Allergy

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LETTER OPEN ACCESS

Association Between Di-(2-Ethylhexyl) Phthalate and Childhood Asthma Through Plasma Metabolome Alterations

Mi Jeong Kim[1] | Seung Hwa Lee[2] | Su Jung Kim[1] | Ha Eun Song[1] | Hyoyeong Lee[1] | Mi Jin Kang[3] | Song-I Yang[4] | Hyo-Bin Kim[5] | So Yeon Lee[6,7] | Jeong-Hyun Kim[2] | Hosub Im[8] | Hoon Je Seong[9] | Yong Joo Park[10] | Jeonghun Yeom[11] | Ji-Hye Oh[12] | Eom Ji Choi[13] | Dong In Suh[14] | Kyung Won Kim[15] | Kangmo Ahn[16] | Youn Ho Shin[17] | Soo-Jong Hong[3] | Hyun Ju Yoo[1]

[1]Department of Convergence Medicine and Department of Digital Medicine, Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea | [2]Department of Medicine, University of Ulsan College of Medicine, Seoul, Republic of Korea | [3]Department of Pediatrics, Humidifier Disinfectant Health Center, National Medical Center, Seoul, Republic of Korea | [4]Department of Pediatrics, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea | [5]Department of Pediatrics, Inha University Hospital, Inha University College of Medicine, Incheon, Republic of Korea | [6]PHI Digital Healthcare, Seoul, Republic of Korea | [7]Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Republic of Korea | [8]Institute for Life & Environmental Technology, Smartive Corporation, Hanam-si, Republic of Korea | [9]Department of Biological Science, Kunsan National University, Gunsan, Republic of Korea | [10]College of Pharmacy, Kyungsung University, Gyeongsan-si, Gyeongsangbuk-do, Republic of Korea | [11]Prometabio Research Institute, Prometabio Co. Ltd., Hanam-si, Republic of Korea | [12]Bioinformatics Core Laboratory, Convergence Medicine Research Center, Asan Institute for Life Sciences, Asan Medical Center, Seoul, Republic of Korea | [13]Department of Pediatrics, CHA Medical Center, CHA University College of Medicine, Seoul, Republic of Korea | [14]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea | [15]Department of Pediatrics, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea | [16]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea | [17]Department of Pediatrics, Kyunghee University College of Medicine, Seoul, Republic of Korea

Correspondence: Soo-Jong Hong (sjhong@nmc.or.kr) | Hyun Ju Yoo (yoohyunju@amc.seoul.kr)

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To the Editor,

Exposure to environmental factors has been linked to increased asthma risk. However, few studies have investigated the complex relationships among exposome, metabolites, and asthma. Existing research suggests that environmental exposures shape omics profiles associated with respiratory outcomes. A recent study of preschool children found that metabolomic clusters associated with asthma risk varied by neighborhood resources, suggesting that environmental triggers may induce both metabolic and disease severity [1]. The Human Early Life Exposome project linked prenatal and childhood exposures to serum metabolomic shifts potentially predisposing children to asthma [2]. Despite this progress, the interplay among exposome, metabolites, and disease pathogenesis remains insufficiently explored,

particularly in childhood asthma. This study aimed to elucidate the integrated relationships among urinary exposome, plasma metabolites, and childhood asthma.

We analyzed 139 children aged 6–7 years from the general population-based ECHO-COCOA (Exposome and Child Health with Omics–Cohort for Childhood Origin of Asthma and allergic diseases) birth cohort study, 26 children with asthma and 113 children without asthma and atopic dermatitis (Table S1). Informed consent was obtained from all individual participants included in the study.

Mass spectrometry–based methods were used to quantify 74 urinary exposome components (Table S2) and plasma metabolites (Table S3). Global metabolomic profiling identified asthma-related metabolites, followed by targeted quantification of selected features, mainly glycerophospholipids, amino acids, and derivatives. These target metabolome data were analyzed in relation to urinary exposures and asthma-related outcomes.

