Original Article

Prenatal and postnatal exposure to Bisphenol A and Asthma: a systemic review and meta-analysis

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Background: Bisphenol A (BPA) is a plasticizer with high production and ubiquitous usage in polycarbonate plastics and epoxy resins. The association between prenatal or postnatal exposure to BPA and childhood wheeze/asthma has not been well established. Our study aimed to provide further justification for the current studies.

Methods: Studies were searched from PubMed, Web of Science, Scopus and Embase from inception until Sep 15, 2020. Meta-analysis was performed to calculate pooled adjusted odds ratios (aOR). The methodological quality of included studies was assessed by using the Newcastle Ottawa Scale (NOS).

Results: Of 2,814 screened articles, 9 studies with 3,885 participants were included in the final analysis. When all studies were pooled, postnatal exposure to BPA was associated with a higher risk of childhood asthma (aOR =1.43; 95% CI: 1.28–1.59) or childhood wheeze (aOR =1.38; 95% CI: 1.18–1.62). Prenatal exposure to BPA had a small but significant increased risk of childhood asthma (aOR =1.17; 95% CI: 1.01–1.34). An increased risk of childhood wheeze was related to prenatal exposure to BPA at 16 weeks' gestation (aOR =1.29; 95% CI: 1.07–1.55), but not at 26 weeks' gestation (aOR =1.07; 95% CI: 0.88–1.29) nor at random-time gestation (aOR =1.02; 95% CI: 0.89–1.16).

Conclusions: Prenatal and postnatal exposure to BPA was related to an increased risk of childhood asthma. However, only postnatal and early gestational exposure (at 16 weeks) to BPA could induce the risk of childhood wheeze, but not late gestational exposure (at 26 weeks).

Keywords: Bisphenol A (BPA); asthma; wheeze; children; meta-analysis

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Introduction

Asthma is one of the most significant pediatric diseases in the world (1,2). Its prevalence in children has increased dramatically over a relatively short period of time, which is suspected to be associated with the expanded urbanization and industrialization (2-5). Given that increase of asthma shares an approximately similar timeframe with widespread use of industrial chemicals, some researchers have hypothesized that industrial chemicals may be significant

contributors to the rising trend of pediatric asthma (6).

Bisphenol A (BPA), a critical endocrine disrupting chemical, has gained a lot of attention recently for its ubiquitous exposure (7). It is produced in large quantities and used in manufacture of polycarbonate plastics (toys, water bottles, dental sealants, *et al.*) or epoxy resins (coating the insides of cans for beverages and food) (8,9). International biomonitoring evidences show that there is higher BPA exposure in children than in adults and BPA exposure affects more than 90% of all children in America, Asia, Europe and Australia (10). The continuous daily BPA exposure, numerous BPA sources and various BPA exposure routes (mouth, skin and inhalation) cannot be ignored, although it is at low-level concentration in human body and is rapidly metabolized and excreted (7,10,11).

Prenatal and postnatal BPA exposure should be paid more attention to because the high dietary intake and long-term indoors time of pregnancy women/young children and hand to mouth behaviors for food consumption of infants and toddlers (10). Moreover, the immaturity of children's lungs and immune systems might make irreversible, deleterious and long-lasting impact on allergic manifestation later in life (12).

Some animal evidences have confirmed that BPA had the immunomodulatory ability to influence the balance of Th1 and Th2 immune responses by increasing IL4 and reducing IFN-γ, IL10 (13-16). However, clinical studies which investigated the association between prenatal or postnatal exposure to BPA and childhood wheeze/asthma have inconsistent results (17-25). Therefore, our systemic review and meta-analysis aimed to provide further justification for the current studies.

We present the following article/case in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1550).

Methods

Our systemic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISRM) (26).

Data sources and search strategy

We performed a systematic search by using some databases including PubMed, Web of Science, Scopus and Embase from the databases' inceptions until Sep 15, 2020. The following search items were applied in the search for eligible studies: ("bisphenol A" or "BPA" or "endocrine disrupting chemical" or "endocrine disrupting compounds" or "endocrine disruptors" or "EDCs") and ("prenatal" or "maternal" or "postnatal") and ("asthma" or "wheeze" or "wheezing") and ("offspring" or "children" or "childhood" or "child" or "infant" or "infancy"). Reference lists of identified articles were scanned to avoid omission.

Study selection

All studies that fulfilled the following inclusion criteria were considered: (I) study investigation: the association between prenatal or postnatal exposure to BPA and the risk of childhood asthma or wheeze. (II) Study data: results should be reported as adjusted odds ratio (aOR) or adjusted relative risk (aRR) or adjusted hazard ratio (aHR) with the corresponding 95% confidence intervals (95% CIs). (III) Study language: only articles written in English. (IV) Studies type: original articles. The exclusion criteria were studies with no available data for outcome measures.

Data extraction and quality assessment

Two reviewers (M Wu and Q Weng) reviewed all included studies and extracted crucial information by using a data extraction form independently. The information included author, country, sample size, enrolling period, exposure detection, outcome measure, asthma assessment, pregnancy trimester, point estimate, results adjustment and so on. Quality of the included studies was assessed by Newcastle Ottawa Scale (NOS) (27). We regarded total scores of 0 to 3, 4 to 6, 7 to 9 as low, moderate, and high quality, respectively. A star assessment system was applied to evaluate the quality according to NOS.

