Effect of Prenatal Phthalate Exposure on Childhood Atopic Dermatitis: a Systematic Review and a Meta-analysis of Birth Cohort Studies

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Abstract

Background: The association between prenatal exposure to phthalate and childhood atopic dermatitis (AD) has been previously investigated; however, the results are inconsistent. 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 the MEDLINE, Embase, and Cochrane library databases. Studies were critically appraised, and meta-analyses were performed.

Results: Among 129 articles identified, 11 studies met the eligibility criteria. Included studies originated from Europe (n = 5), USA (n = 4), and Asia (n = 2). The study sample size ranged from 147 to 1024 mother-child pairs. Quality assessment using the Newcastle–Ottawa scale of all studies had scores of six or greater. 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 > 0.05).

Conclusions: Our study suggests a positive association between prenatal exposure to MBzP and the development of childhood AD.

Introduction

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. Recent studies have 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] Several 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 exposure to phthalates during pregnancy is associated with the development AD in childhood.[20, 21]

However, epidemiological 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

Database search and study selection

We systematically searched the MEDLINE (1946 to 26th May 2019), Embase (1947 to 26th May 2019), and Cochrane (1947 to 26th May 2019) databases 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, Pennsylvania, USA) was used to manage the references extracted from the databases. Studies could be cohort, case-control, or cross-sectional designs. Duplicates from different database searches were removed and transferred to a duplicated library.

Two reviewers (YMP and MJ) independently and in duplicate, screened titles and abstracts 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 providing the incidence of AD data. Exclusion criteria were (1) animal or laboratory studies, (2) non- English studies, (3) studies not presenting original data (conference, review articles, editorials, guidelines, and reports), and (4) studies measuring phthalate not from humans. The primary outcome was the incidence of AD in children. A protocol of this study is registered online at Prospero (registration number CRD42020158654).

Data extraction

Two reviewers (MJ and JK) independently extracted data and the discrepancy was resolved in consultation with an expert investigator (KA). The following data were extracted from all articles using a data-extraction sheet: first author, year of publication, study design, country, sample characteristics (age, sex, and sample size), exposure characteristics (phthalate metabolite and its specimen, units of concentration in phthalate, timing at measurement of phthalate), and outcome characteristics (assessment timing to diagnose AD). Relative risk, odds ratio (OR), and 95% confidence interval (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 (NOS) to assess the quality of nonrandomized studies including case-control and cohort. The system allowed for a maximum of nine points which indicates the highest quality, with scores of six or higher 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 using R 3.6.1 (Vienna, Austria; http://www.R-project.org/), package 'metafor.' Only studies with similar exposure to phthalate metabolites were used for meta-analysis. Studies with clinical or different methodological heterogeneity were excluded when pooling the data to improve comparability among studies. A meta-analysis was performed for every specific compound whenever three or more compounds estimated with heterogeneity compatible to a meta-analysis were available. 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 using forest plots. The OR from a study with categorical exposure was transformed to OR for the continuous scale exposure using weighted linear regression of the central values between the categories of exposure on the corresponding ORs. After pooling ORs from exclusive age groups[22], 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's Q test was less than 0.10 and I^2 exceeded 50%, we considered heterogeneity to be substantial.[23] We used the random-effect model in our meta-analysis. The potential for publication bias was assessed using a funnel plot analysis and the weighted Egger's regression test.

Results

Study selection and characteristics

Our searches identified 129 potentially relevant studies 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. Fifteen studies were identified for full text-review, and 11 articles were finally included in the systematic review because two studies did not have available eczema data and the other two 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), USA (n = 4), and Asia (n = 2). The study sample size ranged from 147 to 1024 mother-child pairs. All selected articles were from cohort studies which were published between 2012 and 2019. Both boys and girls were included in 10 studies, whereas one study recruited only boys. The diagnosis of AD in the included studies was assessed at age 0–9 years using the International Study of Asthma and Allergies in Childhood (ISSAC) questionnaires and the incidence of AD ranged from 9.7–34.6% during the study period. Quality assessment of all studies using the NOS scale had scores of six or greater (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 (ΣDEHP).

