

Association of Endocrine Disrupting Chemicals, Bisphenol A and Phthalates, with Childhood Obesity: A Systematic Review

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Abstract

Context: Exposure to endocrine-disrupting chemicals (EDCs) can contribute to the risk of childhood and adolescent obesity.

Objectives: The aim of this study was to systematically review the literature concerning the association of bisphenol A (BPA) and phthalates with obesity in children and adolescents.

Data Sources: Scopus, ISI Web of Science, PubMed, Google Scholar, and Medline were searched to identify studies published up to January 2017. A secondary reference review of all extracted articles was, also, conducted.

Study Selection: All studies that had assessed the relationship between BPA and phthalates with obesity in children and adolescents were included in the present systematic review. Finally, 35 studies were relevant.

Data Extraction: The current review was conducted and reported in accordance with the Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) statement.

Results: Thirty-five original studies met the inclusion criteria, consisting of 20 cross sectional, 4 case control, and 11 cohort studies. Nineteen studies reported that childhood exposure to environmental chemicals including BPA and phthalic acid esters (PAEs) during childhood could increase the risk of excess weight. In addition, 10 studies found no correlation between these compounds and obesity.

Conclusions: The effects of BPA and phthalates have diverse mechanisms; these chemicals disrupt some functional, structural, and epigenetic mechanisms that control energy homeostasis, appetite regulation, lipid metabolism, and adipogenesis. However, additional longitudinal studies are needed to confirm and validate the current findings.

Keywords: Endocrine Disrupters, Bisphenol A, Phthalates, Obesity, Children

1. Context

Endocrine disrupting chemicals (EDCs) are environmental chemicals that can interfere with different aspects of hormone action. Moreover, EDCs bind to hormone receptors and can repress, or activate and/or interfere with hormone metabolism and synthesis. EDCs act via nuclear receptors, nonnuclear steroid hormone receptors, orphan receptors, enzymatic pathways involved in steroid biosynthesis and/or metabolism, and several other mechanisms that converge upon endocrine controlled and reproductive systems (1). A growing body of evidence has focused attention on how the exposure to industrial compounds may interfere with the programming of complex endocrine pathways (2). EDCs are ubiquitous in environment; their main role on fetal life and childhood seems to be associated with the increasing rates of low birth weight, premature birth, disorders of sex development, and obesity. They might, also, affect the weight extent with other direct effects, particularly during childhood (3). Over the past

decades, childhood obesity has emerged as a public health problem worldwide, even in developing countries (4).

The number of infants and preschool children who were overweight and obese worldwide increased from 32 million in 1990 to 42 million in 2013, and this total is estimated to increase to 70 million by 2025 (5). Of concern, obese children and adolescents are at a high risk for chronic disorders including type 2 diabetes, osteoarthritis, cancer, and cardiovascular disease (6). The escalating trend in the prevalence of obesity at young age clearly suggests that some environmental factors might have an underlying role in the current obesity epidemic (7). Emerging investigation is now examining the role of EDCs, particularly the group known as “obesogens,” and their role in the obesity epidemic. It is postulated that certain environmental chemicals including bisphenol A (BPA) and phthalates (6), phthalic acid esters (PAEs), are widely produced (1, 8). Actually, BPA is used extensively in polycarbonate plastics, epoxy resins, and several other applications (9). Human exposure to low BPA levels is ubiquitous

and occurs mainly through dietary intake by migration from beverage container and food (10). Warming food in polycarbonate containers and epoxy-coated cans increases BPA leaching into the food. Furthermore, resin-based composites, which are used as enamel-colored dental fillings, have been revealed to leach BPA (11). A number of studies reported a positive association of perinatal exposure to BPA with emotional and social behavior in children (12, 13). Moreover, some epidemiological studies among adults revealed the association of BPA with consequences of obesity, ie, cardiovascular disease, glucose intolerance, insulin resistance, and type 2 diabetes (14). Phthalates or PAEs are the most abundantly produced plasticizers that are used in the production of polyvinyl chloride (PVC), also as ingredients in many consumer products including cosmetics. The widespread human exposure to PAEs has raised concerns for the susceptible subpopulations such as pregnant women and children. Exposure to PAEs in children is generally higher than in adults (9, 15). The ubiquitous presence of BPA and PAEs in environment leads to human exposure via ingestion of drinking water and contaminated food, inhalation of contaminated air, and dermal absorption. Because of this extensive exposure, BPA and phthalate metabolites are highly detectable in urine samples of various populations around the world (16).

2. Objectives

The objective of this study is to systematically review the literature concerning the association of BPA and phthalates with childhood obesity.