Statistical analysis

We used aOR and corresponding 95% CIs for meta-analysis to assess the association between prenatal or postnatal exposure to BPA and the risk of childhood asthma or wheeze. Heterogeneity between studies was identified by the I^2 statistic. We assigned I^2 values of 25%, 50%, and 75% for low, moderate, and high heterogeneity, respectively. Random-effect meta-analysis was performed to calculate a pooled aOR if I^2>50% otherwise fixed-effect was used. When there was high heterogeneity, sensitivity analysis would be conducted to find out which study contributed to the largest heterogeneity. Egger's test and Begg's test were performed to evaluate potential publication bias. All analyses were conducted by

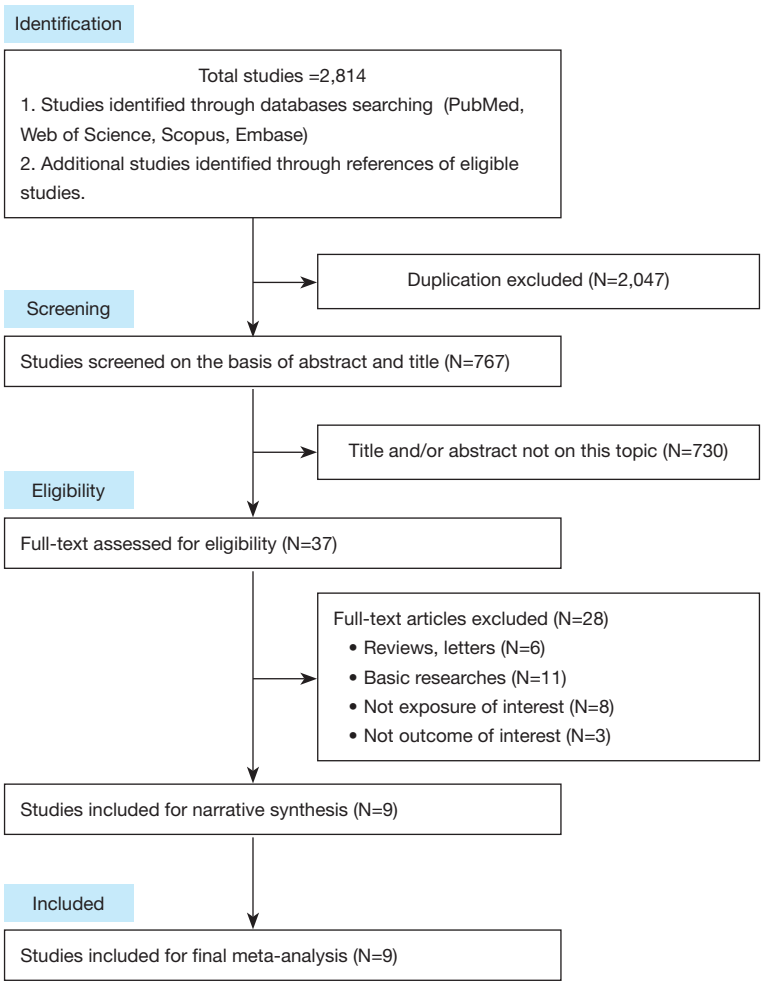

Figure 1 Flow diagram for search strategy.

StataSE12.0. A P value <0.05 could help make conclusion that the result was statistically significant.

Results

Eligible studies and characteristics

There were totally 2,814 studies identified from databases. Of these, the first screening excluded 2,047 duplications and 730 studies based on title and/or abstract, leaving 37 studies for full-text review. Finally, we found that nine studies satisfied inclusion criteria for meta-analysis. The detailed steps of the study selection process are shown in *Figure 1*. Detailed characteristics of the included studies were demonstrated in *Tables 1,2*. All included studies were cohort studies. Urine samples were used for BPA exposure detection. Asthma or wheeze measure was identified mainly on the basis of questionnaires. Five studies (17-21) merely focused on prenatal exposure and two studies (22,23) only talked about postnatal exposure. Others (totally 2 studies) paid attention to both prenatal and postnatal exposure (24,25). Of the 9 studies, Wang *et al.* (22), Kim *et al.* (23), Donohue *et al.* (24) and the 2 studies from Spanier *et al.* (21,25) conducted several time-point exposure measurements, which offered us more data to do meta-analysis. The methodological quality of the 9 studies were assessed according to the NOS tool (Table S1). Furthermore, we also summarized the limitations of each included studies (Table S2).

Results of meta-analysis

Prenatal exposure to BPA and childhood asthma

Of these studies identified, 5 reported the association

Table 1 General characteristics of included studies

Author (year)	Country	Sample	Enrolling period	Exposure detection		Outcome measure	Asthma/wheeze assessment	Pregnancy trimester	Effect size	NOS score
				Source	Period					
Berger K (2019) (17)	California, USA	329	1999–2000	Urine	Prenatal	Asthma	Questionnaires	NA	aOR	8
Buckley JP (2018) (18)	New York, USA	404	1998–2002	Urine	Prenatal	Asthma	Questionnaires	NA	aOR	8
Vernet C (2017) (19)	Nancy/Poitiers, France	587	NA	Urine	Prenatal	Asthma wheeze	Questionnaires	NA	aHR	8
Wang IJ (2016) (22)	Taiwan, China	453	NA	Urine	Postnatal	Asthma	Questionnaires	NA	aOR	8
Gascon M (2015) (20)	Catalonia, Spain	654	2004–2008	Urine	Prenatal	Asthma wheeze	Questionnaires	NA	aRR	8
Spanier AJ (2014) (25)	Ohio, USA	398	2003–2006	Urine	Prenatal postnatal	Wheeze	Questionnaires	16 weeks 26 weeks	aOR	8
Kim KN (2014) (23)	Seoul, Korea	127	2005–2009	Urine	Postnatal	Asthma wheeze	Questionnaires	NA	aOR	8
Donohue KM (2013) (24)	New York,USA	568	1998–2006	Urine	Prenatal postnatal	Asthma wheeze	Wheeze by questionnaires at 5,6,7y and asthma by physicians once between 5y and 12y.	NA	aOR	9
Spanier AJ (2012) (21)	Ohio, USA	365	2003–2006	Urine serum	Prenatal	Asthma wheeze	Questionnaires and ige levels	16 weeks; 26 weeks	aOR	8