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

Authors (year)	Country	No. of mother-child pairs	Age at which the outcomes were assessed (years)	Incidence of cases (%)	Outcome definition	Samples	Point estimate	Phthalate metabolites	Adjustment variables
Herberth *et al.* (2017) [20]	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 months
Stelmach *et al.* (2015) [24]	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 breastfeeding
Bamai *et al.* (2018) [21]	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
Berger *et al.* (2019) [25]	USA	531	7	7	validated questionnaires	Urine	OR	MBzP, MCNP, MCOP, MCPP, ∑DEHP	maternal age, parity, household income as a proportion of poverty at baseline, child's family history of asthma, maternal education level, MCPP, MiBP, and MnBP
Soomro *et al.* (2018) [26]	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, MECPP, MEHHP, MEOHP, MEHP, MBzP, MCOP, MCPP, MCNP, ∑DEHP	parental asthma/rhinitis/eczema, maternal smoking, maternal age, maternal BMI, maternal education level, gestational age, number of siblings, and recruitment center
Just *et al.* (2012) [32]	USA	407	2	30	validated questionnaires	Urine	RR	MBzP	specific gravity, race/ethnicity, and sex
Berger *et al.* (2018) [27]	USA	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, MCPP, MiBP, and MnBP

Abbreviations; AD, atopic dermatitis; OR, odds ratio; RR, relative risk; β, beta coefficient; BMI, body mass index;; ∑DEHP, the sum of di (2-ethylhexyl) phthalate (MEHP, MEHHP, MEOHP, and MECPP); DiNP, diisononyl; ETS, environmental tobacco smoke; ISSAC, International Study of Asthma and Allergies in Childhood; MBzP, monobenzyl phthalate; MCiOP, ono-(carboxy-iso-octyl) phthalate; MCNP, monocarboxy-isononyl phthalate; MCOP, monocarboxyisooctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEP, monoethyl phthalate; MHiNP, mono-(hydroxyiso-nonyl) phthalate; MiBP, mono (2-isobutyl phthalate); MnBP, mono-n-butyl phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MOiNP, mono-(oxo-iso-nonyl) phthalate

Authors (year)	Country	No. of mother-child pairs	Age at which the outcomes were assessed (years)	Incidence of cases (%)	Outcome definition	Samples	Point estimate	Phthalate metabolites	Adjustment variables
Buckley *et al.* (2018) [28]	USA	404	6–7	34.6	validated questionnaires	Urine	OR	MEP, MnBP, MiBP, MCPP, MBzP, ∑DEHP	creatinine, maternal age, race/ethnicity, pre-pregnancy BMI, education, marital status, type of home ownership, smoking during pregnancy, person in household with asthma, person in household with allergies, number of occupants in the home, and pets in the home
Smit *et al.* (2015) [31]	Greenland, Ukraine	1024	5–9	12.9	validated questionnaires	Blood	OR	DEHP (MEOHP. MEHHP, MECPP), DiNP (MCiOP, MOiNP, MHiNP)	maternal allergy, smoking during pregnancy, educational level, maternal age, child sex, child age at follow-up, gestational age at blood sampling, parity, breastfeeding, birthweight
Gascon *et al.* (2015) [29]	Spain	657	0.5, 1.5, 4, and 7	12.9, 18.7, 23.8, and 17.7	validated questionnaires	Urine	RR	∑DEHP (MEHP, MEHHP, MEOHP, MECPP), MBzP, MEP, MiBP, MnBP	maternal education, number of siblings, maternal smoking during pregnancy, maternal history of asthma/allergy and maternal BMI
Wang *et al.* (2014) [30]	Taiwan	483	2, 5	17.4 and 15.7	validated questionnaires	Urine	OR	MEP, MBP, MEHP, MBzP	gender, gestational age, maternal education, maternal history of atopy, and prenatal ETS exposure

Abbreviations; AD, atopic dermatitis; OR, odds ratio; RR, relative risk; β, beta coefficient; BMI, body mass index;; ∑DEHP, the sum of di (2-ethylhexyl) phthalate (MEHP, MEHHP, MEOHP, and MECPP); DiNP, diisononyl; ETS, environmental tobacco smoke; ISSAC, International Study of Asthma and Allergies in Childhood; MBzP, monobenzyl phthalate; MCiOP, ono-(carboxy-iso-octyl) phthalate; MCNP, monocarboxy-isononyl phthalate; MCOP, monocarboxyisooctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEP, monoethyl phthalate; MHiNP, mono-(hydroxyiso-nonyl) phthalate; MiBP, mono (2-isobutyl phthalate); MnBP, mono-n-butyl phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MOiNP, mono-(oxo-iso-nonyl) phthalate