Asthma-associated urinary exposures were initially identified (Figure 1). Then, metabolites related to these

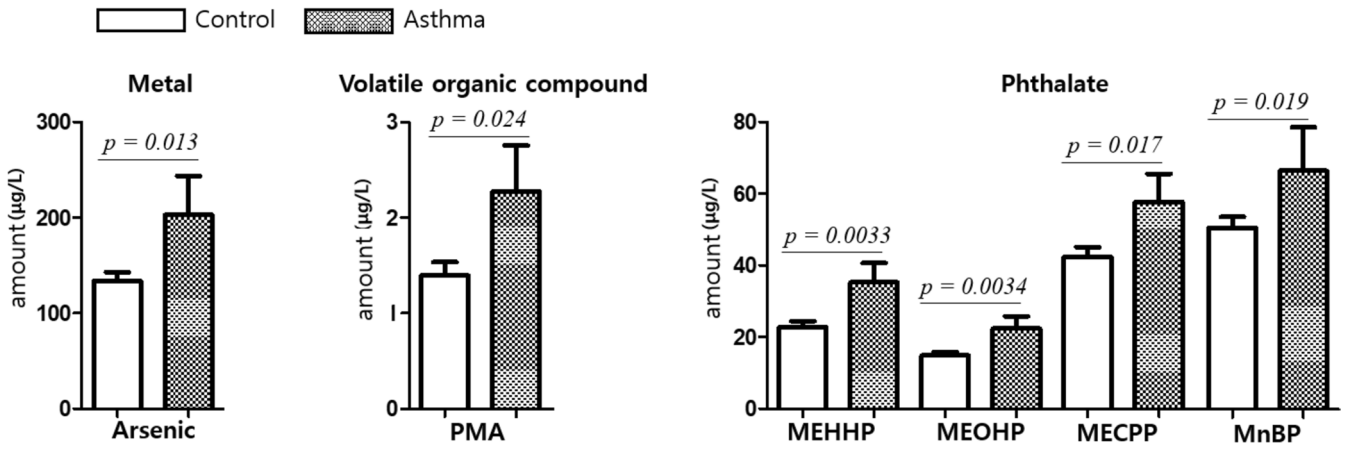

FIGURE 1 | Urinary exposures associated with asthma (logistic regression adjusted for age and sex). Only significant results are shown. Error bars represent relative standard deviations. Arsenic; PMA (phenylmercapturic acid); MEHHP (mono-(2-ethyl-5-hydroxyhexyl) phthalate); MEOHP (mono-(2-ethyl-5-oxohexyl) phthalate); MECPP (mono(2-ethyl-5-carboxypentyl) phthalate); MnBP (mono-n-butyl-phthalate).

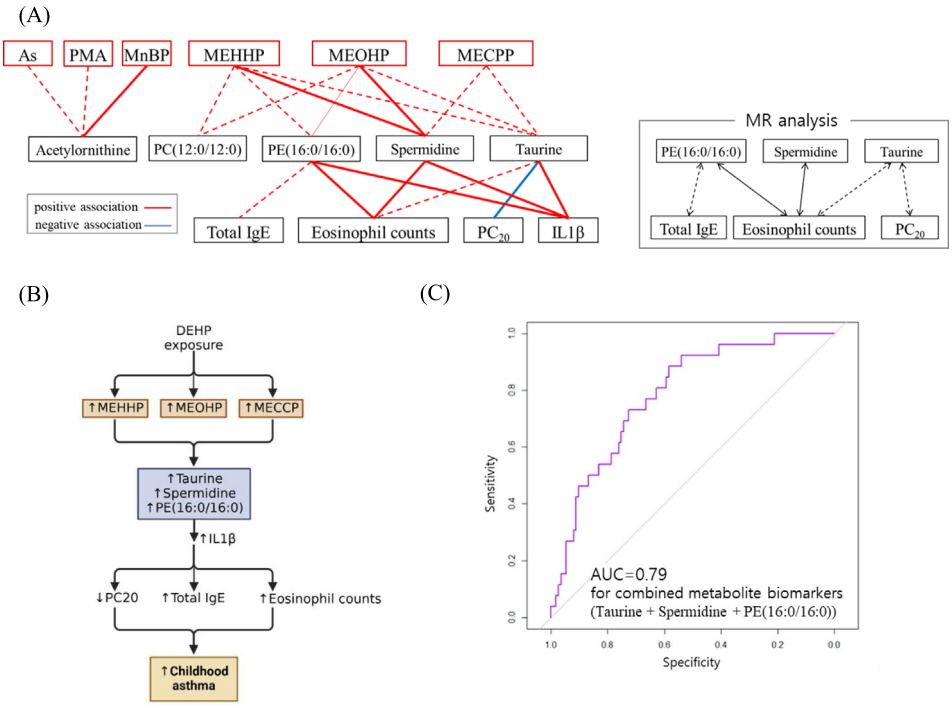

FIGURE 2 | (A) Interrelations among metabolites, urine exposome, and clinical parameters in asthma. Causal links based on Mendelian randomization (MR) analysis were shown in a separate box. Only significant results are displayed in (A) and (B); a dotted line indicates raw $p < 0.05$, and a solid line indicates Bonferroni $p < 0.05$ (statistical details in the Supporting Information). (B) Proposed mechanism of metabolite biomarker upon DEHP exposure in asthma. (C) ROC curve analysis for DEHP-associated plasma biomarkers in asthma. ROC analysis was performed using combined potential metabolite biomarkers (taurine, spermidine, and PE (16:0/16:0)).

