

Effect of prenatal phthalate exposure on childhood atopic dermatitis: A systematic review and meta-analysis

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ABSTRACT

Background: The association between prenatal exposure to phthalate and childhood atopic dermatitis (AD) has previously been investigated; however, the results are inconsistent.

Objective: We aimed to perform a systematic review and meta-analysis of birth cohort studies to investigate whether prenatal exposure to phthalate increases the risk of developing AD in children.

Methods: We performed an electronic search of medical literature data bases. Studies were critically appraised, and a meta-analysis was performed.

Results: Among 129 articles identified, 11 studies met the eligibility criteria. Included studies originated from Europe ($n = 5$), the United States ($n = 4$), and Asia ($n = 2$). The study sample size ranged from 147 to 1024 mother-child pairs. Quality assessment by using the Newcastle–Ottawa scale of all the studies had scores of ≥ 6 . A meta-analysis of data from eight selected studies suggested that monobenzyl phthalate (MBzP) exposure was significantly associated with the risk of AD development (odds ratio 1.16 [95% confidence interval, 1.04–1.31]; $I^2 = 17.36\%$). However, AD development was not associated with other phthalate metabolites, such as mono-(2-ethylhexyl) phthalate, monoethyl phthalate, mono-isobutyl phthalate, mono-*n*-butyl phthalate, and the sum of di-[2-ethylhexyl] phthalate on the development of AD (all p values were > 0.05).

Conclusion: Our meta-analysis suggested that prenatal exposure to phthalates may be associated with the development of childhood AD. However, further research is needed because only MBzP showed statistical significance and the number of articles in the literature is still insufficient.

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Atopic dermatitis (AD) is a common childhood chronic inflammatory skin disease with a prevalence of 15–20% in children.^{1,2} AD is associated with multiple comorbidities, such as asthma and allergic rhinitis, causes sleep disturbance, and results in an

impaired quality of life.^{3–5} The pathogenesis of AD is heterogeneous and multifactorial. Results of recent studies demonstrated that immune dysregulation, microbial dysbiosis, and epidermal barrier defects contribute to the pathophysiology of AD.⁶ In addition to genetic predisposition, environmental factors or interactions between them are known to affect the development of AD.⁷ Phthalates are diesters of phthalic acid (1,2-benzenedicarboxylic acid) and are commonly used as stabilizers and plasticizers in personal care products, plastics, toys, hair sprays, shampoos, food packing, home furnishings, and building materials.^{8,9} Because of their widespread use and property to leach, human exposure to phthalates arises mainly from ingestion, inhalation, and skin absorption.^{10,11}

Results of a number of studies have shown that higher concentrations of urinary metabolites were found in women than in men,¹² and pregnant women as well as fetuses could be highly sensitive to the potential harmful effects of toxic metabolites of phthalates.^{13,14} Phthalates can cross the placental barrier and have been measured in amniotic fluid in studies on humans.^{15,16} Furthermore, phthalates have potential immunomodulatory properties in animal models.^{17–19} Because the prenatal period is critical in the development of the immune system, several studies have been performed to demonstrate that the

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exposure to phthalates during pregnancy is associated with the development AD in childhood.^{20,21} However, epidemiologic data on the development of AD in relation to phthalate exposure during the fetal period remain inconsistent. Therefore, we aimed to identify the association between prenatal phthalate exposure and childhood AD by performing a systematic review with a meta-analysis.

METHODS

Data Base Search and Study Selection

We systematically searched the MEDLINE (National Library of Medicine, Bethesda, MD, 1946 to May 26, 2019), Embase (Elsevier B.V, Amsterdam, Netherlands, 1947 to May 26, 2019), and Cochrane (Cochrane, London, United Kingdom, 1947 to May 26, 2019) data bases for all studies on AD and phthalate. The search strategy for MEDLINE and Cochrane *via* Medical Subject Headings (MeSH) terms included the following combinations of keywords: (((((((((((“dermatitis, atopic”[MeSH]) or atopic dermatitis [tw]) or atopic neurodermatitis [tw]) or “eczema”[MeSH]) or eczema [tw]) or atopic eczema [tw]) or childhood eczema [tw]) or infantile eczema [tw]) or “neurodermatitis”[MeSH]) or neurodermatitis [tw]) or atopic eczema dermatitis syndrome [tw]) and (“diethylhexyl phthalate” or “dibutyl phthalate” or “phthalate”). We used the following combinations of keywords for EMBASE: (((((((((((atopic dermatitis [emtree]) or atopic dermatitis [tw]) or atopic neurodermatitis [tw]) or “eczema” [emtree]) or eczema [tw]) or atopic eczema [tw]) or childhood eczema [tw]) or infantile eczema [tw]) or “neurodermatitis” [emtree]) or neurodermatitis [tw]) or atopic eczema dermatitis syndrome [tw]) and (“phthalic acid” [emtree] or “phthalic acid dibutyl ester” [emtree] or phthalate*). EndNote version 8.0 (Clarivate Analytics, Philadelphia, Pennsylvania) was used to manage the references extracted from the data bases. Studies could be cohort, case-control, or cross-sectional designs. Duplicates from different data base searches were removed and transferred to a duplicated library.

