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Urine phthalate levels were associated with skin barrier dysfunction and atopic sensitization in children

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Abstract. – OBJECTIVE: Phthalates can cause immunological disorders and aggravate allergic diseases. Thus, we investigated the relationship between urinary phthalate, skin barrier function, and atopic sensitization in children.

PATIENTS AND METHODS: In total, 448 school children [334 with severe allergic disease; and 123 with severe atopic dermatitis (AD)] aged 10-12 years were enrolled in this study between June and July 2017. Four high-molecular-weight phthalates (HMWP) [Σ4HMWP] and three low-molecular-weight phthalates (LMWP) [Σ3LMWP] metabolites in urine samples, specific immunoglobulin E (IgE), and total eosinophil count were measured. Four-part trans epidermal water loss (TEWL) (cheek, leg, and upper/lower arm; Σ4TEWL) was measured to evaluate the skin barrier function.

RESULTS: After adjusting for confounding variables, Σ4TEWL was significantly associated with the quartiles of urinary Σ4HMWP [adjusted β=7.897, 95% confidence interval (CI): 0.636-15.158, *p*=0.033] and Σ3LMWP (adjusted β=9.670, 95% CI: 2.422-16.919, *p*=0.009). The adjusted analyses revealed that the quartiles of urinary Σ4HMWP and Σ3LMWP were not significantly associated with total eosinophil count, atopic sensitization, and severe AD (*p*>0.05). According to the quartiles of urinary Σ4HMWP and Σ3LMWP, there were significant differences in the TEWL of the lower arm and leg (*p*<0.05) but not in cheek and upper arm.

CONCLUSIONS: Exposure to HMWPs and LMWPs was significantly associated with skin barrier dysfunction but not with atopic sensitization. These results suggest that children exposed to phthalates may be more susceptible to fragile skin barrier function.

Key Words:
Phthalate, Skin barrier dysfunction, Atopic sensitization, Atopic dermatitis.

Abbreviations

AD: atopic dermatitis, TEWL: transepidermal water loss, AR: allergic rhinitis, ISAAC: International Study of Asthma and Allergies in Childhood, VAS: visual analogue scale, WHO: world Health Organization, BMI: body mass index, MiBP: mono-(iso-butyl) phthalate, MnBP: mono-n-butyl phthalate, MBzP: mono-benzyl phthalate, MCPP: mono-(3-carboxypropyl) phthalate, MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate, MEOHP: mono-(2-ethyl-5-oxohexyl) phthalate, MECPP: mono-(2-ethyl-5-carboxypentyl) phthalate, HMWPs: high-molecular weight phthalates, LMWPs: low molecular weight phthalates, Σ4HMWP: the sum of four major high-molecular weight phthalate, Σ3LMWP: the sum of the three major low molecular weight phthalate, SE: standard error, CI: confidence interval, β: Beta, OR: Odds ratio, IgE: immunoglobulin E, IQR: interquartile range.

Introduction

Phthalate is a synthetic compound in many plastics[1]. It is divided into lower- and high-molecular-weight phthalates, a substance added to plastics to increase their flexibility and longevity[2]. Owing to these advantages, children are more likely to be exposed to phthalates relative to adults due to their greater consumption of foods from containers lined with phthalates-containing plastics[3,4]. However, phthalate could disrupt the

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endocrine system and aggravate the allergic disease[4-9]. Studies in animals revealed that phthalates reduced regulatory T cells, interleukin (IL)-10, and Interferon (IFN)-γ levels and increased IL-4 and antigen-specific immunoglobulin E (IgE) levels[5,6]. Additionally, other studies[8,9] have demonstrated that indicators of phthalate exposure had strong positive associations with airway dysfunction and aggravation of allergic diseases.

Meanwhile, atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases in children and affects 17-24% of the pediatric population[10]; in particular, AD is a starting point of allergic march[11]. The underlying pathology of AD has complex pathogenesis, including barrier dysfunction and immune dysregulation driven by interactions of genetic and environmental factors[12]. The skin barrier is critical in preventing allergen and microbial penetration into the human body, and thus a dysfunction in the skin barrier may trigger the development of AD[13]. Several methods have been used for evaluating skin barrier function, including transepidermal water loss (TEWL), which is a noninvasive measurement widely used in a previous study[14].

Atopic sensitization is a complex interplay between the allergen in its environmental context and the tendency of the host's innate and adaptive immune cells to be skewed towards allergic inflammation[15]. Thus, determining sensitivity to allergens is essential in predicting allergic diseases in children[16]. We hypothesized that phthalate exposure might be associated with AD, skin barrier function, and atopic sensitization in children from the general pediatric population. However, the levels of TEWL and atopic sensitization following exposure to environmental pollutants or other chemicals remains to be elucidated. Therefore, in this study, we attempt to determine the associations of phthalate exposure with skin barrier dysfunction and atopic sensitization among school children in Korea.