asthma-associated exposures were explored. Asthma-associated exposures included arsenic, phenylmercuric acetate, and mono-n-butyl phthalate, which were linked to increased acetylornithine. Phosphatidylcholine (PC) (12:0/12:0), phosphatidylethanolamine (PE) (16:0/16:0), taurine, and spermidine were significantly associated with diethylhexyl phthalate (DEHP) metabolites (mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)) (Figure 2A). Notably, PE (16:0/16:0), taurine, and spermidine also correlated with asthma-related clinical markers. Taurine showed a negative correlation with PC_{20} and a positive association with eosinophil count. PE (16:0/16:0) and spermidine positively correlated with eosinophils, while PE (16:0/16:0) also associated with total IgE levels. Mendelian randomization (MR) analysis revealed possible causal relationships between taurine and PC_{20}; PE (16:0/16:0) and IgE; and taurine, spermidine, PE (16:0/16:0) and eosinophils (Table S4). These metabolites are also associated with IL-1β, a central pro-inflammatory cytokine in asthma. These findings suggest that taurine, spermidine, and PE (16:0/16:0) could be promising candidate biomarkers of asthma in the context of DEHP exposure.

Taurine, spermidine, and PEs are recognized regulators of autophagy and antioxidants, mitigating oxidative stress and inflammation in asthma [3–5]. Elevated levels of these metabolites might reflect a compensatory response or indicate regulatory mechanisms of autophagy. Additionally, arachidonic acid metabolism—implicated in asthma inflammation—has been linked to taurine efflux, which may explain the increased taurine levels in asthmatics [6]. Elevated spermidine and PEs have also been observed in adult asthma. However, mechanisms underlying DEHP's effects on these metabolites remain unclear. Nonetheless, these metabolites may serve as potential biomarkers for DEHP-associated childhood asthma (Figure 2B,C).

Although DEHP has a short half-life (~1 day), its widespread presence in consumer products results in chronic, low-level pseudo-persistence in the body. Although the low prevalence of childhood asthma in the general population of Korea may limit statistical power, our results are strengthened by MR analysis and receiver operating characteristic (ROC) analysis. These methods helped us minimize the influence of confounding factors and distinguish metabolite biomarkers between asthmatic and non-asthmatic children. Further research, especially longitudinal and extended cohort and mechanistic validations, is needed to validate our result. Multiple urinary sampling or 24-h urine collection could improve the assessment of long-term exposures. Overall, our findings highlight taurine, spermidine, and PE (16:0/16:0) as potential biomarkers of phthalate-related childhood asthma.

Author Contributions

Methodology: M. J. Kim, S. J. Kim, H. E. Song, and H. Lee, Resources: S. H. Lee, M. J. Kang, S.-I. Yang, H.-B. Kim, S. Y. Lee, J.-H. Kim, H. Im, H. J. Seong, Y. J. Park, J. Yeom, E. J. Choi, D. I. Suh, K. W. Kim, K. Ahn, Y. H. Shin, and S.-J. Hong, Data analysis and interpretation of data: J.-H. Oh, S. Hong and H. J. Yoo, Writing, review and editing: M. J. Kim, S. H. Lee, S.-J. Hong, and H. J. Yoo.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Mi Jeong Kim
Seung Hwa Lee
Su Jung Kim
Ha Eun Song
Hyoyeong Lee
Mi Jin Kang
Song-I Yang
Hyo-Bin Kim
So Yeon Lee
Jeong-Hyun Kim
Hosub Im
Hoon Je Seong
Yong Joo Park
Jeonghun Yeom
Ji-Hye Oh
Eom Ji Choi
Dong In Suh
Kyung Won Kim
Kangmo Ahn
Youn Ho Shin
Soo-Jong Hong
Hyun Ju Yoo

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Clinical characteristics of study subjects. *p*-values were calculated using Chi-squared test or Mann–Whitney test. **Table S2:** 74 environmental substances were measured in the urine of the study subjects. **Table S3:** List of target metabolites measured in the plasma of the study subjects. **Table S4:** One sample bi-directional Mendelian randomization. *p*-value and bonf.*p*-value represents the raw.*p*-value and Bonferroni.*p*-value, respectively. N.snps: the number of SNPs used in constructing genetic risk scores.