Table 2
Newcastle–Ottawa quality assessment of included studies

Study	Year	Selection	Comparability	Outcome/Exposure	Score
Herberth *et al.*[20]	2017	□□□□	□□	□□	8
Stelmach *et al.*[24]	2015	□□□□	□□	□□□	8
Bamai *et al.*[21]	2018	□□□□	□□	□□	7
Berger *et al.* [25]	2019	□□□□	□□	□	7
Soomro *et al.*[26]	2018	□□□	□□	□□	7
Just *et al.*[32]	2012	□□□	□	□□	6
Berger *et al.*[27]	2018	□□□□	□□	□	7
Buckley *et al.*[28]	2018	□□□□	□□	□□	8
Smit *et al.*[31]	2015	□□□□	□□	□□	8
Gascon *et al.*[29]	2015	□□□□	□□	□□	8
Wang *et al.*[30]	2014	□□□□	□□	□□	8
The score ranged from 0 to 9 (selection ≤ 4, comparability ≤ 2, outcome or exposure ≤ 3).					

Association between prenatal phthalate exposure and childhood AD

Of the 11 studies included in the systematic review, a total of eight studies were included in the meta-analysis,[20, 24–30] excluding three papers that could not be synthesized (e.g., phthalate measurement from blood,[21, 31] and binary estimates.[32] The forest plot addresses the association between prenatal phthalate exposure and AD development until age 7 years (Fig. 2). Our results suggest 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. 2A). 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 ΣDEHP (OR 1.04, 95% CI 0.99–1.09, I^2 = 0%) analyses (Fig. 2B-F). Subgroup analyses performed for early-onset AD is presented in Table 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%).

Table 3
Subgroup analyses among prenatal phthalate exposure and the risk of early-onset atopic dermatitis

Phthalates	Number of studies	OR (95% CI)	*P*-value	I^2 (%)
MBzP	5	1.22 (1.00–1.49)	0.047	29.65
MEHP	5	1.21 (0.80–1.83)	0.373	84.17
MEP	5	1.19 (0.98–1.45)	0.074	39.48
MiBP	4	1.30 (0.98–1.73)	0.065	37.57
All analyses were performed using a random effect model				
OR: odds ratio; CI: confidence interval; MBzP; monobenzyl phthalate, MEHP; mono(2-ethylhexyl) phthalate, MEP; monoethyl phthalate, MiBP; mono (2-isobutyl phthalate)				

Publication bias

Publication bias was not shown as judged by no significant Egger regression test for any of the above-mentioned outcomes ($P \geq 0.078$). The funnel plot is shown in Supplemental Figure S1.

Discussion

To the best of our knowledge, the present study is 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 ΣDEHP were investigated in this meta-analysis. The forest plot of MBzP with low heterogeneity (I^2 = 17.36%) suggests that prenatal MBzP exposure was significantly positively associated with the development 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 ΣDEHP) and the development of childhood AD. Our result indicates that fetal exposure to phthalate may act as one of the environmental triggers that increase 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.[33, 34] MEHP (urinary metabolites of DEHP), MiBP (urinary metabolites of diisobutyl phthalate), and MBzP (urinary metabolites of benzylbutyl phthalate) are high molecular weight phthalates (ester side-chain lengths, five or more carbon) which are used as plasticizers in polyvinyl chloride products for building materials, medical devices, and food packaging.[35] Ingestion is believed to be the major route of exposure to DEHP,[36] whereas dermal exposure to personal care products is known to be an important source of exposure to diethyl phthalate.[37] A Swedish study of 1,674 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.[38]