Patients and Methods

Study Design

A total of 620 children from 11 elementary schools aged 10-12 years participated in the Seongnam atopy project 2017 and were enrolled between June and July 2017. The Seongnam City Government sponsored this study for the prevention and education of allergic diseases in Korean children. The parents were asked to respond to the questionnaires before the physical examination. The questionnaires were used to record the physicians' diagnoses of the children's illnesses [e.g., allergic rhinitis (AR), asthma, urticaria (AD)], and were based on the International Study of Asthma and Allergies in Childhood (ISAAC)[17]. Moreover, the visual analogue scale (VAS), which is a psychometric response scale, was used to question the children with AD[18]. Among the 620 children, 454 had their parents returned the completed questionnaires and agreed to provide blood and urine samples for testing. Pediatricians and well-trained pediatric technicians performed the physical examinations, which included measurements of weight, height, and collection of blood and urine samples. Body mass index (BMI) z-scores are based on age- and sex standardized measures of adiposity in children from World Health Organization (WHO) growth standards, which are based on optimal growth in children[19].

Measurement of Phthalate Metabolites

Urine samples were collected in sterile cups between 9 and 12 am and were stored at -70°C freezer for up to three months before the analysis. Phthalate metabolite concentrations were determined using gas chromatography/tandem mass spectroscopy[20]. Reported phthalate concentrations were expressed relative to urinary creatinine (μg/g UCr) to control for urine dilution. A total of 448 urine samples were analyzed for the following seven phthalate metabolites: mono-(iso-butyl) phthalate (MiBP), mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-(3-carboxypropyl) phthalate (MCPP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP). Phthalate metabolites were grouped based on molecular weight and reported as the sum of four major high-molecular weight phthalate (Σ4HMWP) metabolites (MEHP, MEOHP, MECPP, and MCPP), or the sum of the three major low molecular weight phthalate (Σ3LMWP) metabolites (MiBP, MnBP, and MBzP). They were further divided into quartiles according to concentration (lowest to highest, Q1 to Q4). Previous research[2,9] demonstrated that these two groups of metabolites have different physicochemical properties.

Measurement of TEWL

TEWL measurements ($g/m^2/h$) were obtained from 443 (98.8%) children using open chamber

Tewameter (Courage & Khazaka Electronic GmbH, Köln, Germany). In line with international recommendations[21], we included measurements performed at room temperature between 20°C and 25°C only, while accepting humidity within the range of 6-73% [mean 29%, standard deviation (SD) 12.7]. Three successive measurements were performed on four body parts, keeping the room temperature as close to 22°C as possible, while noting for ambient temperature and humidity. Measurements are only performed on calm children, and the windows and doors were kept shut. In this study, TEWL is reported as the sum of four body parts: cheek, left upper and low lateral arm, and left low lateral leg (Σ4TEWL).

Measurement of Eosinophil and Specific IgE

Blood samples from all participants were analyzed using the ImmunoCAP system (Phadia, Uppsala, Sweden) to assess the percentage of blood eosinophils and specific IgE against the six significant aeroallergens in South Korea (*Dermatophagoides farinae*, birch, Japanese hop, cat, dog, and *Alternaria*). In this study, a total eosinophil count of >4% is defined as positive, and a child with one or more positive reactions (>0.35 U/L) were considered allergic. Children were categorized as non-sensitized, mono-sensitized (positive result for a single antigen), or poly-sensitized (positive results for multiple antigens)[16].

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). Continuous data are expressed as means with standard deviations or as medians with the interquartile ranges, depending on the data distribution. The relationships of the concentrations of different of urinary phthalates with sum of TEWL, total eosinophil count, atopic sensitization, were analyzed using linear regression. Beta (β) and standard error (SE) from continuous variables (TEWL and VAS), as well as odds ratio (OR) and 95% confidence interval (CI) from dichotomous variable (total eosinophil count 4%, atopic sensitization, and AD) were calculated using a generalized linear mixed model with the gamma or logit function, adjusted for age, sex, BMI z score, prematurity, and low birth weight, as well as random effect with school using the identity function. A p-value ≤ 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

A total of 448 fifth- and sixth-grade students were recruited for this study (Table I). There were 244 males (54.5%), and the mean age was 11.0 years (95% CI: 10.9-11.1). Among the 334 children with one or more allergic diseases (severe), 271 (60.6%) had AR, 123 (27.5%) had AD, and 55 (12.3%) had asthma. The median TWEL levels of the cheek, upper arm, lower arm, and leg were 15.3 g/m^2/h (IQR: 13.3-19.3), 11.0 g/m^2/h (8.8-13.9), 13.1 g/m^2/h (10.7-19.6), and 12.6 g/m^2/h (10.0-20.0), respectively. Among the 289 chil-

Table I. Demographic and clinical characteristics of study participants (n = 448).