Two reviewers (YMP and MJ) independently and screened duplicated titles and abstracts by using a standardized protocol. Disagreements were resolved by discussion with a third researcher (KA). Titles and abstracts were initially reviewed and then the final selection was based on the full text according to the following inclusion criteria: (1) birth cohort studies, (2) studies in which prenatal phthalate exposure was measured, and (3) studies that provided the incidence of AD data. Exclusion criteria were (1) animal or laboratory studies, (2) studies published in non-English, (3) studies that did not present original data (conference, review articles, editorials, guidelines, and reports), and (4) studies that measured phthalates not from humans. The primary outcome was the incidence of AD in

children. A protocol of this study is registered online at Prospero (registration CRD42020158654).²²

Data Extraction

Two reviewers (MJ and JK) independently extracted data, and discrepancies were resolved in consultation with an expert investigator (KA). The following data were extracted from all the articles by using a data-extraction sheet: first author, year of publication, study design, country, characteristics of the subjects (age, sex, and sample size), exposure characteristics (phthalate metabolite and its specimen, units of concentration of phthalates, timing at measurement of phthalate), and outcome characteristics (assessment timing to diagnose AD). Relative risks, odds ratios (OR), and 95% confidence intervals (CI) of the association between prenatal phthalate exposure and the incidence of AD in children were also extracted. If the estimated data were not found in those articles, we contacted the corresponding authors to ask for the detailed data.

Quality Assessment

We used the Newcastle–Ottawa scale to assess the quality of nonrandomized studies, including case-control and cohort. This scale allowed for a maximum of 9 points, which indicates the highest quality, with scores of ≥ 6 denoting high quality. There are three categories: selection (0–4 points), comparability (0–2 points), and outcome or exposure (0–3 points).

Statistical Analysis

Data were analyzed by using R 3.6.1 package “metafor” (Vienna, Austria).²³ Only studies with similar exposure to phthalate metabolites were used for the meta-analysis. Studies with clinical or different methodological heterogeneity were excluded when pooling the data to improve comparability among the studies. We performed meta-analysis when estimates of three or more phthalate compounds were present in the included study. Summary estimates based on adjusted OR and 95% CIs were used to assess the association between phthalate exposure and risk of childhood AD and were visualized by using forest plots. The OR from a study with categorical exposure was transformed to OR for the continuous scale exposure by using weighted linear regression of the central values between the categories of exposure on the corresponding ORs. After pooling ORs from exclusive age groups,²⁴ a meta-analysis was conducted to investigate the association between prenatal phthalate exposure and development of AD, regardless of timing of outcome assessment. To determine if prenatal phthalate exposure has a more significant association with early onset AD, we performed subgroup analysis by selecting a study with an outcome assessment within 3 years after birth. If the *p* value for the Cochrane Q test was < 0.10 and $I^2 > 50\%$, we considered