All studies were designed as cohort studies. BPA, Bisphenol A; NA, not available; aOR, adjusted odds ratio; aRR, adjusted rate ratio; aHR, adjusted hazard ratio; NOS, the New Castle-Ottawa Scale for cohort studies.

Table 2 Detailed characteristics of included studies

Author	Exposure measures	Questionnairemeasure time	Wheeze	Asthma	Adjustment
Prenatal					
Berger K (2019) (17)	Maternal urinary samples: at 16 and 26 weeks' gestation	Children' age at 7 years	NA	aOR, 1.03 (0.68–1.55)	Maternal age, parity, household income as a proportion of poverty at baseline, child's family history of asthma, maternal education, monocarboxyisooctyl phthalate, propyl paraben, 2,4-dichlorophenol
Buckley JP (2018) (18)	Maternal urinary samples at third trimester (31.5±5.1 weeks)	Children' age between 6 and 7 years	NA	aOR,1.66 (1.04–2.66); boys: aOR,3.04 (1.38–6.68); girls: aOR, 0.94 (0.48–1.84)	Creatinine, maternal age, race/ethnicity, pre-pregnancy body mass index, 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, pets in the home, age at follow-up, and child's sex
Vernet C (2017) (19)	Maternal urinary samples: once during 23–29 gestational weeks	Children' ages from 8 months until 5 years	Only male offspring aHR, 0.97 (0.82–1.15)	Only male offspring; aHR, 1.23 (0.97–1.55)	Center, residence area, parental history of asthma or allergies, maternal ethnicity, maximal parental education level, maternal or passive smoking during pregnancy, postnatal passive smoking, older siblings, and child care
Gascon M (2015) (20)	Maternal urinary samples: at 12 and 32 weeks' gestation	Children' ages from birth until 7y	From birth until 7y: aRR, 1.20 (1.03–1.40)	At 7y: aRR, 1.21 (0.94–1.57)	Maternal education, number of siblings and maternal smoking during pregnancy
Spanier AJ (2014) (25)	Maternal urinary samples: at 16 and 26 weeks' gestation	Children' ages from birth until 5 years every 6 months	BPA (16 weeks): aOR, 1.79 (1.16–2.78); BPA (26 weeks): aOR, 1.06 (0.65–1.74); BPA (every 10-fold increase); aOR, 1.55 (0.91–2.63)	NA	Prenatal tobacco exposure, season, breastfeeding history, family history of asthma, family history of allergy, child eczema, child allergy, birth weight, maternal parity, pet ownership, and cockroach exposure
Donohue KM (2013) (24)	Maternal urinary samples at third trimester (31.5±5.1 gestational weeks)	Children' ages at 5, 6 and 7 years	Wheeze (5y): aOR, 0.7 (0.5–0.9); wheeze (6y): aOR, 0.8 (0.5–1.3) wheeze (7y): aOR, 0.8 (0.5–1.1)	aOR, 0.8 (0.5–1.1)	Maternal history of asthma, sex, race/ethnicity, prenatal and postnatal environmental tobacco smoke exposure, and urine specific gravity. Models for asthma were additionally controlled for the child's age at the time of evaluation because this assessment was performed once per child between ages 5 and 12 years
Spanier AJ (2012) (21)	Maternal urine and serum samples: at enrollment (15.9±1.9 weeks/gestation), 26 gestational weeks, and birth	Children' ages from birth until 3 years every 6 months	BPA(16 weeks) aOR,1.2(1.0, 1.5) BPA(26 weeks) aOR,1.07(0.86,1.3) BPA(at birth) aOR,0.89(0.71,1.12)	NA	Maternal education, race/ethnicity, occupation, income, house volume, health insurance, prenatal tobacco exposure, health insurance status, prenatal tobacco exposure, season, history and duration of breast-feeding, family history of asthma, family history of allergy, child eczema, child allergy, neonatal characteristics, pet ownership and cockroach exposure

Table 2 (*continued*)

Table 2 (*continued*)