	Variable
Male sex, n (%)	244 (54.5)
Mean age, years (95% CI)	11.0 (10.9-11.1)
BMI, z-score (95% CI)	-0.01 (-0.11-0.09)
Allergic disease (ever), n (%)	334 (74.6)
Allergic rhinitis	271 (60.6)
Urticaria	124 (27.9)
Atopic dermatitis	123 (27.5)
Asthma	55 (12.3)
Healthy control, n (%)	114 (25.4)
TEWL, g/m^2/h, median (IQR)	
Cheek	15.3 (13.3-19.3)
Upper arm,	11.0 (8.8-13.9)
Lower arm	13.1 (10.7-19.6)
Leg	12.6 (10.0-20.0)
Total IgE (IU/mL)*, median (IQR)	102.0 (40.3-289.8)
Blood eosinophil, 10^9 cells/L^4, median (IQR)	171.8 (104.9-279.9)
Vitamin D (ng/mL), (IOR)	
Sufficient (≥ 30)	36 (8.3)
Insufficient (20-29.9)	213 (49.1)
Deficient (< 20)	185 (42.6)
Atopic sensitization* n (%)	
None	145 (33.4)
Mono-	148 (34.1)
Poly-	141 (32.5)

BMI, body mass index; IgE, immunoglobulin E; IQR, interquartile range. *Inhalant allergen-specific IgE > 0.35 kU/L for at least one of six allergens (Alternaria, birch, cat dander, dog dander, Dermatophagoides farina, Japanese hop).

dren with sensitization to allergens, 148 (34.1%) had mono-sensitization, and 141 (32.5%) had poly-sensitization (Table I). Phthalate metabolites were grouped based on molecular weight and reported as the sum of four major high-molecular-weight phthalates (Σ4HMWP) metabolites (MEHP, MEOHP, MECPP, and MCPP) or the sum of the three major low molecular weight phthalate (Σ3LMWP) metabolites (MiBP, MnBP, and MBzP). They were further divided into quartiles according to concentration (lowest to highest, Q1 to Q4) (Table II).

Association of Urinary Phthalate Concentration with Total Eosinophil Count and Atopic Sensitization

We examined the relationships between the quartiles of urinary high and low MWP metabolites (Σ4HMWP and Σ3LMWP) and total eosinophil count and atopic sensitization (Table III). The unadjusted analyses showed that the quartiles of urinary Σ4HMWP and Σ3LMWP were not significantly associated with total eosinophil count or atopic sensitization (all comparisons, $p>0.05$). The analysis adjusted for multiple covariates revealed that the quartiles of urinary Σ4HMWP and Σ3LMWP were not significantly associated with total eosinophil count or atopic sensitization (all comparisons, $p>0.05$) (Table III).

Association of Urinary Phthalate Concentration with TEWL

The relationships of the quartiles of urinary high and low MWP metabolites and TEWL level is shown in Table III. The unadjusted analysis indicated that Σ4TEWL was significantly associated with the quartiles of Σ4HMWP (crude β=10.096, 95% CI: 2.346-17.846, $p=0.011$). The adjusted analysis for multiple covariates indicated that ∑4TEWL was significantly associated with the quartiles of Σ4HMWP (adjusted β=7.897, 95% CI: 0.636-15.158, $p=0.033$). The unadjusted analysis indicated that ∑4TEWL was significantly associated with the quartiles of Σ3LMWP (crude β=13.450, 95% CI: 5.785-21.141, $p=0.001$). The analysis adjusted for age, sex, BMI z-score, prematurity and/or low birth weight, severe AD revealed that ∑4TEWL level was significantly associated with the quartiles of Σ3LMWP (adjusted β=9.670, 95% CI: 2.422-16.919, $p=0.009$) (Table III).

The associations of the quartiles of urinary Σ4HMWP level with TEWL level in four body parts are depicted in Figure 1. The quartiles of urine Σ4HMWP level was significantly associated with the TEWL level of the lower arm ($p=0.002$) and leg ($p=0.004$), respectively; it was not associated with the upper arm ($p=0.385$) and cheek ($p=0.917$), respectively. The associations of the quartiles of urinary Σ3LMWP level with TEWL level in the four body parts are shown in Figure 2. According to quartiles of urinary Σ3LMWP, there were significant differences in the TEWL level of the lower arm ($p=0.001$) and leg ($p<0.001$), respectively. However, there were no significant differences in the upper arm ($p=0.436$) and cheek ($p=0.572$), respectively.

Association of Phthalate Concentration with severe AD and VAS

The relationships between urinary high and low MWP metabolites and severe AD are shown in Table IV. Severe AD was not significantly associated with Σ4HMWP and Σ3LMWP. However,

Table II. The level of high and low molecular phthalate in study participants (expressed in μg/g creatinine) (n = 448).

Phthalate	Metabolite	Q1	Q2	Q3	Q4	> 95 percentile
High molecular	MEHHP	< 11.0	11.0-18.4	18.4-28.7	> 28.7	> 61.3
	MEOHP	< 4.2	4.2-6.8	6.8-10.4	> 10.4	> 23.3
	MECPP	< 16.7	16.7-27.5	27.5-44.0	> 44.0	> 101.5
	MCPP	< 0.7	0.7-1.5	1.5-3.0	> 3.0	> 6.6
Low molecular	MiBP	< 11.4	11.4-19.4	19.4-35.0	> 35.0	> 127.9
	MnBP	< 34.3	34.3-56.4	56.4-84.9	> 84.9	> 174.5
	MBzP	< 1.0	1.0-3.1	3.1-8.6	> 8.6	> 40.0
Sum of molecular	$\sum_4$ *High MW*	< 32.6	32.6-52.5	52.5-81.8	> 81.8	> 181.7
	$\sum_3$ *Low MW*	< 55.9	55.9-87.3	87.3-136.3	> 136.3	> 304.7

MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MCPP, mono-(3-carboxypropyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-(iso-butyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MnBP, mono-n-butyl phthalate (MnBP); MBzP, mono-benzyl phthalate.

