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Phthalate Exposure and Pediatric Asthma: A Case Control Study Among Egyptian Children

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Phthalates, which are diesters of phthalic acid, are commonly used as plasticizers and additives in various consumer products. Several phthalates have been identified as substances of high concern. Exposure to phthalate esters (PAEs) has been linked to asthma in children, but the specific impacts of PAEs on asthmatic children were not well understood. The objective of this study was to compare urinary phthalate concentrations in asthmatic and non-asthmatic children and to identify potential sources of exposure as risk factors for asthma. Methods: A case control study was conducted for 100 Egyptian children aged 8-16 years (50 asthmatics and 50 healthy controls). Asthma was identified using GINA guidelines. Socio-demographic and probable risk factors were assessed, in addition to measuring phthalate levels in urine samples using high-performance liquid chromatography. Mean urinary Mono-methyl as well as Mono-benzyl levels were highly significant in asthmatic children compared to control group (895.26ng/ mL vs 548.55 ng/mL and 13.5 ng/mL vs 2.07 ng/mL respectively) (p= 0.001). The number of asthmatic children living in houses painted with non-plastic paint was significantly lower (P<0.05) than children living in houses painted with other paints. No association between floor type and asthma was reported. The frequent use of personal care products and plastic painting of walls were identified by multiple logistic regression analysis as the highly significant predictors of asthma in the studied subjects. The declared higher levels of urinary phthalate metabolites (Mono-methyl and Mono-benzyl) in Egyptian asthmatic children may reveal the probable risk of phthalate exposure in triggering bronchial asthma.

Keywords: Egyptian Children; Environmental Risk Factors; Pediatric Asthma; Phthalate Exposure; Urinary phthalates.

Bronchial asthma is a widespread chronic disease in childhood, affecting up to 20% of children worldwide with significant geographic variations in prevalence, severity, and mortality [1]. According to WHO records, asthma affected more than 339 million people globally in 2016, resulting in a significant burden of the disease globally, with approximately 10-15% of children affected.[2].In Egypt, the prevalence of asthma ranges between 7.7-8.2% [3,4]. The international variations of asthma burden are still unclear, although genetic predisposition is evident. Environmental factors

such as infections and exposure to environmental endotoxins may act as risk factors [5].

Suggested theory assumed that one potential risk factor for the raising prevalence of atopic (IgE-mediated) allergic diseases especially asthma in different countries, is exposure to constituents as environmental pollutants and plasticizers such as phthalates that act as adjuvants. Specified frequently used phthalate plasticizers, such as di-(2-ethylhexyl) phthalate, was linked to this regard [6]. In Egypt, few studies investigated the exposure of phthalates in children and documented that plastic toys and bottled water are the main sources of exposure [7-9].

Phthalates are plasticizers, solvents, and additives that are added to PVC (polyvinyl chloride) plastics and several personal care products. Phthalates are synthetic organic compounds that are phthalic acid diesters [10]. More than 25 phthalates are used in commercial items, which raises the quality of the item they are incorporated in [11].

Many commercial products may have phthalates in their consistency including: building supplies, medical devices, packages of food, makeup products, fragrances, children's toys, shampoos, teethers, epoxy resins, decorating paint, floorboards, hair sprays, soaps, nail polishes, and cleaners [10-12].

The production of phthalates was increased yearly worldwide from 4.7000,000 metric tons in 2006 [13] up to ~8 million metric tons in 2015 [14] The estimated global market of phthalates in 2020 has reached 10 billion dollars and are still widely used in plastic devices and products [15].

Exposure to phthalates in humans begins principally from eating, consumption, inhalation, and absorption through skin [16,17]. Studies in humans have assessed serum phthalate [18] and phthalate metabolites in human urine [19,20], semen [21,22] and breast milk [23,24].

Although it is assumed that exposure to phthalates may prompt oxidative stress and provoke respiratory consequences, it is doubtful in what way phthalates worsen respiratory function and initiate airway inflammation in asthmatic patients [16] .

Recent studies demonstrated the association of urinary phthalates concentration and exacerbation of asthmatic children [15,25-27].

This study aims to compare urinary phthalates concentrations in asthmatic children with those in a control group and to identify potential sources of phthalates exposure as risk factors for asthma development.

METHODS

This study was held as a case control study on children selected from those attending pulmonary clinic at Abo El Reesh Specialized Pediatric Hospital, Cairo University. Children aged between 8 and 16 years. Fifty children were selected at random out of asthmatic children with variable degrees of severity corresponding to (GINA) Guidelines [28]. Fifty apparently healthy children were recruited from the relatives of patients of matched age and gender, who lived in another house and/or environment through an announcement.