Author	Exposure measures	Questionnaire measure time	Wheeze	Asthma	Adjustment
Postnatal					
Wang IJ (2016) (22)	Children urinary BPA glucuronide levels: at 3 and 6 years	Children' ages at 3 and 6 years	NA	BPAG(3y) with: asthma(3y): aOR, 1.29 (1.08–1.55); asthma(6y): aOR, 1.27 (1.04–1.55); BPAG(6y) with: asthma(6y): aOR, 1.50 (1.06–2.11)	Urine creatinine, maternal age, maternal education, maternal history of atopy, breast feeding and ETS exposure
Spanier AJ (2014) (25)	Urine samples of annual child visits	Children' ages from birth until 5 years every 6 months	Concurrent wheeze: aOR, 1.06 (0.75–1.51); future wheeze: aOR, 1.08 (0.65–1.78)	NA	Prenatal tobacco exposure, season, breastfeeding history, family history of asthma, family history of allergy, child eczema, child allergy, birth weight, maternal parity, pet ownership and cockroach exposure
Kim KN (2014) (23)	Children urinary BPA: between 11 and 12 years	Along with exposure measure	aOR, 2.48 (1.15–5.31)	Current asthma: aOR, 2.35 (1.03–5.32); incident asthma: aHR, 2.13 (1.51–3.00)	Gender, parental asthma history, fetal and environmental tobacco smoke exposure, pet ownership and grade at enrollment
Donohue KM (2013) (24)	Children urinary samples at 3, 5 and 7 years	Children' ages at 5, 6 and 7 years	BPA(mean) with: wheeze(5y): aOR, 1.5 (1.1–2.0); wheeze(6y): aOR, 1.4 (1.0–1.9); wheeze(7y): aOR, 1.4 (1.0–2.0)	BPA(mean): aOR, 1.6 (1.2–2.1)	Maternal history of asthma, sex, race/ethnicity, environmental tobacco smoke exposure, and urine specific gravity. Models for asthma were additionally controlled for child's age at the time of evaluation because this assessment was performed once per child between ages 5 and 12 years

Donohue KM (2013) (24) and Spanier AJ (2014) (25) investigated both prenatal and postnatal exposure to BPA and childhood asthma/wheeze. Thus, their results were summarized and shown in different subgroup respectively. BPA, Bisphenol A; NA, not available; aOR, adjusted odds ratio; aRR, adjusted rate ratio; aHR, adjusted hazard ratio.

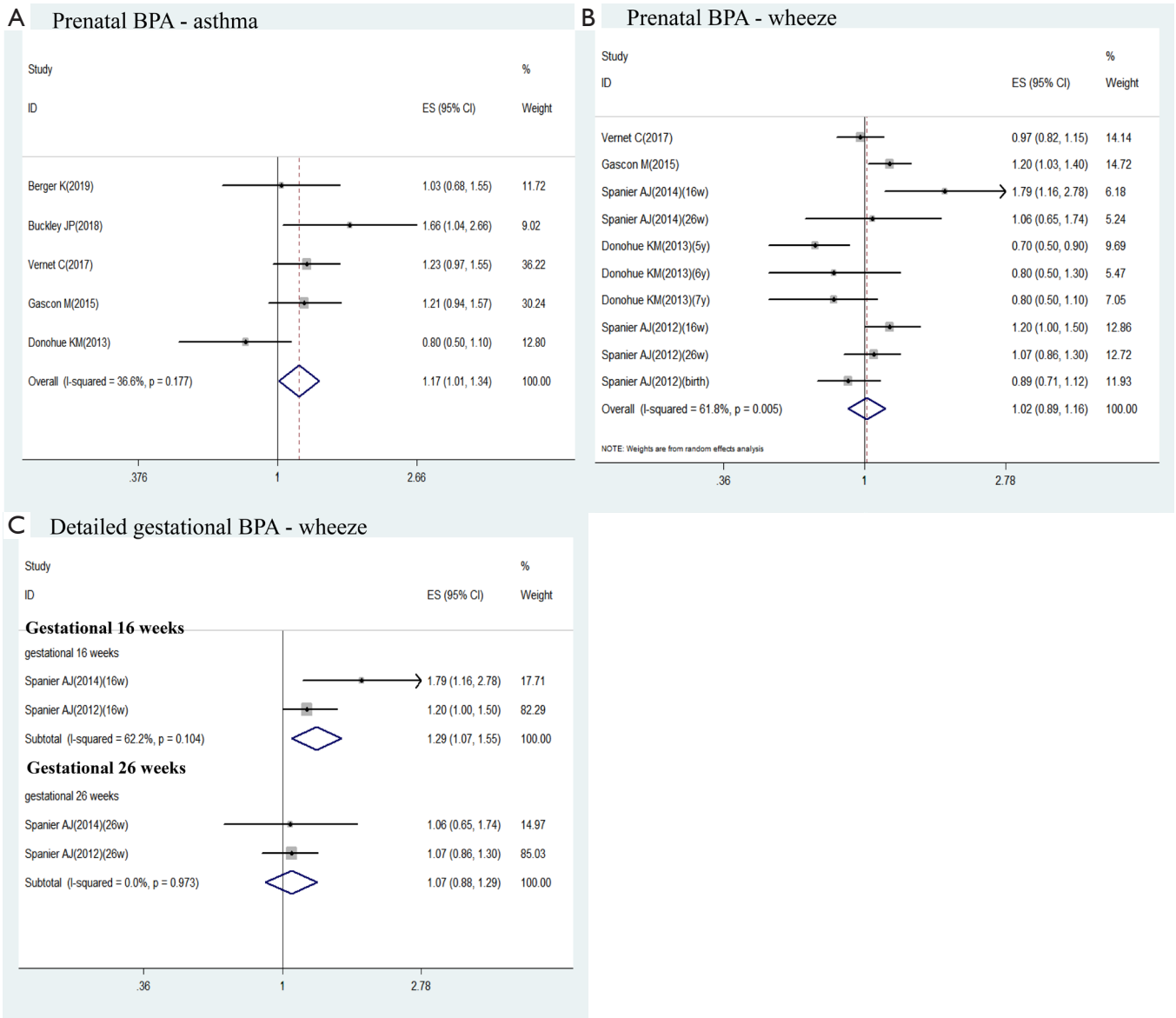

Figure 2 Effect sizes in the meta-analysis on prenatal exposure to BPA and children asthma and wheeze. (A) Meta-analysis on prenatal exposure to BPA and children asthma. (B) Meta-analysis on prenatal exposure to BPA and children wheeze. (C) Meta-analysis on detailed gestational exposure to BPA and children wheeze. Note: (I) two studies (21,25) investigated different exposure detection time was shown as Spanier AJ (2014) (16 w), Spanier AJ (2014) (26 w) and Spanier (2012) (16 w), Spanier (2012) (26 w), Spanier (2012) (birth). (II) One study (24) investigated different end-point childhood ages was shown as Donohue KM (2013) (5 y), Donohue KM (2013) (6 y) and Donohue KM (2013) (7 y).