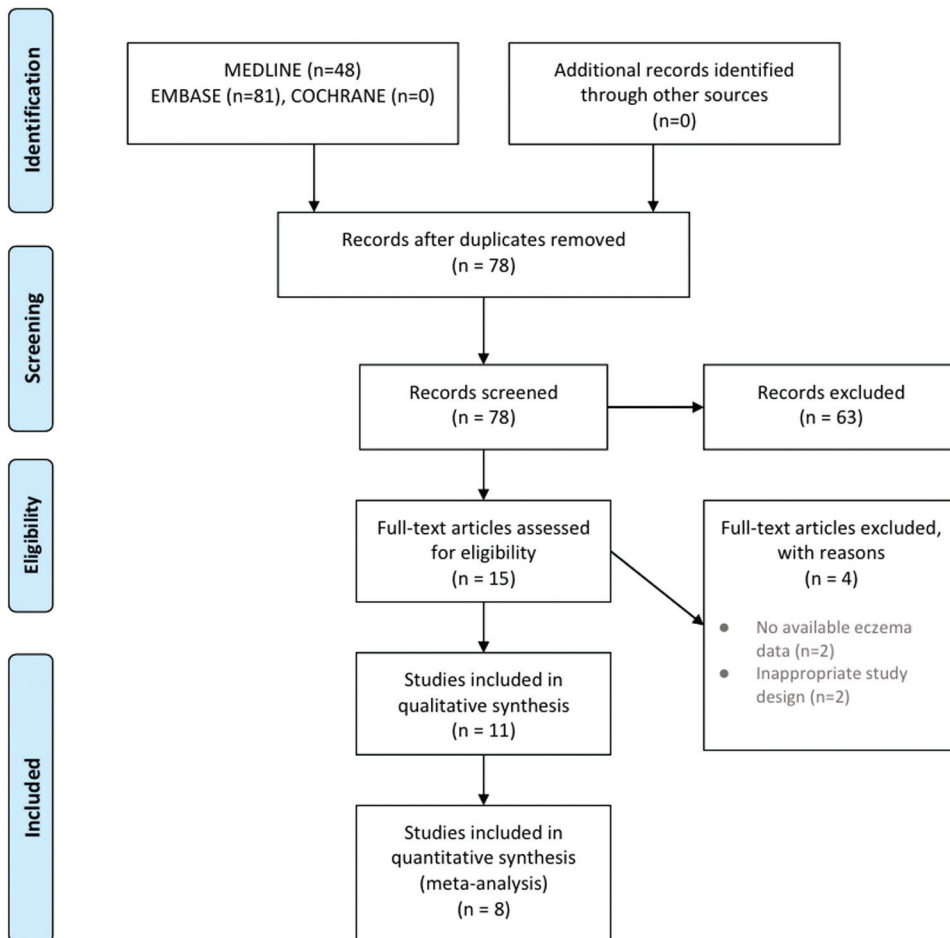


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

heterogeneity to be substantial.²⁵ We used the random-effects model in our meta-analysis. The potential for publication bias was assessed by using a funnel plot analysis and the weighted Egger regression test.

RESULTS

Study Selection and Characteristics

Our searches identified 129 potentially relevant studies by using a systematic search strategy. After the duplicate records were removed, 78 unique publications were reviewed with titles and abstracts according to our inclusion criteria. Of these, 63 articles were excluded: 1 non-English article, 2 conference abstracts, 15 animal or laboratory articles, 45 non-birth cohort studies (10 case-control studies, 4 case reports, 14 cross-sectional studies, 16 review articles and editorials, and 1 intervention study). Fifteen studies were identified for full-text review, and 11 articles^{20,21,26–34} were finally included in the systematic review because 2 studies did not have available eczema data and the other 2 studies were not birth cohort studies (Fig. 1). The characteristics of the included studies are presented in Table 1. Included studies originated

from Europe ($n = 5$),^{20,26,28,32,33} the United States ($n = 4$),^{27,29–31} and Asia ($n = 2$).^{21,34}

The study sample size ranged from 147 to 1024 mother-child pairs. All selected articles were from cohort studies that were published between 2012 and 2019. Both boys and girls were included in 10 studies,^{20,21,26,27,29–34} whereas 1 study²⁸ recruited only boys. The diagnosis of AD in the all included studies was assessed at ages 0–9 years by using the International Study of Asthma and Allergies in Childhood questionnaires, and the incidence of AD ranged from 9.7% to 34.6% during the study period. Quality assessment of all the studies by using the Newcastle–Ottawa scale had scores of ≥ 6 (Table 2). The congeners or metabolites of phthalates in the meta-analyses were as follows: mono-benzyl phthalate (MBzP), mono-(2-ethylhexyl) phthalate (MEHP), mono-ethyl phthalate (MEP), mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), and the sum of di-[2-ethylhexyl] phthalate (Σ DEHP).

Association between Prenatal Phthalate Exposure and Childhood AD

Of the 11 studies included in the systematic review, a total of 8 studies were included in the meta-analysis.

Table 1 Characteristics and key results of studies on the association between exposure to prenatal phthalates and the incidence of atopic dermatitis