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-analysis, the categorical scale of prenatal urinary phthalate exposure levels was converted to a continuous scale following Soomro *et al*.[26] and Wang *et al*.[30] The transformed OR might affect the overall results. However, the transformed OR from those two studies were significant not only for MBzP but also for MEHP, MEP, and MiBP; nevertheless, only MBzP was significant in a meta-analysis. Indeed, the findings from a birth cohort study by Just *et al*.[32] also support our results by showing 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 to a continuous scale. It remains unclear why only MBzP was found to be significant, but ethnic differences may be a reason because only Taiwan and French cohort studies showed significant associations.[26, 39] Other factors such as housing type, lifestyle, or socioeconomic status of the patients may contribute to a statistical significance if these factors cause 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 2-dominant expression of eosinophilic inflammation and mast cell degranulation.[40] Lanson *et al*.[41] reported dibutyl phthalate could drive T helper 2 responses following skin exposure via induction of thymic stromal lymphopoietin (TSLP) gene expression. Diisononyl phthalate aggravated AD-like skin lesion induced by house dust mites in atopic-prone NC/Nga mice, which involves 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)[42] In contrast, MBzP might increase the risk of eczema via a nonallergenic mechanism. Just *et al*.[32] showed that there was no association between prenatal urinary MBzP and sensitization to indoor allergens or total IgE in children with AD. A Canadian cohort study of pregnant women showed that urinary concentration of MBzP was not significantly associated with the levels of cord blood IgE, IL33, and TSLP expression which were known to be associated with allergic immune response.[43]

The strength of this study is that it is the first systematic review and meta-analysis of all relevant birth cohort studies to investigate the effect of prenatal exposure to phthalate on the development of childhood AD. Nonetheless, our review had several limitations. There was a lack of papers reported till date; therefore, the number of studies in the present meta-analysis was small. Furthermore, it was hard to pool the data because they used different exposure units and different measured samples of exposure. If more studies are reported in the future, more objective results can be observed through a systematic review and meta-analysis. Another limitation is that most studies included in our meta-analysis evaluated phthalate metabolites using a single spot urine sample except Gascon *et al*.[29] 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 that are rapidly excreted by urine.[44] Nevertheless, our observation that MBzP showed statistical significance could further provide strong support to the premise that prenatal MBzP exposure is associated with the occurrence of AD in children.

Conclusion

This meta-analysis showed that prenatal MBzP exposure is associated with the development of childhood AD. Our results suggest that minimizing the exposure of MBzP during pregnancy may be needed to prevent the development of AD.

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent publication

Not applicable

Availability of supporting data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare pertaining to this article.

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Author's contributions

YMP, JK, MK, JYL and KA contributed to the conception and design of the study. MJ, YK, MK, MJK, SK, MK, JYL and JK researched the strategies and performed database searches for related articles. MJ, YMP and KA identified the studies for inclusion. MJ, JK and KA extracted the data and assessed the quality of the included studies. MJ, MJK, MK, JYL, HIJ and BRL contributed to the interpretation of the results. MJK and SK performed the meta-analysis. MJ wrote the first draft of the paper. YMP and KA finalized the paper. All authors reviewed and approved the final version of the manuscript. MJ, JK, YMP, and KA had full access to all of the data in the study. YMP and KA had final responsibility for the decision to submit for publication.