between prenatal exposure to BPA and childhood asthma (17-20,24). Meta-analysis result showed that prenatal exposure to BPA was associated with an increased risk of childhood asthma by using fixed-effects model (aOR =1.17, 95% CI, 1.01–1.34; *Figure 2A*). Low heterogeneity was observed (I^2=36.6%; P=0.177; *Figure 2A*).

Prenatal exposure to BPA and childhood wheeze

Five studies reported the association between prenatal exposure to BPA and childhood wheeze (19-21,24,25). There were two studies investigated different exposure detection time as following: Spanier AJ [2014] at 16/26 weeks (25) and Spanier [2012] at 16/26weeks/at birth (21).

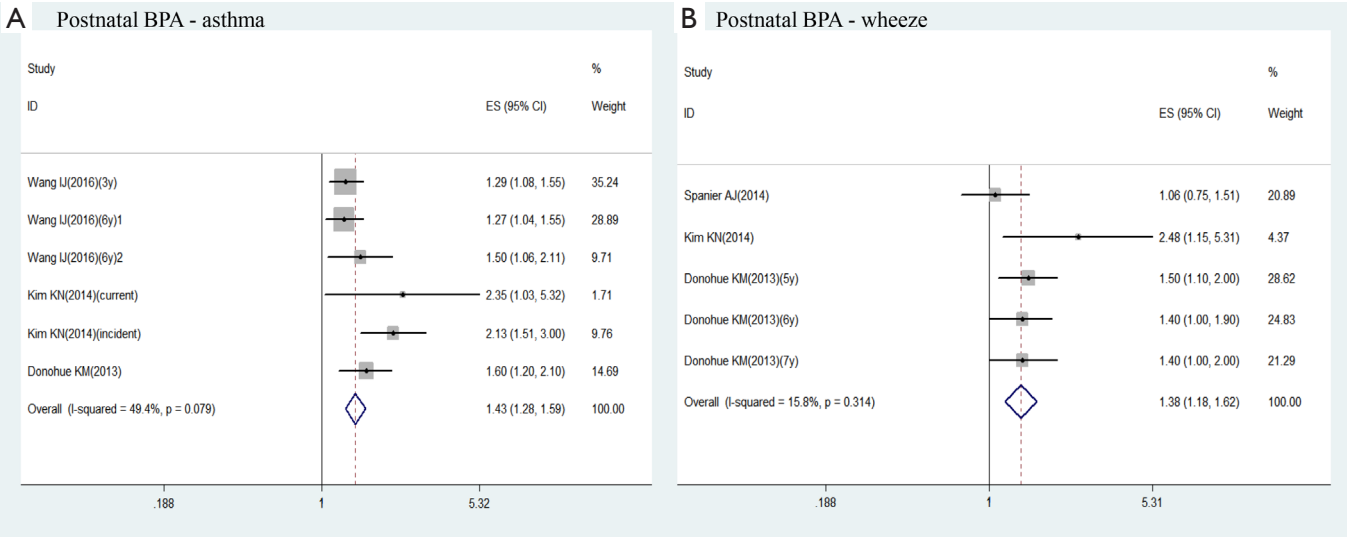

Figure 3 Effect sizes in the meta-analysis on postnatal exposure to BPA and children asthma and wheeze. (A) Meta-analysis on postnatal exposure to BPA and children asthma. (B) Meta-analysis on postnatal exposure to BPA and children wheeze. Note: (I) reference: (22). Wang IJ (2016) (3 y): postnatal exposure to BPA at 3 years and childhood asthma at 3 years. Wang IJ (2016) (6 y)1: postnatal exposure to BPA at 3 years and childhood asthma at 6 years. Wang IJ (2016) (6 y)2: postnatal exposure to BPA at 6 years and childhood asthma at 6 years. (II) Kim KN (23) observed two kinds of childhood asthma outcomes (incident asthma and current asthma) was shown as Kim KN (2014) (current) and Kim KN (2014) (incident). (III) Donohue KM (24) investigated different end-point childhood ages was shown as Donohue KM (2013) (5 y), Donohue KM (2013) (6 y) and Donohue KM (2013) (7 y).

And Donohue KM investigated different end-point outcome at 5, 6 and 7 years (24). Since heterogeneity was moderate, we used random-effect rather than fixed-effect model to do the meta-analysis (I^2=61.8%, P=0.005; *Figure 2B*). However, no significant association was found between prenatal exposure to BPA and childhood wheeze (aOR =1.02; 95% CI: 0.89–1.16; *Figure 2B*).

Gestational-week exposure to BPA and childhood wheeze

As the gestation period was too long to be vulnerable to BPA exposure, we made a further subgroup meta-analysis in the association between different gestational-week BPA exposure and childhood wheeze. Two studies collected maternal urinary BPA concentration at two exposure time points (gestational 16 and 26 weeks) during pregnancy (21,25). As the results shown, an increased risk of childhood wheeze was related to prenatal exposure to BPA at 16 weeks' gestation (aOR =1.29; 95% CI: 1.07–1.55; I^2=62.2%, P=0.104; *Figure 2C*), but not at 26 weeks' gestation (aOR =1.07; 95% CI: 0.88–1.29; I^2=0%, P=0.973; *Figure 2C*).