Study, y	Country	No. Mother-Child Pairs	Age When Outcomes Were Assessed, y	Incidence of Case, %	Outcome Definition	Samples	Point Estimate	Phthalate Metabolites	Adjustment Variables
Herberth <i>et al.</i> , ²⁰ 2017	Germany	629	0–3	13.5	Validated questionnaires	Urine	OR	MEP, MiBP, MnBP, MBzP, MEHP	Sex, maternal AD, maternal smoking and/or ETS exposure at home, siblings, maternal education level, cat ownership, and breast-feeding until 6 mo
Steinmach <i>et al.</i> , ²⁶ 2015	Poland	147	2	12.4	Validated questionnaires	Urine	OR	MBzP, MEHP, MEP, MiBP, MnBP	Atopy in the family, paternal education level, frequency of house cleaning, and breast-feeding
Bamai <i>et al.</i> , ²¹ 2018	Japan	504	1.5, 3.5, and 7	14.9, 19.4, and 22.8	Validated questionnaires	Blood	β	MEHP	Maternal age at delivery, maternal history of allergies, and parity, sex
Berger <i>et al.</i> , ²⁷ 2019	U.S.	531	7	7	Validated questionnaires	Urine	OR	MBzP, MCNP, MCOP, MCPP, Σ DEHP	Maternal age, parity, household income as a proportion of poverty at baseline, child's family history of asthma, maternal education level
Somroo <i>et al.</i> , ²⁸ 2018	France	604	1, 2, 3, 4, and 5	9.7, 15.7, 21.0, 26.6, and 30.4	Validated questionnaires	Urine	OR	MEP, MBP, MiBP, MECP, MEHP, MEOP, MEHP, MBzP, MCOP, MCPE, MCNP, Σ DEHP	Parental asthma, rhinitis, eczema; maternal smoking; maternal age; maternal BMI; maternal education level; gestational age; no. siblings; and recruitment center
Just <i>et al.</i> , ²⁹ 2012	U.S.	407	2	30	Validated questionnaires	Urine	RR	MBzP	Prenatal exposure to environmental tobacco smoke, maternal age, maternal education, marital status, self-report of asthma, log total IgE, specific gravity, race and/or ethnicity, and sex
Berger <i>et al.</i> , ³⁰ 2018	U.S.	517	7	7	Validated questionnaires	Urine	OR	MEP, MnBP, MiBP	Maternal age, parity, season of birth, household income as a proportion of poverty at baseline, child's family history of asthma, active and passive smoking during pregnancy, furry pets in the home during pregnancy, housing density during pregnancy, sex
Buckley <i>et al.</i> , ³¹ 2018	U.S.	404	6–7	34.6	Validated questionnaires	Urine	OR	MEP, MnBP, MiBP, MCPP, MBzP, Σ DEHP	Creatinine, maternal age, race and/or ethnicity, pre-pregnancy BMI, education, marital status, type of home ownership, smoking during pregnancy, person in household with asthma, person in household with allergies, no. occupants in the home, pets in the home, sex

Table 1 Continued

Study, y	Country	No. Mother-Child Pairs	Age When Outcomes Were Assessed, y	Incidence of Case, %	Outcome Definition	Samples	Point Estimate	Phthalate Metabolites	Adjustment Variables
Smit <i>et al.</i> , ³² 2015	Greenland, Ukraine	1024	5–9	12.9	Validated questionnaires	Blood	OR	DEHP (MEOHP, MEHHP, MECPP), DiNP (MCiOP, MOiNP, MHNP)	Maternal allergy, smoking during pregnancy, educational level, maternal age, child's sex, child's age at follow-up, gestational age at blood sampling, parity, breast-feeding, birth weight
Gascon <i>et al.</i> , ³³ 2015	Spain	657	0.5, 1.5, 4, and 7	12.9, 18.7, 23.8, and 17.7	Validated questionnaires	Urine	RR	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP), MBzP, MEP, MiBP, MnBP	Maternal education, no. siblings, maternal smoking during pregnancy, maternal history of asthma and/or allergy and maternal BMI, sex
Wang <i>et al.</i> , ³⁴ 2014	Taiwan	483	2, 5	17.4 and 15.7	Validated questionnaires	Urine	OR	MEP, MBP, MEHP, MBzP	Sex, gestational age, maternal education, maternal history of atopy, and prenatal ETS exposure

OR = Odds ratio; MEP = monoethyl phthalate; MiBP = mono (2-isobutyl phthalate); MnBP = mono-n-butyl phthalate; MBzP = monobenzyl phthalate; MEHP = mono(2-ethylhexyl) phthalate; AD = atopic dermatitis; ETS = environmental tobacco smoke; MCNP = monocarboxy-isononyl phthalate; MCOP = monocarboxy-isononyl phthalate; MCPP = mono(3-carboxypropyl) phthalate; ΣDEHP = the sum of di (2-ethylhexyl) phthalates (MEHP, MEHHP, MEOHP, and MECPP); MBP = Monobutyl phthalate; MECPP = mono(2-ethyl-5-carboxypentyl) phthalate; BMI = body mass index; MEHHP = mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP = mono(2-ethyl-5-oxohexyl) phthalate; RR = relative risk; IgE = immunoglobulin E; DiNP = diisononyl; MCiOP = mono-(carboxy-iso-octyl) phthalate; MOiNP = mono-(oxo-iso-nonyl) phthalate; MHNP = mono-(hydroxyiso-nonyl) phthalate.