Table III. Association of high and low MWP metabolites with TEWL, total eosinophil count, and atopic sensitization.

Quartiles of urinary phthalate	Total eosinophil count (none *vs.* positive, 4%)				Atopic sensitization			
	OR (95% CI)	*p*	aOR (95% CI)*	*p**	OR (95% CI)	*p*	aOR (95% CI)*	*p**
High MWP Q1	Ref		Ref		Ref		Ref	
Q2	0.608 (0.336-1.102)	0.101	0.5721 (0.310-1.050)	0.072	0.596 (0.339-1.048)	0.073	0.597 (0.334-1.067)	0.082
Q3	0.800 (0.447-1.432)	0.452	0.775 (0.425-1.413)	0.405	0.865 (0.484-1.547)	0.625	0.864 (0.476-1.566)	0.630
Q4	0.946 (0.534-1.674)	0.848	0.834 (0.460-1.510)	0.834	0.818 (0.458-1.460)	0.496	0.743 (0.407-1.356)	0.743
Low MWP Q1	Ref		Ref		Ref		Ref	
Q2	1.019 (0.567-1.832)	0.950	0.922 (0.503-1.689)	0.792	1.084 (0.621-1.893)	0.776	0.940 (0.530-1.668)	0.832
Q3	0.994 (0.548-1.803)	0.984	0.895 (0.485-1.654)	0.724	1.229 (0.700-2.159)	0.473	1.187 (0.661-2.128)	0.566
Q4	1.244 (0.692-2.238)	0.466	1.088 (0.595-1.990)	0.785	1.196 (0.680-2.104)	0.534	1.059 (0.592-1.892)	0.847

Quartiles of urinary phthalate	$\sum_4$TEWL (continuous variable)			
	Crude β (95% CI)	*p*	Adjusted β (95% CI)**	*p***
High MWP Q1	Ref	-	Ref	-
Q2	7.436 (-0.403-15.274)	0.063	6.631 (-0.626-13.888)	0.073
Q3	7.000 (-0.785-14.784)	0.078	8.169 (0.961-15.376)	0.026
Q4	10.096 (2.346-17.846)	0.011	7.897 (0.636-15.158)	0.033
Low MWP Q1	Ref	-	Ref	-
Q2	4.005 (-3.720-11.731)	0.310	2.698 (-4.536-9.931)	0.465
Q3	9.928 (2.149-17.701)	0.012	4.676 (-2.667-12.019)	0.212
Q4	13.450 (5.758-21.141)	0.001	9.670 (2.422-16.919)	0.009

TEWL, transepidermal water loss; MWP, molecular weight phthalate; OR, odds ratio; CI, confidence interval; $\sum_4$TEWL, sum of cheek, leg, upper arm, and lower arm. *Adjusted for age, sex, BMI z-score, and prematurity and/or low birth weight, and p from a generalized linear regression with the logit function. **Adjusted for age, sex, BMI z-score, prematurity and/or low birth weight, ever atopic dermatitis, and p from a generalized linear mixed model with the gamma or logit function, random effect school.