Postnatal exposure to BPA and childhood asthma

There were 3 studies investigated the association between the postnatal exposure to BPA and childhood asthma (22-24). Kim observed two kinds of childhood asthma outcomes (incident asthma and current asthma) (23). And Wang surveyed the relationship between postnatal exposure to BPA at 3 years and childhood asthma at 3 or 6 years, which was showed as Wang (3y) and Wang (6y)1 in *Figure 3A* (22). Moreover, he also investigated the relation between postnatal exposure to BPA at 6 years and childhood asthma at 6 years, which was showed as Wang (6y)2 in *Figure 3A* (22). Our result demonstrated that postnatal exposure to BPA exposure is a risk factor to childhood asthma (aOR =1.43; 95% CI: 1.28–1.59; *Figure 3A*). The statistical heterogeneity was moderate (I^2=49.4%, P=0.079; *Figure 3A*).

Postnatal exposure to BPA and childhood wheeze

Three studies surveyed the relation between the postnatal exposure to BPA and the risk of childhood wheeze (23-25). Among them, Donohue KM investigated different end-point outcome at 5, 6 and 7 years (24). According to the meta-analysis results, postnatal exposure to BPA was

associated with a higher risk of childhood wheeze (OR =1.38; 95% CI: 1.18–1.62; *Figure 3B*). And heterogeneity was low (I^2=15.8%, P=0.314; *Figure 3B*).

Sensitivity analysis

The subgroup meta-analysis with I^2 high than 50% was analyzed with random-effect model and was further done with sensitivity analysis to find out the source of heterogeneity. However, we failed to find any obvious studies contributing to high heterogeneity.

Publication bias

We used Egger's test and Begg's test to assess the publication bias, whose P value of each meta-analysis group were exhibited in Table S3. The figures of all the Begg's test were showed in Figure S1. The results convinced us that there was no publication bias in our meta-analysis (P>0.05).

Discussion

To the best of our knowledge, this meta-analysis provides the first quantitative estimates of the association between prenatal or postnatal exposure to BPA and childhood wheeze/asthma. Our meta-analysis of 9 included studies (3,885 participants) shows that postnatal exposure to BPA was associated with a higher risk of childhood asthma and wheeze. Prenatal exposure to BPA had a small but significant increased risk of childhood asthma. An increased risk of childhood wheeze was related to prenatal exposure to BPA at 16 weeks' gestation, but not at 26 weeks' gestation nor at random-time gestation.

BPA is a synthetic environmental chemical with small molecular weight (228 Da) and high lipophilicity, which makes it pass through human epithelial barrier much more easily (28). BPA exposure is ubiquitous for its high production and wide application. Dietary and non-dietary (dermal absorption, inhalation and sublingual absorption) sources could contribute to total daily exposure in human. Moreover, residual BPA concentration can't be ignored, which has been reported in the range of 1–140 mg/kg in polycarbonate plastics generally (29).

Nowadays, accumulating evidences have demonstrated that BPA exposure are associated with some adverse health outcome, such as obesity, hyperactivity and asthma (30,31). Our meta-analysis results provided further justification for the current studies and demonstrated that the prenatal and postnatal exposure to BPA were related with an increased risk of childhood asthma/wheeze. Until now, there are three potential mechanisms supporting the role of BPA exposure in pathological processes of asthma/wheeze. Firstly, BPA was reported to have immunomodulatory effects by increasing the production of proallergic Th2 cytokine and antigen-specific IgE (14,16,32), reducing the levels of IFN-r/IL-10/regulatory T CD41CD251 cells (14) and enhancing bronchial eosinophilic inflammation/allergic sensitization (6,16). Secondly, as an endocrine disrupting chemical, BPA also has the ability to enhance or inhibit the hormone signaling pathway by bounding to estrogen receptors (ERs), estrogen-related receptors (ERRs), toll-like receptors (TLRs) and others (33). It is acknowledged that ERs, ERRs and TLRs are expressed in most immune cells which allows BPA to act on immune systems. Activation of ERs was suggested to encourage the Th2 polarization with increased proallergic inflammatory cytokines, production of IgE in B cells and degranulation of mast cells (34,35). Lastly, some researches demonstrated that BPA-induced damage was related with the oxidative stress and mitochondrial dysfunction (36,37). And it is well known that the progress of asthma has a certain relationship with oxidative stress (38). Thus, BPA-causing oxidative stress might enhance the susceptibility to asthma to an extent. However, despite mechanisms mentioned above, whether results from laboratory rodent studies are applicable to human still remains unknown.