Table 2 Newcastle–Ottawa quality assessment of included studies

Study	Year	Selection	Comparability	Outcome or Exposure	Score*
Herberth <i>et al.</i> ²⁰	2017	★★★★	★★	★★	8
Stelmach <i>et al.</i> ²⁶	2015	★★★★	★★	★★★★	8
Bamai <i>et al.</i> ²¹	2018	★★★★	★★	★★	7
Berger (2019) <i>et al.</i> ²⁷	2019	★★★★	★★	★	7
Soomro <i>et al.</i> ²⁸	2018	★★★★	★★	★★	7
Just <i>et al.</i> ²⁹	2012	★★★★	★	★★	6
Berger (2018) <i>et al.</i> ³⁰	2018	★★★★	★★	★	7
Buckley <i>et al.</i> ³¹	2018	★★★★	★★	★★	8
Smit <i>et al.</i> ³²	2015	★★★★	★★	★★	8
Gascon <i>et al.</i> ³³	2015	★★★★	★★	★★	8
Wang <i>et al.</i> ³⁴	2014	★★★★	★★	★★	8

★★★★ = 4 scores; ★★ = 2 scores; ★★★ = 3 scores; ★ = 1 score.

*The score ranged from 0 to 9 (selection ≤ 4, comparability ≤ 2, outcome or exposure ≤ 3).

sis,^{20,26–28,30,31,33,34} excluding 3 articles that could not be synthesized (e.g., phthalate measurement from blood,^{21,32} and binary estimates.²⁹ A forest plot was used to address the association between prenatal phthalate exposure and AD development until age 7 years (Fig. 2). Our results suggested that MBzP exposure was significantly associated with the risk of AD development (OR 1.16 [95% CI, 1.04–1.31]; $I^2 = 17.36\%$) (Fig. 2 A). No significant results were observed in MEHP (OR 1.11 [95% CI, 0.94–1.31]; $I^2 = 58.1\%$), MEP (OR 1.10 [95% CI, 0.99–1.22]; $I^2 = 12.34\%$), MiBP (OR 1.21 [95% CI, 0.93–1.57]; $I^2 = 64.03\%$), MnBP (OR 1.03 [95% CI, 0.86–1.23]; $I^2 = 0\%$), and Σ DEHP (OR 1.04 [95% CI 0.99–1.09]; $I^2 = 0\%$) analyses (Fig. 2 B–F). Subgroup analyses performed of the studies^{20,26,28,33,34} that evaluated AD in early childhood (0–3 years old) are presented in Fig. 3; only prenatal exposure to MBzP had a significant association with the risk of early childhood AD (OR 1.22 [95% CI, 1.00–1.49]; $I^2 = 29.65\%$) ($p = 0.047$).

Publication Bias

Publication bias was not present for the pooled studies using the Egger test ($p > 0.078$). The funnel plot is shown in the Supplemental Fig. 1.

DISCUSSION

To the best of our knowledge, the present study was the first systematic review and meta-analysis on the association between prenatal exposure and childhood AD. Six types of urinary phthalate metabolites, including MBzP, MEHP, MEP, MiBP, MnBP, and Σ DEHP, were investigated in this meta-analysis. Analysis of the forest plot of MBzP with low heterogeneity ($I^2 = 17.36\%$) suggested that prenatal MBzP exposure was significantly positively associated with the develop-

ment of childhood AD (OR 1.16 [95% CI, 1.04–1.31]). In contrast, there were no significant associations between other urinary phthalate metabolites (MEHP, MEP, MiBP, MnBP, and Σ DEHP) and the development of childhood AD. Our results indicated that fetal exposure to phthalates may have acted as one of the environmental triggers that increased the risk of developing AD after birth.

Phthalates have often been classified into two groups based on their molecular weight. Among phthalate metabolites included in our study, MEP (urinary metabolites of diethyl phthalate) and MnBP (urinary metabolites of dibutyl phthalate) are low-molecular-weight phthalates, which are used as solvents in the manufacture of personal care products (e.g., cosmetics, shampoos, perfumes, and nail polish), paints, and adhesives.^{35,36} MEHP (urinary metabolites of DEHP), MiBP (urinary metabolites of diisobutyl phthalate), and MBzP (urinary metabolites of benzyl-butyl phthalate) are high-molecular-weight phthalates (ester side-chain lengths, five or more carbons), which are used as plasticizers in polyvinyl chloride products for building materials, medical devices, and food packaging.³⁷ Ingestion is believed to be the major route of exposure to DEHP³⁸; whereas dermal exposure to personal care products is known to be an important source of exposure to diethyl phthalate.³⁹ A Swedish study of 1674 pregnant women showed that polyvinyl chloride flooring in the kitchen and the parents' bedrooms was associated with higher levels of urinary MBzP in the first trimester.⁴⁰

In the present study, a positive correlation was only found between urinary MBzP concentrations and the development of AD in a meta-analysis. During the process of merging data for meta-analyses, the categorical scale of prenatal urinary phthalate exposure levels^{28,34} was converted to continuous scale. The transformed