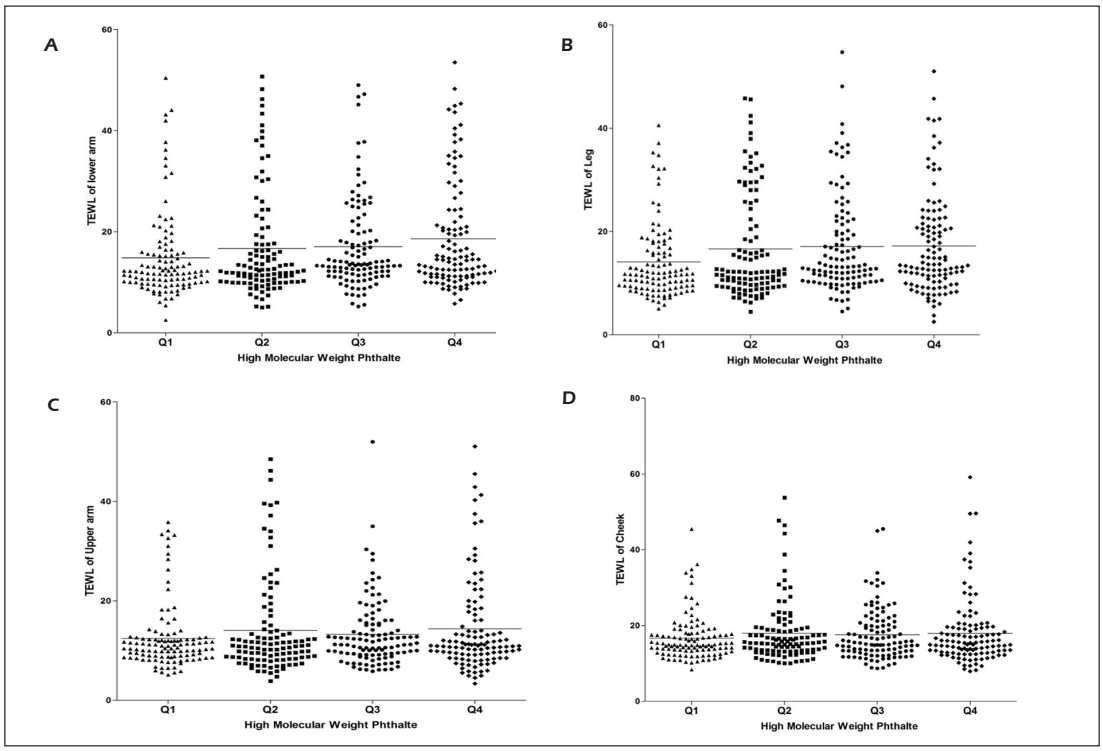

Figure 1. Comparison of TEWL in children with different levels of Σ4HMWP metabolites. **A**, Lower arm. **B** Leg. **C**, Upper arm. **D**, Cheek. TEWL, transepidermal water loss; Σ4HMWP, four high-molecular-weight phthalates.

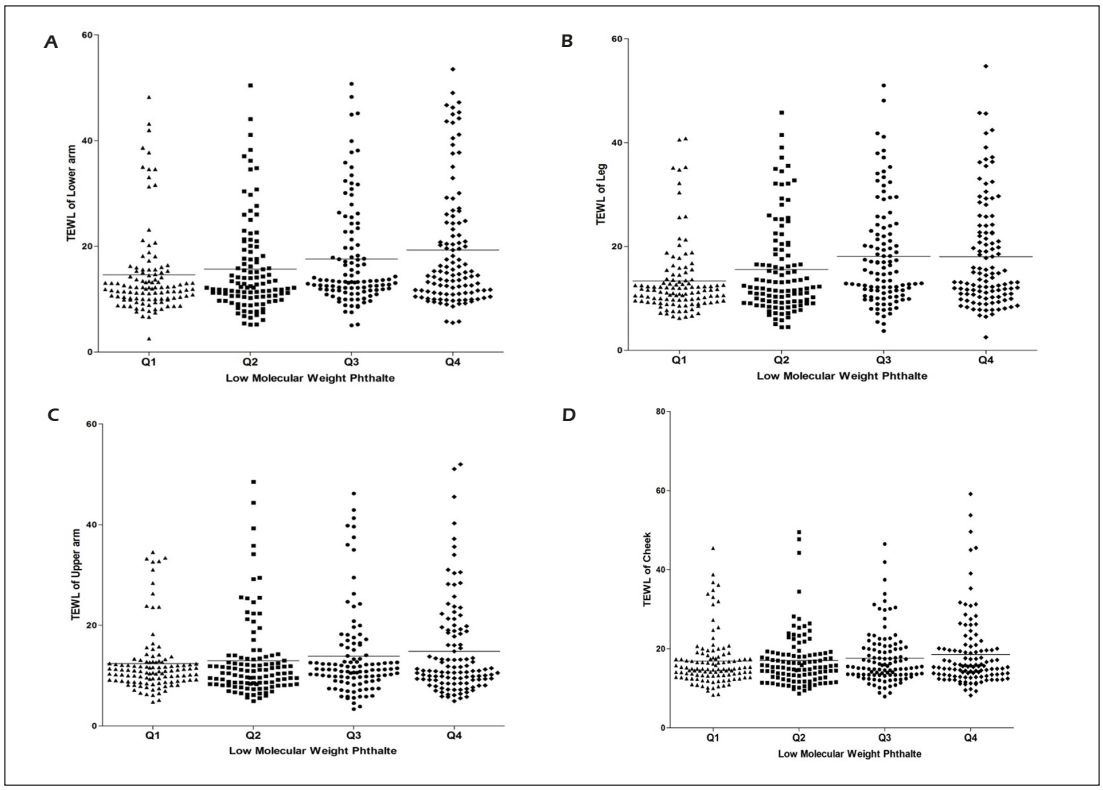

Figure 2. Comparison of TEWL in children with different levels of Σ3LMWP metabolites. **A**, Lower arm. **B**, Leg. **C**, Upper arm. **D**, Cheek . TEWL, transepidermal water loss; Σ4HMWP, four high-molecular-weight phthalates.

Table IV. Association of AD (n = 123) and VAS (n = 123) with high and low MWP metabolites.

Quartiles of urinary phthalate	AD (severe)				VAS score			
	β (95% CI)	*p*	aβ (95% CI)	*p*	β (95% CI)	*p*	aβ (95% CI)*	*p**
High Q1	Ref	Ref	Ref	-	Ref	-		
Q2	0.595 (0.293-1.206)	0.149	0.535 (0.259-1.105)	0.091	0.704 (-0.335-1.743)	0.182	0.911 (-0.133-1.956)	0.911
Q3	1.166 (0.539-2.524)	0.696	1.074 (0.488-2.363)	0.860	0.409 (-0.737-1.555)	0.409	0.591 (-0.544-1.726)	0.304
Q4	1.002 (0.470-2.137)	0.995	0.936 (0.425-2.064)	0.870	**1.463 (0.359-2.567)**	**0.010**	**1.469 (0.344-2.593)**	**0.011**
Low Q1	Ref	Ref		Ref	-	Ref	-	
Q2	1.202 (0.595-2.429)	0.608	1.190 (0.575-2.464)	0.639	0.570 (-0.553-1.692)	0.317	0.439 (-0.704-1.581)	0.448
Q3	1.282 (0.627-2.621)	0.495	1.194 (0.573-2.491)	0.635	0.057 (-1.078-1.193)	0.921	0.200 (-0.944-1.344)	0.729
Q4	1.339 (0.653-2.745)	0.424	1.290 (0.615-2.704)	0.499	0.212 (-0.864-1.288)	0.697	0.377 (-0.730-1.484)	0.501

