014; Tran et al., 2016), as summarised in Table 7. Compared with the PAE concentrations in developed countries, the levels of the PAEs studied in the present research were relatively low except for DiBP. The DEP concentrations reported in the present study are lower than in any studied developed countries. The highest median concentrations of DMP, DEP, DBP, and

Table 7

Concentrations distribution of PAEs in indoor dust among different countries (µg/g).

Districts	Year	Sample sites	Sample size	PAEs ^a						Reference
				DMP	DEP	DiBP	DBP	BBP	DEHP	
German	2002	Home	199		3.3		42	15	416	Becker et al. (2002)
American	2003	Indoor	33		4.98		20.1	45.4	340	Rudel et al. (2003)
Bulgaria	2008	Children's room	177	0.28	0.34		9.93	0.34	960	Kolarik et al. (2008b)
Sweden	2010	Bedroom	500		1.7	27	15	3.7	210	Langer et al. (2010)
Japan	2011	Home	41		0.33	2.9	19.8	4.2	880	Kanazawa et al. (2010)
Canada	2013	Floors	126	0.12	2	5.17	16.8	42.3	462	Kubwabo et al. (2013)
Kuwait	2013	Floors	21	0.03	1.8		45	8.6	2256	Gevao et al. (2013)
Italy	2013	Surface of the furniture	13	15	31		799	99	304	Orecchio et al. (2013)
France	2014	Home	10	2.55	8.24	6.67	33.3	98.7	552	Mercier et al. (2014)
Vietnam	2014	Floors	16	0.0204	0.0209	0.425	0.47	0.217	19.4	Tran et al. (2016)
Shanghai, China-present study	2013	Door & window's frame	266	0.19	0.30	20.53	18.51	0.37	235.55	–

^a Median concentrations of PAEs were shown in Table 7.

BBP were all observed in Italy. The maximum DEHP concentration in Kuwait (2256 µg/g) was approximately 10 times higher than that in Shanghai (235.55 µg/g). The concentrations of the studied PAEs in Shanghai were significantly higher than those in Vietnam, and the PAE concentrations in Vietnam were the lowest compared with the studied countries. The concentration differences of dust-phase PAEs in different countries may be related to different economic levels, lifestyles, and different sample sites (such as dust samples being collected from floors and door & window frames). Moreover, different chemical treatments and different sampling methods for dust samples are also possible reasons for the concentration differences.

4.7. Limitations

First, recall and selection biases may have been present in this study. Second, although diagnosed asthma was diagnosed by doctors, other asthmatic symptoms and environmental exposures were all reported by parents, so that reporting biases and errors pertaining to asthma are likely. Childhood asthma and asthmatic symptoms that are caused by different common allergens (e.g., pets, dust mites, mould, and pollen) were not included in the present study. A more detailed study of other possible risks should be done in future studies. Third, the PAEs in settled household dust contributed only a portion of the total indoor PAE level, and other exposure routes of PAEs were not considered in our present study. Dietary exposure, for example, is a critical pathway for exposure to PAEs. Fourth, on-site inspections were conducted in the Shanghai residences only once, and the impacts of season and other environmental factors on the PAE concentrations were not considered. According to Deng's study, exposure to outdoor air pollutants increased the prevalence of childhood asthma (Deng et al., 2015b). Using mechanical ventilation could reduce the risk of childhood wheezing symptoms (Liu et al., 2014), and ventilation rates exhibit a strong impact on the emissions of DEHP and other SVOCs from plastic products (Kashyap and Agarwal, 2018). Pei et al. reported a significant impact of temperature on concentrations of dust-phase PAEs (Pei et al., 2013). Cong et al. found that temperature drops are significantly associated with asthma, especially in children (Cong et al., 2017). Therefore, although several covariates were considered in the regression analyses, many other risk factors, such as outdoor ambient air pollutants (Deng et al., 2015b), ventilation (Kashyap and Agarwal, 2018; Liu et al., 2014) and temperature (Cong et al., 2017; Pei et al., 2013), might also affect the final target associations.

4.8. Recommendations

The use of PAE plasticizers in daily life is increasing. The key sources of indoor PAEs are household decoration materials, personal care products, and plastic products. To decrease the exposure to PAEs, it is recommended that PVC materials and laminated wood not be used in

household renovation (Bamai et al., 2014a; Zhang et al., 2020; Koniecki et al., 2011). Personal care products that have PAEs should also be avoided. Various fatty foods with plastic packaging, for example meats and dairy products, have been shown to absorb package PAEs and should be eaten in moderation. Adequate ventilation can decrease indoor PAE concentrations.

5. Conclusion

PAEs are widely found in household dust. There are significantly positive associations of high concentrations of PAEs with childhood wheeze, as well as with diagnosed asthma. We observe a negative association between DiBP and current cough. Girls experience a higher risk from DMP and DEP for asthmatic symptoms than boys. In conclusion, exposure to PAEs in household dust may be a risk factor for childhood asthmatic symptoms, especially for girls. These findings provide a basis for avoiding adverse health effects in children from PAEs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2021.111760>.

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Associations between phthalic acid esters in household
dust and childhood asthma in Shanghai, China

Table S1.1 Prevalence of studied asthmatic symptoms in 152 samples and 266 samples (%)

Prevalence Samples	Lifetime wheeze	Current wheeze	Current cough	Diagnosed asthma
152 samples	61.6%	27.6%	25.3%	34.0%
266 samples	54.8%*	21.0%	19.3%	26.5%

*: $p < 0.05$. Figures in bold indicate p -values < 0.05 .