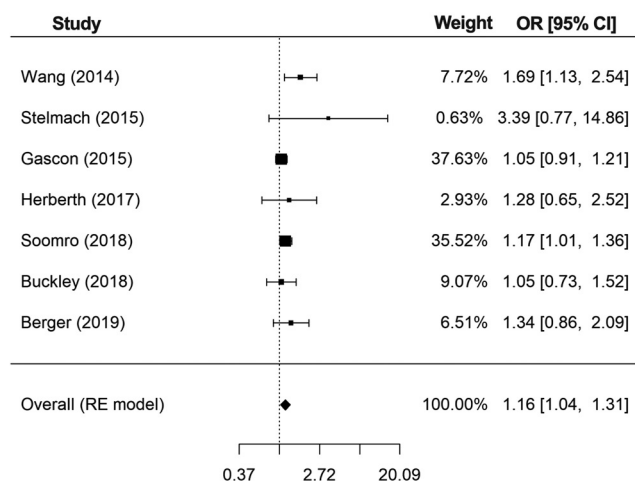
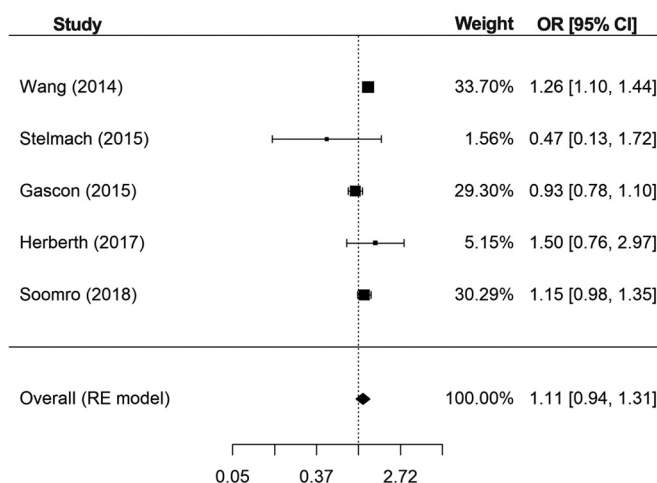
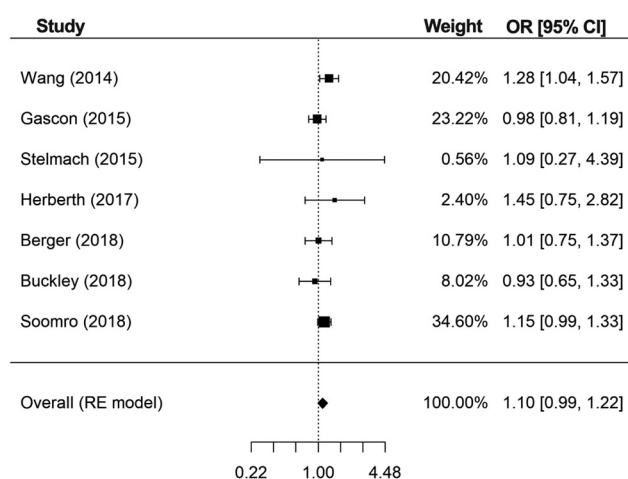
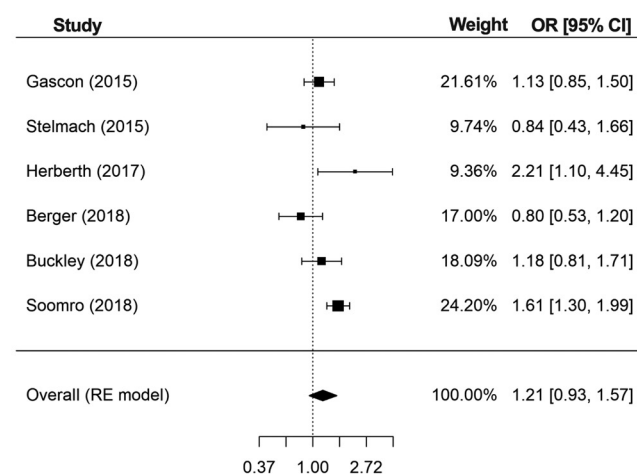
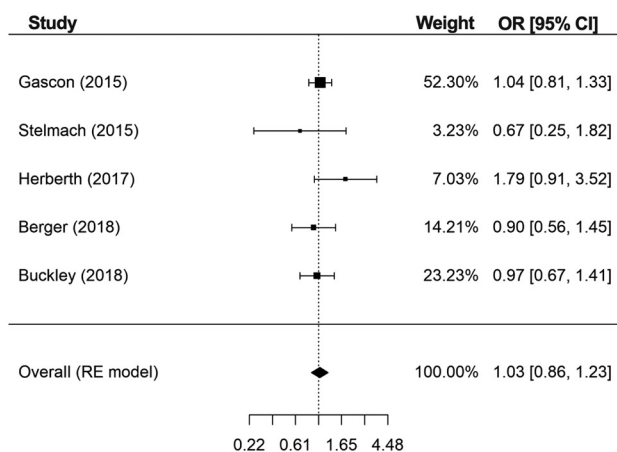
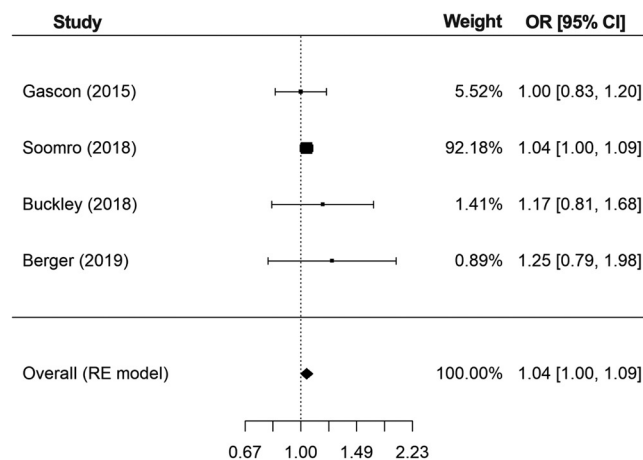
(A) MBzP**(B) MEHP****(C) MEP****(D) MiBP****(E) MnBP****(F) ΣDEHP**