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Figures

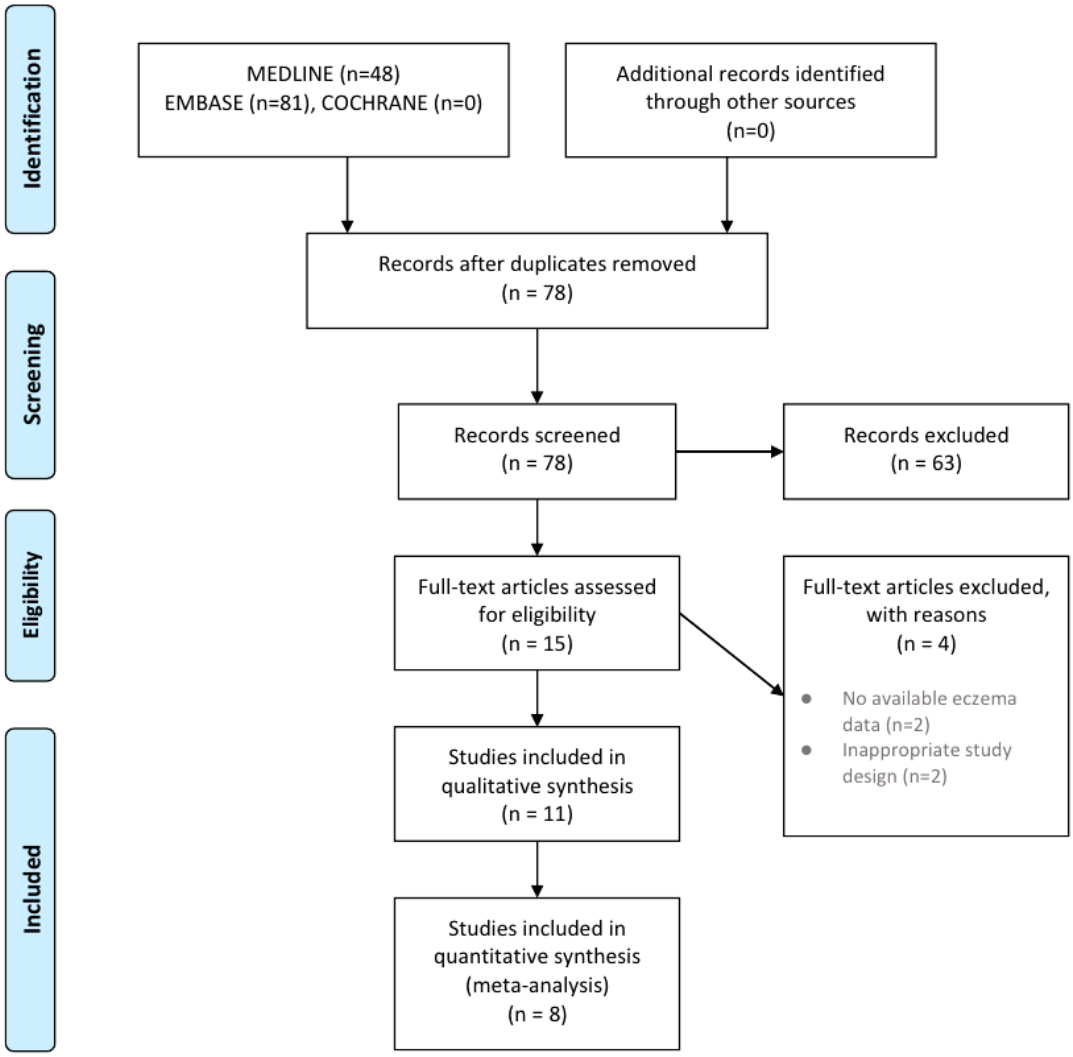
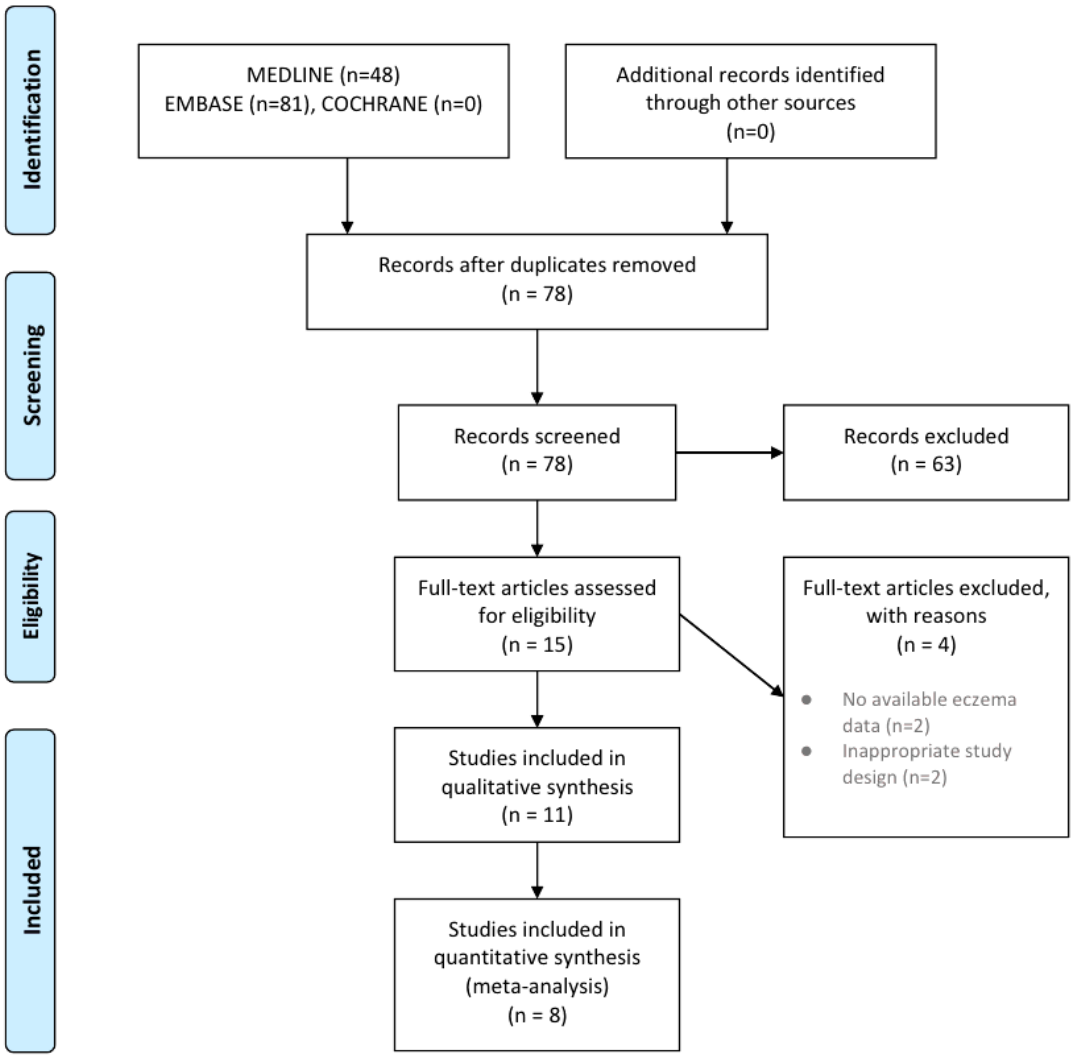