Ethical approval

"Ethical approval was obtained from the Medical Ethics Committee of the National Research Centre, Egypt (approval number 16-368). Written informed consent was obtained from all parents or legal guardians of the participating children. The study adhered to the International Ethical Guidelines for Biomedical Research Involving Human Subjects[29].

Inclusion criteria and Exclusion criteria

Children diagnosed with asthma, either in remission or during an acute attack, based on clinical presentation. Exclusion criteria: Children with a history of renal, liver, thyroid, or endocrine diseases were excluded from both the case and control groups."

Data collection and clinical examination

Data collection involved administering a questionnaire to the children and their guardians, covering socio- demographic variables and potential risk factors such as the age of the residential building, indoor environmental exposure (e.g., plastic/vinyl flooring, type of home painting), exposure to passive smoking, and the frequent use of personal care products (e.g., shampoo, hair gel/ spray, lotions, toothpaste, perfumes). Both groups underwent a general and chest clinical examination. Asthma was assessed using the GINA 2019 guidelines, and chest radiographs were reviewed for the asthmatic group to verify the diagnosis. Early morning urine samples were collected from

both asthmatic and control children and stored at -70°C until analysis."

Laboratory investigations

Urinary phthalates were the definite biomarkers of phthalate exposure in previous studies [30,31] As phthalates are metabolized to their mono-esters in few hours or maximum days. Urinary phthalate mono-esters are valuable biomarkers for evaluating human phthalate exposure [32]. One spot urine sample is adequately expressive for six months exposure [33].

Urinary creatinine was included as a covariate in all analyses as to correct dilution, We adjusted all metabolite concentrations for creatinine levels and was expressed as ìg/g Cr.

Urine samples were thawed and sonicated for 10–15 min, then (100 ìl) was loaded into a glass vial (2 ml) containing ammonium acetate (AA, 20 ìl, >98%, Sigma Aldrich Laboratory, Inc., St. Louis, MO, USA), â-glucuronidase (10 ìl, E.coli K12, Roche Biomedical, Mannheim, Germany), and a combination of ten isotopic 13C4) phthalate metabolite standards (100 ìl. Cambridge Isotope Laboratory, Inc., Andover, MA, USA). Afterward, the samples were incubated (37!, 90 min), a 270 ìl solution (5% ACN), Merck, Darmstadt, Germany) with 0.1% formic acid (FA, Merck, Darmstadt, Germany) was added and sealed with the PTEF cap for analysis. Monoethyl phthalate, monomethyl phthalate, monobenzyl phthalate, monobutyl phthalate, and bis2ethylhexylphthalate were purchased from SigmaAldrich. â-glucuronidase was purchased from Roche. Stock solutions of standards were prepared in acetonitrile (3000ng/ml). Eleven-point calibration curve was constructed for each standard (0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and 1000 ng/ml). Sample preparation was done by solid-phase extraction according to the method described [28] After evaporation of eluting, the residue was reconstituted in 100 µl 20% acetonitrile in water and injected.

Phthalate metabolites were assessed as an alternative of their parent compounds to lower the potential for exposure misclassification. A combination of solid phase extraction, high pressure liquid chromatography, and tandem mass spectrometry were used to measure phthalate metabolite levels using methods described by a group of researches [34] .

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation and compared using the student's t- test. Categorical variables were presented as frequencies and percentages and analyzed using the two-tailed chi-square test. Odds ratios (OR), 95% confidence intervals (CI), and logistic regression analyses were conducted to identify potential risk factors and predictors of bronchial asthma. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 presents the descriptive data of the studied groups. The mean age of the asthmatic group was 11.78 ± 1.28 years, and the control group was 12.35 ± 1.44 years, with no significant

Table 1. Urinary phthalate metabolites level between asthmatics versus control groups

	Groups	Mean ± SD	p-value
Ag	Bronchial asthma	11.78± 1.28	0.132
	control	12.35± 1.44	
Mono (2ethylhexyl) phthalate (MEHP) (ng/ml)	Bronchial asthma	61.50± 9.77	0.965
	control	60.56 ± 24.72	
Mono-methyl phthalate(ng/ml)	Bronchial asthma	895.26±102.68	0.001*
	control	548.55±46.97	
Mono-benzyl phthalate(ng/ml)	Bronchial asthma	13.50±17.09	0.001*
	control	2.07 ± 0.96	
Mono-butyl phthalate(ng/ml)	Bronchial asthma	28.59± 9.38	0.089
	control	32.10±6.60	

*p < 0.05 is significant.