Figure 2. A forest plot of the studies in the meta-analysis for the association between each prenatal phthalate metabolite and development of childhood atopic dermatitis (AD). (A) Monobenzyl phthalate (MBzP) and AD, (B) mono-(2-ethylhexyl) phthalate (MEHP) and AD, (C) monoethyl phthalate (MEP) and AD, (D) mono-isobutyl phthalate (MiBP) and AD, (E) mono-n-butyl phthalate (MnBP) and AD, and (F) the sum of di-[2-ethylhexyl] phthalate (ΣDEHP) and AD. RE model = Random-effects model.

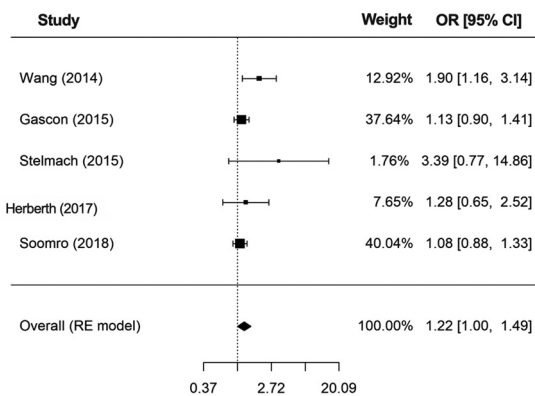
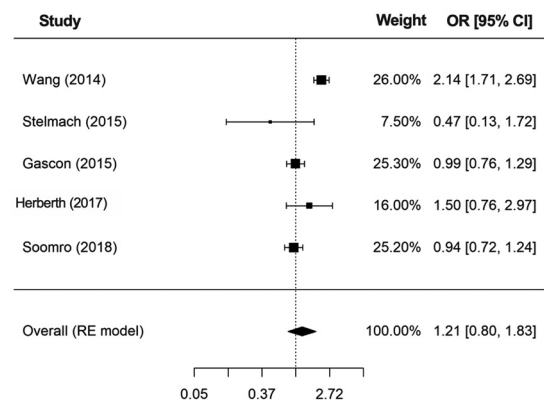
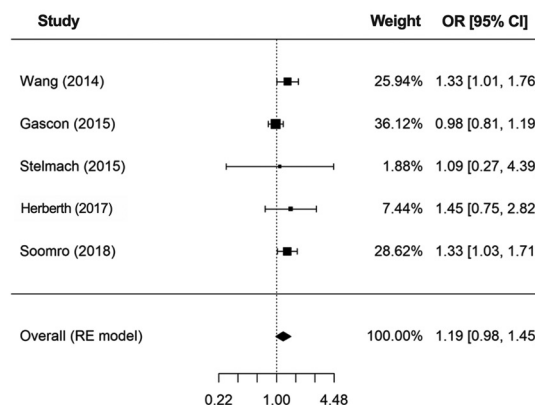
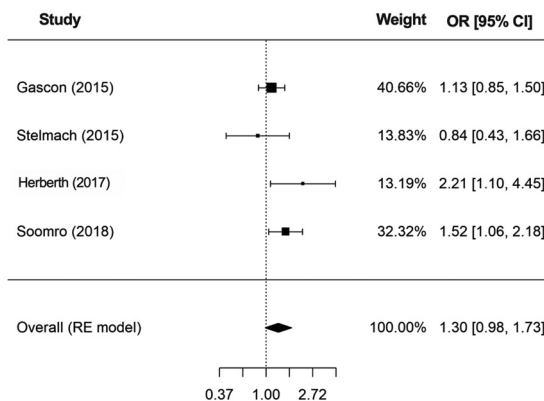
(A) MBzP**(B) MEHP****(C) MEP****(D) MiBP**

Figure 3. A forest plot of studies in the meta-analysis for association between each prenatal phthalate metabolite and development of early childhood atopic dermatitis (AD). (A) Monobenzyl phthalate (MBzP) and AD, (B) mono-(2-ethylhexyl) phthalate (MEHP) and AD, (C) monoethyl phthalate (MEP) and AD, and (D) mono-isobutyl phthalate (MiBP) and AD.