It is acknowledged that in early life, even subtle alterations can have the potential to alter normal human growth and development, and result in irreversible, deleterious and long-lasting changes later in life (12). Its exposure and adverse affection in children are more severe than adults due to the following factors (10). During the fetal period, placenta was unable to provide effective barrier against fetus exposure to BPA (39). Another notable factor was complex metabolism of BPA in the maternal-fetal unit. About 90% BPA that pregnant mice ingested after 24 hours was accumulated in the placental unit (40,41). Although free BPA (an active BPA) was conjugated as BPA-glucuronide (an inactive metabolite) in maternal rat liver, the conjugated BPA could be absorbed and deconjugated back to free BPA in placenta (42). Even worse, fetal hepatic detoxification systems was not mature enough to provide enzymes to metabolize free BPA to conjugated BPA. Thus, fetus was exposed to higher active BPA concentration. In regard to children, BPA are predicted to have higher concentration and longer retention time in children

than adults (43). Firstly, higher requirement of dietary intake for growth and development makes children more vulnerable to BPA than adults because dietary exposure routes are the most important source of BPA (44). Besides, sucking, chewing and frequent hand-to-mouth action, special behaviors in infants and toddlers, can result in additional indirect ingestion sources of BPA when some BPA-containing products (plastics, pacifiers and toys) are placed in mouth (44). Secondly, degeneration of BPA-containing consumer products can release BPA into air, dust and contact surfaces, which makes BPA be a ubiquitous pollutant in daily living environment (45,46). Thus, dermal absorption is a critical non-dietary exposure route in neonates due to comparatively higher surface area to body mass ratio and immature skin barrier function. Besides, compared with skin, the respiratory tract has more mucosal surface and some chemicals can be absorbed by respiratory epithelium (47). Higher oxygen requirements per kilogram body weight, faster respiratory rate and long-term indoor time make children more susceptible to inhalation contamination. Thus, inhalation route may not be ignored for BPA exposure. Lastly, it is well established that free BPA is first-pass metabolized by liver via UDP glucuronosyltransferase enzymes family and is eliminated through kidney (48,49). However, hepatic detoxification systems have not yet been fully developed in infants and toddlers.

Nowadays, some governments have taken measures to reduce the BPA exposure in human. European Food Safety Authority (EFSA) sets the tolerable daily intake of BPA to be no more than 4 μg/kg/day in 2014. Most European countries have adopted such criteria and the regulatory restriction on the use of BPA in children feeding products is implemented in Canada, the United States, Japan and so on (50-52). But there are no surveillance biomonitoring researches to assess the BPA exposure before and after restriction implementation and whether current regulatory restriction could effectively reduce BPA exposure remains unknown. In addition, BPA analogues and derivatives, as BPA substitute, have been used increasingly in manufacture and advertised and marketed as "BPA free", including bisphenol S, bisphenol B, and bisphenol F (53). Nevertheless, a systematic review demonstrated that these BPA substitute had similar property to BPA. Therefore, multiple bisphenol exposure should be noteworthy.

Several limitations should be acknowledged and the corresponding suggestions are given for future studies. First of all, some included studies only measured urine BPA exposure once. In consideration of its short half-time and rapid excretion, BPA concentration had better to be detected more than once and taken the average value (49,54). Second, it is imprecise to use maternal urine BPA concentration as prenatal BPA exposure levels because only 6% of BPA that pregnant mice ingested after 24 hours was excreted in maternal urine (40,41). However, it is difficult to gain amniotic fluid or fetal blood as exposure measurement although that is more precise. Third, most included studies used parent-reported asthma/wheeze data as outcome assessment which were depended on parent recall. Only Donohue assessed asthma by physicians and Spanier used questionnaires combined with experimental IgE levels to determine asthma or wheeze (21,24). Thus, more accurate outcome assessments such as combination of diverse measurement are recommended to take into consideration to avoid outcome misclassification. Fourth, due to the manufacture of BPA substitute, multiple bisphenol exposure might be potential confounders. Besides, other chemicals like phalates which also have the immunomodulatory properties can influence the results if not ruled out. Potential confounders should receive great attention from researchers for it may affect result accuracy to a large extent. Fifth, the timing of exposure and outcome measurement was inconsistent among all included studies which might contribute to the discrepancy between each studies and heterogeneity in our meta-analysis. Therefore, standardized criteria are required for future researches including measure method of exposure, outcome assessment and elaborate confounders. At last, some surveillance biomonitoring researches are needed to make sure whether regulatory restriction could reduce the BPA exposure effectively by assessing the general BPA exposure before and after regulatory restriction implementation.

Conclusions

Prenatal and postnatal exposure to BPA was related to an increased risk of childhood asthma. However, only postnatal and early gestational exposure (at 16 weeks) to BPA could induce the risk of childhood wheeze, but not late gestational exposure (at 26 weeks). Future studies with standardized criteria and larger sample sizes are warranted.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1550

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1550). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Quality Assessment of Included Studies using the NOS tool[#]

Author/year/country	Overall quality assessment	Selection				Comparability	Outcome		
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up was long enough for outcomes to occur	Adequacy of follow-up of cohorts
Berger K/2019/USA	8	*	*	*	*	*	—	*	*
Buckley JP/2018/USA	8	*	*	*	*	*	—	*	*
Vernet C/2017/France	8	*	*	*	*	*	—	*	*
Wang IJ/2016/China	8	*	*	*	*	*	—	*	*
Gascon M/2015/Spain	8	*	*	*	*	*	—	*	*
Spanier AJ/2014/USA	8	*	*	*	*	*	—	*	*
Kim KN/2014/Korea	8	*	*	*	*	*	—	*	*
Donohue KM/2013/USA	9	*	*	*	*	*	*	*	*
Spanier AJ/2012/USA	8	*	*	*	*	*	—	*	*

[#], the New Castle-Ottawa Scale for cohort studies. The score ranges from 0 to 9.