Table 2. Exposure to potential sources of phthalate in asthmatic versus control groups

			Bronchial asthma	control	OR	95% CI	P-value
Age of house building	≤ 10 years	Count	10	10	1.053	0.394-2.812	0.919
		% Within age of house building	50.0%	50.0%			
	> 10 years	Count	38	40			
		% Within age of house building	48.7%	51.3%			
Painting of the wall	Non-plastic painting	Count	14	34	0.183	0.078-0.431	0.001*
		% within Painting of the wall	29.2%	70.8%			
	Plastic painting	Count	36	16			
		% within Painting of the wall	69.2%	30.8%			
Exposure to passive smoking	yes	Count	40	23	4.696	‘1.931-11.418	0.001*
		% within Exposure to passive smoking	63.5%	36.5%			
	No	Count	10	27			
		% within Exposure to passive smoking	27.0%	73.0%			
Frequent use of personal care products (more than once / week)	yes	Count	31	5	14.358	4.842-42.579	0.001*
		% within use of personal care products	86.1%	13.9%			
	No	Count	19	44			
		% within use of personal care products	30.2%	69.8%			

*p < 0.05 is significant, Odds ratio (OR)

difference between the groups. The gender distribution was similar, with 56% females and 44% males in the asthmatic group, and 60% females and 40% males in the control group, showing no significant difference. "The children with asthma had higher concentrations of some urinary phthalate metabolites than the control group. Mean Mono-methyl and Mono-benzyl levels were significantly higher in asthmatic children (895.26 ng/mL and 13.5 ng/mL) compared to the control group (548.55 ng/mL and 2.07 ng/mL, respectively; p=0.001) The mean urinary levels of the other two studied phthalate metabolites (Mono 2ethylhexyl and Mono-butyl phthalate) showed insignificant difference (p>0.05).

The association between asthma and potential sources of exposure was reported in table (2), where the number of asthmatic children living in houses painted with non-plastic paint was significantly lower (P=0.001) than children living in houses painted with plastic paints. The presented results showed that, the subjects exposed to passive smoking were significantly more likely to have bronchial asthma compared to those not exposed to passive smoking (p=0.001). Moreover, the subjects who frequently used personal care products were significantly more at risk of having bronchial asthma compared to those not frequently used these products (p =0.001). On the other hand, "Table 2 shows the association between asthma and potential sources of exposure. A significantly lower number of asthmatic children lived in houses painted with non-plastic paint compared to plastic paints (p = 0.001). Exposure to passive smoking was significantly associated with a higher likelihood of bronchial asthma (p = 0.001). Additionally, frequent use of personal care products significantly increased the risk of asthma (p = 0.001). However,

Table 3. Association between floor type and asthma using Chi-square test

			Group Bronchial asthma	control	X^2	p-value
Floor type	Plastic	Count	2	0	4.000	0.135
		% within Floor type	100.0%	0.0%		
	Vinyl	Count	0	2		
		% within Floor type	0.0%	100.0%		
	Others as ceramic	Count	48	48		
		% within Floor type	50.0%	50.0%		

P-value is insignificant(p> 0.05)

Table 4. Bronchial asthma Risk factors in the studied groups by multiple logistic regression analysis

	B	S.E.	p-value	OR	95% CI
Age of housebuilding (≤ 10 years vs> 10 years)	-0.075	0.626	0.904	0.927	0.272- 3.166
Floor type (plastic and vinyl vs others)	-0.913	0.862	0.290	0.401	0.074- 2.174
Wall Painting (Non-plastic vs others)	2.233	0.618	0.001*	9.327	2.780- 31.291
Passive smoking exposure (Yes vs no)	-0.837	0.628	0.183	0.433	0.126- 1.484
Use of personal care products (yes vs no)	-2.684	0.698	0.001*	0.068	0.017- 0.268
Constant	4.956	3.246	0.127	142.022	

B: Standard Coefficient*p < 0.05 is significant.

the age of the residential building showed no association with the risk of developing asthma."

Table (3) indicates no significant association between floor type and the risk of asthma, with statistically insignificant differences in the distribution of asthmatic and control subjects across different floor types (vinyl, plastic, or ceramic) ($p > 0.05$).

Multiple logistic regression analysis (Table 4) showed that the age of the house, passive smoking, and floor type were not statistically significant predictors of bronchial asthma. However, plastic wall painting and frequent use of personal care products were highly significant predictors of asthma ($p = 0.001$). Specifically, plastic wall painting (target 1, non-plastic paint 0) was identified as a significant risk factor for bronchial asthma ($p = 0.001$). In contrast, the absence of frequent use of personal care products (target 1, frequent use 0) was found to be protective against bronchial asthma ($B = -2.684$, $p = 0.001$).

DISCUSSION

The present study documented a significant association between urinary phthalate levels and asthma in children, as significantly higher concentrations of Mono-methyl and Mono-benzyl phthalate metabolites were reported in the asthmatic children than the control group. It is known that one potential contributor in aggravating atopic allergic diseases and asthma in children is exposure to substances that could affect as adjuvants. Phthalate plasticizers, such as Mono-methyl and Mono- benzyl phthalates, have been implicated in the development of asthma. Many recent research studied the effect of phthalate exposure and development of asthma but the exposure mechanism and potential risk factors are still unclear [35-38].