Table S1.2 Frequency distribution of different covariates in 152 samples and 266 samples (%)

Distribution Samples	A (Girl/Boy)	B ($<7 \geq 7$)	C (Yes/No)	D (Yes/No)	E (Yes/No)	F (Urban/Suburban)	G (Yes/No)
152 samples	46.7%/53.3%	65.1%/34.9%	39.1%/60.9%	54.7%/45.3%	50.7%/49.3%	64.0%/36.0%	62.5%/37.5%
266 samples	48.9%/51.1%	22.2%/77.8%**	33.1%/66.9%	51.0%/49.0%	47.2%/52.8%	55.9%/44.1%	66.9%/33.1%

A: Gender (girl vs. boy); B: Children's age (<7 vs. ≥ 7); C: Family atopic history (yes vs. no); D: Family members' smoking behaviour (yes vs. no); E: Early renovation status (yes vs. no); F: Residence location (urban vs. suburban); G: Indoor dampness (yes vs. no). **: $p < 0.01$. Figures in bold indicate p -values < 0.05 .

Table S2 Spearman correlations between different adjusted covariates

Covariates	Gender	Age	Family atopic history	Family members' smoking behaviour	Residence location	Early renovation status	Indoor dampness
Gender	1	0.112	-0.027	-0.068	-0.066	0.044	0.112
Age		1	0.076	-0.071	0.047	-0.061	0.009
Family atopic history			1	-0.100	0.036	0.013	-0.044
Family members' smoking behaviour				1	-0.017	-0.016	0.013
Residence location					1	-0.020	-0.027
Early renovation status						1	-0.027
Indoor dampness							1

Table S3 Associations between PAEs in household dust and childhood asthmatic symptoms in gender-based stratification analysis

Items	Lifetime wheeze-AORs (95% CI)		Current wheeze –AORs (95% CI)		Current cough-AORs (95% CI)		Diagnosed asthma-AORs (95% CI)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
DMP	0.67(0.29-1.51)	1.69(0.75-3.80)	1.71(0.66-4.41)	2.03(0.61-6.76)	0.63(0.19-2.05)	1.91(0.68-5.36)	0.88(0.32-2.43)	3.30(1.24-8.77)*
DEP	0.78(0.34-1.76)	2.25(0.93-5.44)	1.20(0.48-3.00)	3.00(0.75-12.1)	0.56(0.17-1.81)	3.40(1.03-11.2)*	1.09(0.40-2.96)	1.83(0.67-4.99)
DiBP	0.96(0.41-2.22)	1.36(0.61-3.03)	1.23(0.48-3.17)	2.88(0.80-10.4)	0.43(0.12-1.48)	0.23(0.08-0.69)*	1.26(0.46-3.46)	0.81(0.33-2.00)
DBP	1.10(0.49-2.48)	1.19(0.53-2.70)	1.89(0.74-4.82)	0.63(0.19-2.13)	0.87(0.28-2.66)	0.53(0.18-1.52)	0.99(0.67-2.63)	1.50(0.60-3.77)
LMW-PAEs	0.79(0.34-1.82)	1.57(0.70-3.56)	1.51(0.59-3.88)	0.87(0.26-2.84)	0.80(0.25-2.54)	0.41(0.14-1.18)	1.40(0.50-3.88)	0.91(0.36-2.27)
BBP	0.51(0.22-1.16)	2.28(1.00-5.21)*	0.33(0.12-0.89)*	3.72(0.91-15.2)	0.44(0.14-1.43)	1.13(0.40-3.19)	0.48(0.17-1.34)	2.25(0.86-5.84)
DEHP	1.33(0.60-2.95)	1.97(0.86-4.55)	1.69(0.68-4.22)	1.21(0.36-4.01)	1.86(0.62-5.57)	1.21(0.43-3.37)	1.32(0.50-3.48)	2.63(0.97-7.13)
DNOP	1.28(0.55-2.93)	2.28(0.98-5.27)	1.01(0.39-2.60)	7.87(1.51-41.0)**	1.16(0.37-3.62)	2.02(0.69-5.91)	1.28(0.46-3.53)	3.11(1.14-8.49)*
DNP	0.70(0.30-1.63)	1.32(0.59-2.96)	0.66(0.25-1.70)	2.07(0.60-7.17)	0.45(0.14-1.45)	1.84(0.65-5.19)	0.69(0.25-1.92)	1.58(0.62-4.05)
HMW-PAEs	1.33(0.60-2.95)	1.93(0.85-4.37)	1.69(0.68-4.22)	1.15(0.35-3.76)	1.86(0.62-5.57)	1.18(0.43-3.24)	1.32(0.50-3.48)	2.64(1.00-7.01)*
Total PAEs	1.20(0.54-2.67)	1.91(0.85-4.32)	1.32(0.53-3.30)	1.11(0.34-3.62)	1.71(0.57-5.20)	0.97(0.35-2.65)	0.99(0.37-2.62)	1.77(0.70-4.50)

AORs were adjusted for children's gender, age, family atopic history, family members' smoking behaviour, residence location, early renovation status, and indoor dampness. (Reference: Low concentration level, AOR=1.00); AOR, adjusted odds ratio; CI, confidence interval. *: $p<0.05$, **: $p<0.01$. Figures in bold indicate p -values <0.05 .