Figure 1

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram



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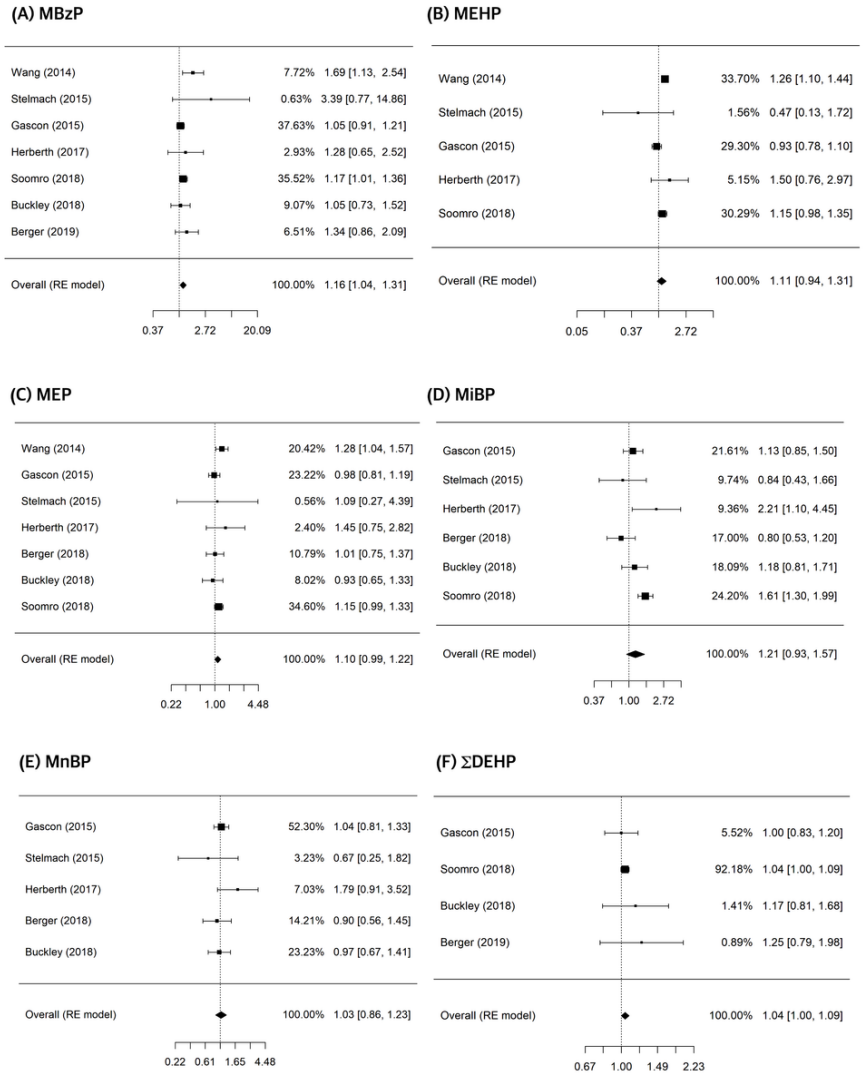
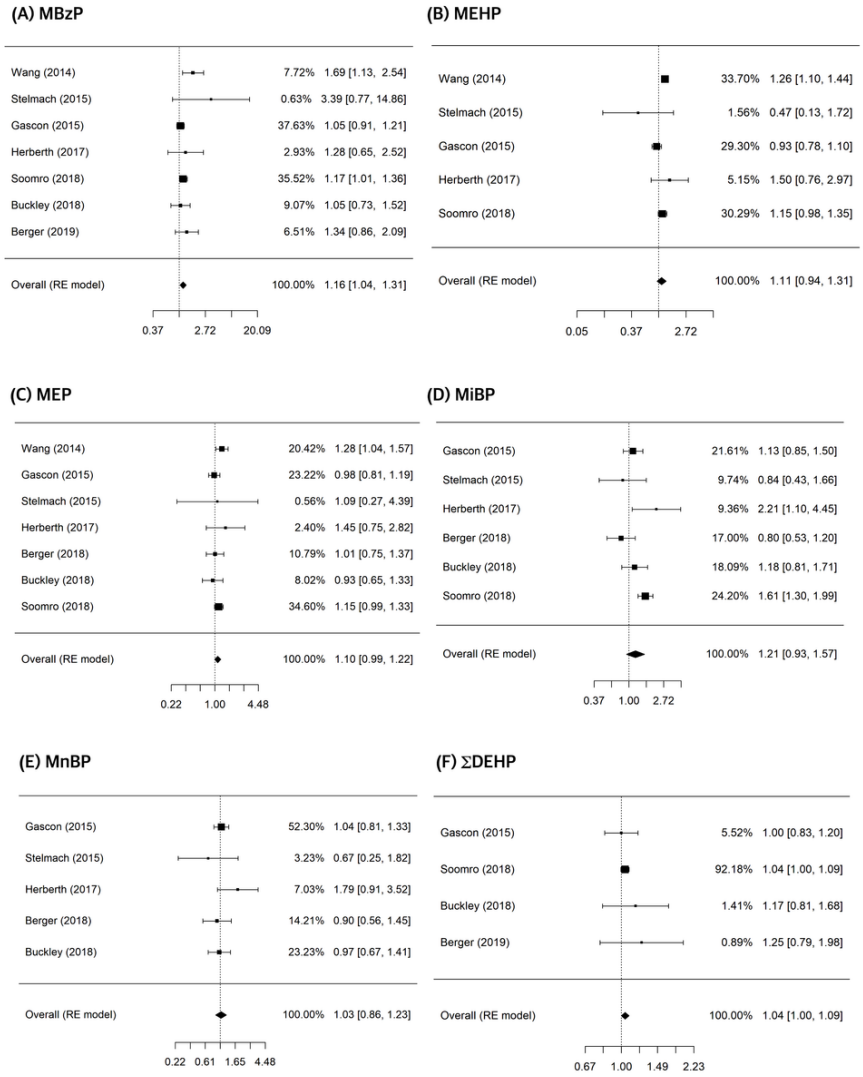


Figure 2

Forest plot of studies in the meta-analyses for 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-effect model.



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