AD, atopic dermatitis; MWP, molecular weight phthalate; OR, odds ratio; CI, confidence interval; VAS score, visual analog scale score. *Adjusted for age, sex, BMI z-score, and prematurity and/or low birth weight, and p from a generalized linear mixed model with the gamma function and random effect school.

adjusted for age, sex, BMI z-score, prematurity and/or low birth weight, and *p* from a generalized linear mixed model with the gamma function and random effect school, VAS score was significantly associated with Σ4HMWP (aβ=1.469, 95% CI: 0.344-2.593, p=0.011), but not Σ3LMWP. Moreover, there were no significant differences in urinary high and low MWP metabolites levels between HC and allergic diseases group (severe), including AR, urticaria, AD, and asthma (all comparisons, p>0.05).

Discussion

Our study of a general population of children indicated that after adjusting for confounding variables, exposure to high-molecular weight phthalates (HMWPs) and low molecular weight phthalates (LMWPs) was significantly associated with the sum of TWEL levels in four body parts. Moreover, phthalate exposure was significantly associated with the TEWL level of the lower arm and leg, but not cheek and upper arm. These findings indicated that increased exposure to phthalate was associated with increased skin barrier dysfunction and inflammation but had varying results depending on the body part.

The role of phthalate exposure on various diseases, including allergic diseases, has been a topic of interest[2,4-9,22]. However, few studies have examined the association of phthalate exposure with skin barrier function and atopic sensitization[23,24]. Dry skin is associated with higher TEWL, and skin barrier dysfunction, measured by increased TEWL, has been found[13,25] to precede AD. The differences in the association between TEWL level and phthalate (LMWPs and HMWPs) in our study, may be attributed to the varying responses of the body parts to LMWPs and HMWPs. The relationship between metabolism of phthalate and skin permeation[26] or frequent emollient use in children with AD[24] have been studied in the past. However, to the best of our knowledge, this is the first study with a large-sample size of children, which comprehensively investigate the relationship between LMWPs and HMWPs exposure and skin barrier dysfunction.

Meanwhile, HMWPs are replacing the LMWPs derived from C3-C6 alcohols with more than six carbons in their backbone, giving them increased permanency and durability[27]. The LMWPs are used in various personal hygiene and cosmetic products, and HMWPs are used in plastic tubing, food packaging, and containers[28,29]. A previous study[30] on 797 Korean aged 12-17 years reported that the urinary mono-(2-ethyl-5-carboxypentyl) phthalate (MECCP) and mono-benzyl phthalate (MBzP) concentrations in the highest quartile were positively associated with AD. Another study[31] showed that urine MBzP at age two was significantly associated with AD, but observed no statistically significant association for other phthalate metabolites with AD. In addition, one meta-analysis[32] showed that prenatal exposure to MBzP was significantly associated with the risk of AD development.

In the present study, we found that LMWPs and HMWPs were not significantly associated with severe AD, in agreement with a previous study[23]. to some studies 30, 31, 33 presenting prior exposure to phthalate and inconsistencies in phthalate. The mentioned epidemiological studies supported associations between phthalate exposures and airway, but dermal allergic diseases were weak. Furthermore, AD has a complex and complicated etiology, including genetic, immunological, and environmental factors that cause skin barrier abnormalities and immune dysfunctions[13].

Interestingly, we found that VAS findings from 123 children with AD are associated with HMWPs, but not LMWPs. The previous studies[18,34] showed that pruritus intensity in AD was assessed using VAS. From our findings, we assumed that moderate or severe AD with high pruritus might be strongly associated with exposure to HMWPs, which are typically obtained from food packaging and containers in Korean food delivery.

Urine phthalate levels have been reported[35,36] to be correlated with blood eosinophil levels and atopic sensitization. Thus, we initially hypothesized a positive association between LMWPs and HMWPs with atopic sensitization and total eosinophil count. However, our results revealed no association, which corroborates the findings of a previous study[33] demonstrating that phthalates' effect on sensitization was more robust in children with allergic disease, but no direct associations was observed between phthalate exposures and allergic disease. This result may also explain why the relationship between urine phthalate, eosinophil levels, and atopic sensitization has been controversial. Thus, future mechanistic studies are needed to clarify the nature of this relationship.

This study has the following merits. We used a comprehensive and stringent questionnaire and

TEWL that yielded accurate and objective data and evaluated allergic biomarkers, including specific IgE and eosinophil. Additionally, we included a large urine sample size of 448 children from the general population. Moreover, we performed all measurements under the same conditions so that all samples and data were collected at approximately the same time.