ORs might affect the overall results. However, the transformed ORs from these two studies were significant not only for MBzP but also for MEHP, MEP, and MiBP; nevertheless, only MBzP was significant in the meta-analysis. Indeed, the findings from a birth cohort study by Just *et al.*²⁹ also support our results by showing a significant association between prenatal exposure to MBzP and AD development at age 2 years, although this study was not included in the present meta-analysis because it was not possible to convert their data into a continuous scale. It remains unclear why only MBzP was found to be significant, but ethnic differences may be a reason because only Taiwan³⁴ and French²⁸ cohort studies showed significant associations. Other factors, such as housing type, lifestyle, or socioeconomic status of the patients, may contribute to a significant association between prenatal MPzP exposure and childhood AD. Because these factors could be more frequent and continuous exposure to benzylbutyl phthalate in their homes during pregnancy than to other phthalates. Unfortunately, we could not

confirm whether these risk factors are different among the studies included in the present meta-analysis.

The mechanism of AD development by prenatal phthalate exposure has been investigated in several studies. Prenatal and neonatal exposure of mice to DEHP induced AD-like skin lesions in dust mite allergen-sensitized offspring and upregulated the T-helper type 2 dominant expression of eosinophilic inflammation and mast cell degranulation.⁴¹ Larson *et al.*⁴² reported that dibutyl phthalate could drive T-helper type 2 responses after skin exposure *via* induction of thymic stromal lymphopoietin (*TSLP*) gene expression. Diisononyl phthalate aggravated AD-like skin lesions induced by house-dust mites in atopic-prone NC/Nga mice, which involved eosinophilic infiltration, mast cell degranulation, *TSLP* expression, activation of surface markers on bone marrow-derived dendritic cells, and enhanced production of thymus- and activation-regulated chemokine (TARC/CCL17) and macrophage-derived chemokine (MDC/CCL22)⁴³ In contrast, MBzP might increase the risk of eczema *via* a

nonallergenic mechanism. Just *et al.*²⁹ showed that there was no association between prenatal urinary MBzP and sensitization to indoor allergens or total immunoglobulin E in children with AD. A Canadian cohort study of pregnant women showed that urinary concentrations of MBzP were not significantly associated with the levels of cord blood immunoglobulin E, interleukin 33, and *TSLP* expression, which were known to be associated with the allergic immune response.⁴⁴

Our study was the first systematic review and meta-analysis of all relevant birth cohort studies to investigate the effect of prenatal exposure to phthalates on the development of childhood AD in the modern era where the use of phthalates is ubiquitous worldwide. It is meaningful to show the statistically significant association between prenatal exposure to MBzP and the development of AD. Nevertheless, our results should be interpreted with caution for several reasons. First, there was still a lack of related research until now; therefore, the number of studies analyzed in the present meta-analysis was small. Furthermore, it was difficult to pool the data because these studies used different samples with different exposure units at different time points. If more studies that use standardized protocols are reported in the future, then more objective results can be obtained through a systematic review and meta-analysis. Second, the size of effect by the exposure to MBzP was not much higher than those by exposure to other phthalates, which did not show statistical significance. In addition, the possibility of misclassification of outcomes may arise because all cohort studies evaluated outcomes by a parental report, which could cause a recall bias, although there were cohort studies that investigated a large number of subjects, and a validated questionnaire was used.

Moreover, the effect of the prenatal environmental factor on the incidence of AD may diminish over time, when children grow up. Of interest, the effects of MBzP, MEHP, MEP, and MiBP in our subgroup analysis at ages 0–3 years were similar to those of the entire meta-analysis. Third, most studies included in our meta-analysis evaluated phthalate metabolites by using a single spot urine sample, except the study by Gascon *et al.*,³³ in which the exposure levels were measured during the first and third trimesters of pregnancy. Measurement of urinary phthalate metabolites at a single time point does not reflect overall phthalate exposure during pregnancy because phthalates have short biologic half-lives and are rapidly excreted by urine.⁴⁵

CONCLUSION

In this meta-analysis, prenatal exposure to MBzP may be associated with AD development, although

other phthalate metabolites did not show statistical significance. Because of the heterogeneity and small number of studies, further research is needed to confirm the prenatal effect on childhood AD.

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