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Table S2 Limitations of included studies

Source	limitations
Berger K (2019)	The researchers cannot differentiate atopic and nonatopic cases, some of the probable asthma cases may be nonatopic. The result cannot generalize to other population. The study is based on small sample size
Buckley JP (2018)	The researchers assess exposure based on a spot urine samplecollected during the third trimester, may cause misclassified exposure. The result lack of information on postnatal exposure. The study did not have adequate sample size. The study lack of clinical confirmation of outcomes. The researchers failed to follow up and this may lead to selection bias. The result cannot generalize to other population. Sample BPA level may not represent recent exposure
Vernet C (2017)	The researchers were unable to differentiate bronchiolitis and bronchitis occurrences. The result cannot generalize to girls. There is limited sample size. The study did not consider the well-known wheezing phenotypic heterogeneity. The single sample contributes to exposure misclassification. There is no information on postnatal exposures
Wang IJ (2016)	The exposure based on a spot urine sample collected during the third trimester, may cause misclassified exposure . Lack of data on prenatal BPA exposure and cross section design may limit conclusion. There is potential selection bias
Gascon M (2015)	The researchers failed to follow up
Spanier AJ (2014)	A spot urine sample may cause misclassified exposure. Lung function assessment, FEV1, which cannot be available for all the children participated in the study ,cannot predict future lung function and distinguish the effects of BPA. The children who can provide FEV1 result have poorer lung function than children's as reference sample. Parent-report outcomes lead to under or over reported wheeze. Confounders influence the generalizability of the results. Samples recruited in the study were limited to English speaking families. Concurrent exposure may affect results
Kim KN (2014)	The study is on the basis of small sample size. The result cannot be generalized.
Donohue KM (2013)	The exposure based on a spot urine sample collected during the third trimester, may cause misclassified exposure. Unmeasured confounding may affect the results. There is wheeze outcome misclassification because of miss data. The researchers did not use bronchial provocation testing
Spanier AJ (2012)	The study cannot place the three maternal measurements and the three creatinine concentrations in the same analysis. BPA concentrations is changing over time, the collected sample may cause exposure classification. Parent-report outcomes lead to under or over reported wheeze. The sample is not a random sample. There was differential attrition in the study

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Table S3 Publication bias of each subgroup using Stata SE12.0

Subgroup	Included datas	Begg's test	Egger's test
Prenatal BPA-asthma	5	1	0.793
Prenatal BPA-wheeze	5	0.592	0.528
Prenatal BPA-gestation	2	1	0.517
Postnatal BPA-asthma	3	0.133	0.056
Postnatal BPA-wheeze	3	0.806	0.317

All studies were without publication bias (P>0.05).

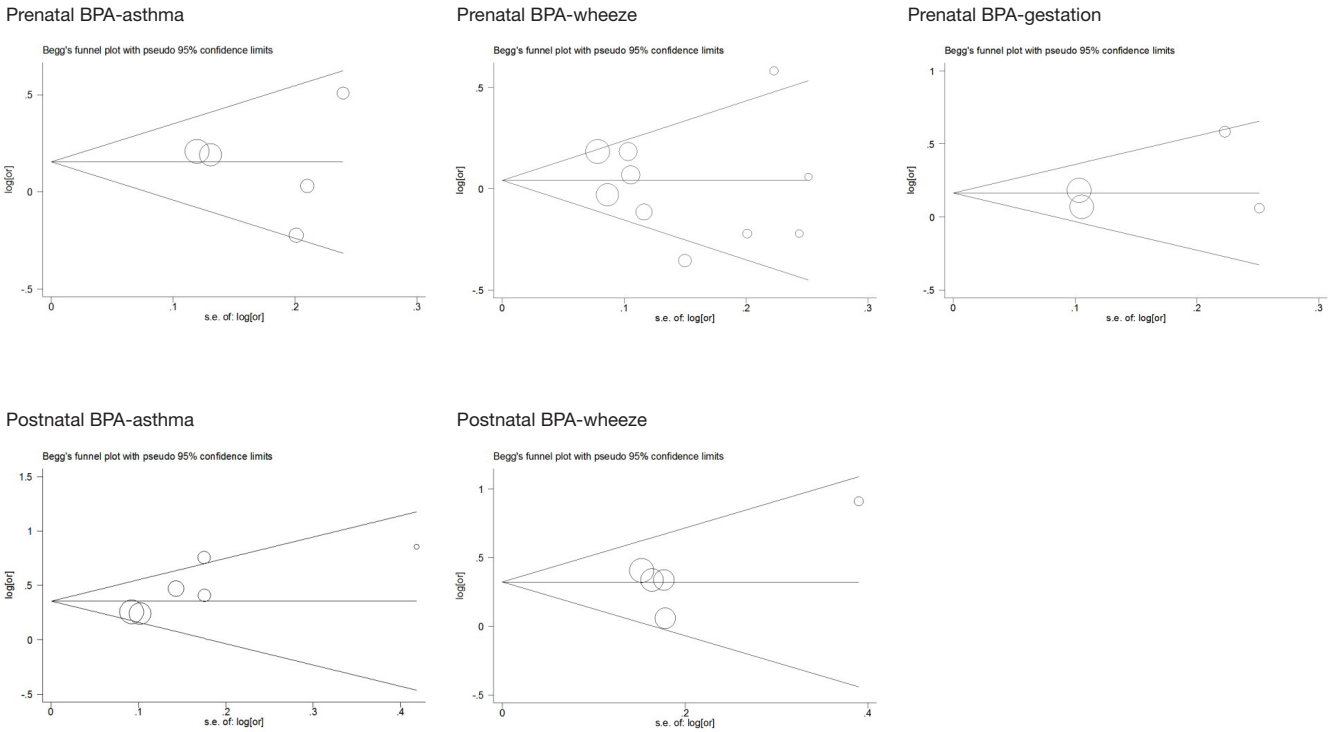

Figure S1 Begg's test of each included studies in all meta-analysis.

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