Limitations

However, the present study had some limitations. Firstly, the correlation between urinary phthalate metabolites and TEWL alone may be insufficient to address the association of barrier dysfunction because the TEWL could be elevated even in temporal dermatitis. Secondly, relative to the small size of this study (123 children with AD), the analysis result for 123 children may show negligible effects of phthalates on AD and may have poor generalizability of the results. However, due to the study's cross-sectional nature, we did not obtain direct evidence for cause-and-effect relationships. Therefore, it is necessary to examine the correlation separately in AD children and healthy subjects or to check the values of urinary phthalates metabolites according to AD severity with large-scale studies on children.

Conclusions

Exposure to high- and low-molecular-weight phthalates may be associated with skin barrier dysfunction in children. Thus, reducing exposure to phthalate in children may help prevent skin barrier dysfunction and pruritus. However, longitudinal studies involving repeated measurements are warranted to analyze the long-term effects of phthalate on skin barrier functions and pruritus.

Conflict of Interest

We declare that there are no real or perceived conflicts of interest to declare related with this submission, and that we have no links with industry.

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Ethics Approval

The study protocol was approved by the Institutional Review Board of the CHA Bundang Medical Center (IRB No. 2017-04-049).

Informed Consent

Written informed consent was obtained from the parents or guardians of all participants following a detailed explanation of the study.

References

1) Ahn K. The Detrimental effects of phthalates on allergic diseases. Allergy Asthma Immunol Res 2022; 14: 285-288.
2) Gascon M, Casas M, Morales E, Valvi D, Ballesteros-Gómez A, Luque N, Rubio S Monfort N, Ventura R, Martínez D, Sunyer J, Vrijheid M.Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol 2015; 135: 370-378.
3) Schettler T. Human exposure to phthalates via consumer products. Int J Androl 2006; 29: 134-139.
4) Yon DK, Cho YS, Ha EK, Jee HM, Song JY, Jung YH, Lee KS, Sheen YH, Han MY. Exposure to phthalates is associated with acute urticaria in children. Pediatr Allergy Immunol 2018; 29: 657-660.
5) Jahreis S, Trump S, Bauer M, Bauer T, Thürmann L, Feltens R,Wang Q, Gu L, Grützmann K, Röder S, Averbeck M, Weichenhan D, Plass C, Sack U, Borte M, Dubourg V, Schüürmann G, Simon JC, Bergen M, Hackermüller J, Eils R, Lehmann I, Polte T. Maternal phthalate exposure promotes allergic airway inflammation over 2 generations through epigenetic modifications. J Allergy Clin Immunol 2018; 141: 741-753.
6) Gascon M, Casas M, Morales E, Valvi D, Ballesteros-Gómez A, Luque N,Rubio S, Monfort N, Ventura R, Martínez D, Sunyer J, Vrijheid M. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol 2015; 135: 370-378.
7) Kim JH, Lim JS. Early menarche and its consequence in Korean female: reducing fructose intake could be one solution. Clin Exp Pediatr 2021; 64: 12-20.

8) Berger K, Eskenazi B, Balmes J, Kogut K, Holland N, Calafat AM, Harley KG. Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatr Allergy Immunol 2019; 30: 36-46.

9) Kim MA, Yon DK, Jee HM, Kim JH, Park J, Lee SW, Sung M, Sheen YH, Han MY. Association of phthalates with nasal patency and small airway dysfunction in first-grade elementary school children. Allergy 2020; 75: 2967-2969.

10) Laughter D, Istvan JA, Tofte SJ, Hanifin JM. The prevalence of atopic dermatitis in Oregon schoolchildren. J Am Acad Dermatol 2000; 43: 649-655.

11) Jeon YH. Dietary restriction misconceptions and food allergy education in children with atopic dermatitis. Clin Exp Pediatr 2022; 65: 83-84.

12) Ravnborg N, Ambikaibalan D, Agnihotri G, Price S, Rastogi S, Patel KR, Singam V, Andersen Y, Halling AS, Silverberg JI, Egeberg A, Thyssen JP. Prevalence of asthma in patients with atopic dermatitis: A systematic review and meta-analysis. J Am Acad Dermatol 2021; 84: 471-478.

13) Kim BE, Leung DYM. Significance of skin barrier dysfunction in atopic dermatitis. Allergy Asthma Immunol Res 2018; 10: 207-215.

14) Toncic RJ, Kezic S, Jakasa I, Hadzavdic SL, Balic A, Petkovic M,Pavicic B, Zuzul K, Marinovic B.Filaggrin loss-of-function mutations and levels of filaggrin degradation products in adult patients with atopic dermatitis in Croatia. J Eur Acad Dermatol Venereol 2020; 34: 1789-1794.

15) Tomoyuki K, Kiwako YH, Mayako SA, Tatsuki F, Yukihiro O. Eczema phenotypes and IgE component sensitization in adolescents: A population-based birth cohort. Allergol Int 2023; 72: 107-115.

16) Sung M, Yon DK, Lee SW, Kim JH, Baek H, Jee HM, Shin YH, Han MY. The relationship between aeroallergen sensitization and chronic cough in school-aged children from general population. Biomed Res Int 2021; 2021: 5513611.