Phthalate plasticizers, such as Mono-methyl and Mono-benzyl phthalate, have been implicated in the exacerbation of asthma. These substances can act as adjuvants, aggravating atopic allergic diseases and asthma. The lack of covalent binding in some phthalate compounds leads to greater environmental exposure as they leach into the air, food, drinks, and personal care products. These compounds enter the human body through ingestion, inhalation, and skin absorption [39].

Our results showed that the metabolites of phthalates were higher in asthmatic children which supports the theory that phthalate exposure may lead to or aggravate asthma. It is unclear how phthalates aggravate airway inflammation in asthmatic patients. Regular exposure to phthalates may aggravate the risk of asthma or could extend its course by peroxisome proliferator activated receptors which facilitate anti-inflammatory process in the respiratory system and immune modulation [40]. Also, increase in the proliferation of the bronchial lung muscle cells could cause airway remodeling [41] as well as in pro-inflammatory IL-6 and IL-8 production in the air way epithelial cells [42] which work as adjuvants by promoting macrophage production of inflammatory cytokines and chemokines [43].Moreover, Phthalate exposure induces oxidative stress that worsens respiratory outcomes. Asthma acute attacks were linked to increased oxidative stress [37, 39, 40] These results are in agreement with recent studies which documented high phthalate exposure in specific asthma subgroups, emphasizing its complex relationship with asthma[44,45].

Another research documented that phthalate-induced enhancements of mast cell degranulation and eosinophilic infiltration, which are important aspects of the early inflammation phase and especially in indoor dust in the homes of asthmatic children compared to non-asthmatic controls, indicating an association between concentrations of phthalates in indoor dust and wheezing among preschool children[46]. In recent pediatric animal module study, the authors provided evidence that high-dose probiotics supplementation might play a modulating role in diethylhexyl phthalate causes of allergic asthma[47] .

Passive smoking is a well-known risk factor for childhood asthma. Tobacco smoke exposure, both direct and second-hand, significantly contributes to asthma pathogenesis in children [48] ; tobacco smoking and exposure to negative smoking are widely acknowledged to be causative factors for asthma in children [49].The current study investigated the passive smoking as a potential source of phthalates in asthmatic children and this is in agreement with studies that reported association between urinary phthalates in smoking mothers and health hazards .This was explained by

the effect of oxidative stress caused by smoking, as a source of phthalates, on childhood asthma [50,51]

Whether allergic reaction towards phthalates occurs due to prenatal maternal exposure, or due to post-natal infant exposure is still controversial. Jøhnk and his colleagues [52] demonstrated that maternal exposure to phthalates was related to development of asthma by the first 5 years of life. In addition, Ku and Co-others [53] suggested that early postnatal exposure has the higher risk [53]. Moreover, a follow up study that investigated the phthalate exposure in both pre and post-natal period, proved that early phthalates exposure is linked to allergic sensitization and play a role in asthma development in the early years of childhood [53].

In the current research urinary phthalate was used as an indicator of exposure. It is well known that a one spot of urine is appropriately expressive of exposure throughout a six months period and justify its use for assessment in epidemiologic studies [54] .

In the present study, we assessed the regular exposure to products containing phthalates, and results showed that the more frequent use of personal care products was a significant predictor of asthma.[55,56].

In addition, living in homes with plastic painting of walls appeared as a significant risk factor for developing bronchial asthma[57], while those living in houses with non-plastic paint, were less likely to be asthmatics. Non-plastic painting of the wall of houses might be protective against bronchial asthma[58]. Moreover, Our findings supported the theory that phthalates exposure has a role in enhancing the immune system response[59].

Limitation of the study

The results of this study cannot be generalized due to the small sample size. Additionally, the study did not account for children's exposures in school settings, where they spend 6-8 hours daily [60]. Also, the questionnaire lacked detailed inquiry about early childhood exposures, which are critical as the early years of life are essential for the maturation of the immune and respiratory systems. Child behavior plays a significant role in the risk of exposure, as infants and toddlers who crawl on dust floors or come into direct contact with floors or house painting are more prone to developing asthma. Further research should focus on assessing exposure in school environments and raising awareness among young mothers about the risks of phthalate exposure.

CONCLUSION

Our study found higher urinary phthalate levels in children with asthma. Moreover Plastic wall paint and frequent use of personal care products were identified as the principal predictors of asthma. With a molecular structure like hormones, phthalates have the potential to disrupt the immune and endocrine system, leading to health concerns regarding their detrimental impacts on development. It is important to note that children are particularly vulnerable and sensitive to phthalates, particularly during the early stages of growth and development.

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Conflict of interest

The authors declare no conflict of interest.

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