17) Lee SI, Shin MH, Lee HB, Lee JS, Son BK, Koh YY, Kim KE, Ahn YO. Prevalences of symptoms of asthma and other allergic diseases in Korean children: a nationwide questionnaire survey. J Korean Med Sci 2001; 16: 155-164.

18) Inami Y, Fukushima M, Murota H. Correlation between histidine decarboxylase expression of keratinocytes and visual analogue scale in patients with atopic dermatitis. J Dermatol Sci 2021; 103: 120-123.

19) Lee SJ, Ha EK, Jee HM, Lee KS, Lee SW, Kim MA, Kim DH, Jung YH, Sheen YH, Sung MS, Han MY. Prevalence and risk factors of urticarial with a focus on chronic urticaria in children. Allergy Asthma Immunol Res 2017; 9: 212-219.

20) Koch HM, Lorber M, Christensen KLY, Pälmke C, Koslitz S, Brüning T. Identifying sources of phthalate exposure with human biomonitoring: Results of a 48h fasting study with urine collection and personal activity patterns. Int J Hyg Environ Health 2013; 216: 672-681.

21) Rogiers V, Group EEMCO. EEMCO guidance for the assessment of transepidermal water loss in cosmetic sciences. Skin Pharmacol Appl Skin Physiol 2001; 14: 117-128.

22) Kim SH, Moon JY, Park HS, Shin YS. The role of Di (2-Ethylhexyl) phthalate as an exacerbating factor in chronic spontaneous urticaria. Allergy Asthma Immunol Res 2022; 14: 339-343.

23) Bekö G, Callesen M, Weschler CJ, Toftum J, Langer S, Sigsgaard T, Høst A, Jensen TK, Clausen G. Phthalate exposure through different pathways and allergic sensitization in preschool children with asthma, allergic rhinoconjunctivitis and atopic dermatitis. Environ Res 2015; 137: 432-439.

24) Overgaard LEK, Main KM, Frederiksen H, Stender S, Szecsi PB, Williams HC, Thyssen J P. Children with atopic dermatitis and frequent emollient use have increased urinary levels of low-molecular-weight phthalate metabolites and parabens. Allergy. 2017; 72: 1768-1777.

25) Rehbinder EM, Endre KMA, Carlsen KCL, Anna A, Bains KES, Berents TL, Carlsen KH, Gudmundsdóttir HK, Haugen G, Hedlin G, Kreyberg I, Nordhagen LS, Nordlund B, Saunders CM, Sandvik L, Skjerven HO, Söderhäll C, Staff AC, Vettukattil R, Værnesbranden MR, Landrø L, study group. Predicting skin barrier dysfunction and atopic dermatitis in early infancy. J Allergy Clin Immunol Pract 2020; 8: 664-673.

26) Hopf NB, Berthet A, Vernez D, Langard E, Spring P, Gaudin R. Skin permeation and metabolism of di(2-ethylhexyl) phthalate (DEHP). Toxicol Lett 2014; 224: 47-53.

27) Kueseng P, Thavarungkul P, Kanatharana P. Trace phthalate and adipate esters contaminated in packaged food. J Environ Sci Health B 2007; 42: 569-576.

28) National Research Council (US) Committee on the Health Risks of Phthalates. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Washington (DC): National Academy Press (US); 2008.

29) Phthalates. Assessing and Managing Chemicals under TSCA. Available at: www.epa.gov. 21 September 2015.

30) Kim SW, Lee J, Kwon SC, Lee JH. Association between urinary phthalate metabolite concentration and atopic dermatitis in Korean adolescents participating in the Third Korean National Environmental Health Survey, 2015-2017. Int J Environ Res Public Health 2021; 18: 2261.

31) Wang IJ, Lin CC, Lin YJ, Hsieh WS, Chen PC. Early life phthalate exposure and atopic disorders in children: a prospective birth cohort study. Environ Int 2014; 62: 48-54.

32) Jung M, Kim MJ, Kim S, Kyung Y, Kim M, Lee JY, Jeong HI, Lee BR, Kim J, Ahn K, Park YM.

Effect of prenatal phthalate exposure on childhood atopic dermatitis: A systematic review and meta-analysis. Allergy Asthma Proc 2021; 42: e116-e125.

33) Bølling AK, Sripada K, Becher R, Bekö G. Phthalate exposure and allergic diseases: Review of epidemiological and experimental evidence. Environ Int 2020; 139: 105706.

34) Jaworek AK, Szafraniec K, Doniec Z, Jaworek M, Wojas-Pelc A, Pokorsk M. Pruritus characteristics in severe atopic dermatitis in adult patients. Adv Exp Med Biol 2021; 1289: 71-77.

35) Wang CW, Wu DW, Chen SC, Chen HC, Lin HH, Su H, Shiea JT, Lin WY, Hung CH, Kuo CH. Associations of dermal diethyl phthalate level with changes in lung function test value mediated by absolute eosinophil count: A panel study of adults in southern Taiwan. Environ Res 2021; 194: 110613.

36) Quoc QL, Bich TCT, Kim SH, Ryu MS, Park HS, Shin YS. Mono-n-butyl phthalate regulates nuclear factor erythroid 2-related factor 2 and nuclear factor kappa B pathway in an ovalbumin-induced asthma mouse model. Food Chem Toxicol 2022; 166: 113171.