3. Data Sources

The search process was conducted in electronic databases including papers published up to January 2017. We searched ISI Web of Science, Scopus, PubMed, Google Scholar, and Medline using key words of “Bisphenol A (BPA)”, “Phthalates”, “Phthalate esters”, “phthalic acid esters (PAEs)”, “Endocrine-disrupting chemicals (EDCs)”, “Obesity”, “Overweight”, “Body mass index”, “Waist circumference”, “Body weight”, “Abdominal obesity”, “Children”, “Adolescents” as well as a combination of them. To extract related articles in PubMed, the following search strategy (corresponding Medical Subject Heading [MeSH] terms) was used:

For bisphenol A:

(“Bisphenol A-Glycidyl Methacrylate”[Mesh] OR “bisphenol A” [Supplementary Concept] OR “bisphenol-A-polycarbonate” [Supplementary Concept]) AND (“Obesity”[Mesh] OR “Pediatric Obesity”[Mesh] OR

“Obesity, Abdominal”[Mesh] OR “Abdominal obesity metabolic syndrome” [Supplementary Concept]) OR “Body Weight”[Mesh]) OR “Waist Circumference”[Mesh] OR “Body Mass Index”[Mesh] OR “Overweight”[Mesh]) AND (“Child”[Mesh] OR “Adult Children”[Mesh] OR “Child, Preschool”[Mesh] OR “Adolescent”[Mesh] OR “Adolescent Development”[Mesh])

For phthalates:

(“1, 2-diglycidyl phthalate” [Supplementary Concept] OR “phthalic acid” [Supplementary Concept] OR “di-n-hexyl phthalate” [Supplementary Concept] OR “diethyl phthalate” [Supplementary Concept] OR “Phthalic Acids”[Mesh]) AND (“Obesity”[Mesh] OR “Pediatric Obesity”[Mesh] OR “Obesity, Abdominal”[Mesh] OR “Abdominal obesity metabolic syndrome” [Supplementary Concept] OR “Body Weight”[Mesh] OR “Waist Circumference”[Mesh] OR “Body Mass Index”[Mesh] OR “Overweight”[Mesh]) AND (“Child”[Mesh] OR “Adult Children”[Mesh] OR “Child, Preschool”[Mesh] OR “Adolescent”[Mesh] OR “Adolescent Development”[Mesh])

For endocrine disrupting compounds:

(“Endocrine Disruptors”[Mesh]) AND (“Obesity”[Mesh] OR “Pediatric Obesity”[Mesh] OR “Obesity, Abdominal”[Mesh] OR “Abdominal obesity metabolic syndrome”[Supplementary Concept] OR “Body Weight”[Mesh] OR “Waist Circumference”[Mesh] OR “Body Mass Index”[Mesh] OR “Overweight”[Mesh]) AND (“Child”[Mesh] OR “Adult Children”[Mesh] OR “Child, Preschool”[Mesh] OR “Adolescent”[Mesh] OR “Adolescent Development”[Mesh])

We, also, conducted a secondary reference review of all extracted articles on the association of BPA and phthalates with obesity in children and adolescents.

4. Study Selection

The inclusion criteria included cross-sectional studies, case-control studies, cohort studies, interventional studies, studies investigating the associations between BPA and phthalates and their association with obesity in children and adolescents. Exclusion criteria consisted of letters, conference abstracts, reviews or editorials, and poor quality articles. Firstly, titles and abstracts of articles were screened and relevant articles were selected by one of the researchers (MZ); duplicates were removed. Then two independent reviewers abstracted the data (PP and MZ). In the case of disagreement, and the discrepancy was resolved in consultation with professional investigators (RK and MA). The following information was extracted from each study: first author, publication year, study type, population, child age, outcome, and main findings.

5. Data Extraction

In the systematic search, 261 studies were identified. The flowchart of the study selection is presented in [Figure 1](#). It shows that 146 studies were excluded on the basis of the criteria. The full texts of 67 original research papers were retrieved and critically reviewed. Thirty five studies focused on the associations between BPA and phthalates exposure with childhood obesity. Data extracted from selected studies included: first author, publication year, study design, population, participants' age, outcome and main results.

5.1. Study Quality Assessment

After determining the titles and contents of studies, their quality was evaluated by using a checklist. It considered the study objective, study method, sample size, sampling method, data collection tool, variables evaluation status, and studied target group. The analyses status was examined by using 12 questions by considering one score for each question (17). At the final stage, those articles that obtained at least the minimum acceptable score were selected and their related information was extracted.

6. Results

The aim of the literature search was to find all studies examining the association between BPA and phthalates exposure with childhood obesity. As previously mentioned, after the selection process, 35 studies were included consisting of 20 cross sectional, 4 case control, and 11 cohort studies. Also, of these studies, 22 papers were about BPA and 13 papers about PAEs. Also, two papers had studied simultaneously both BPA and PAEs. The results are presented separately for BPA and PAEs ([Tables 1](#) and [2](#)). We primarily assessed the obesity-related outcomes including weight gain, body mass index (BMI), waist circumference (WC), body fat percentage (BF%), Fat mass index (FMI), lean body mass index (LBMI), and waist-hip ratio (WHR). All the studies used total BPA and PAEs concentration as the exposure variable.

6.1. Childhood Obesity and Bisphenol A Exposure

Overall, 11 papers reported the positive association of exposure to BPA and childhood obesity (18-28). A study (27) analyzed the relationship between urinary BPA and obesity using a cross sectional study of eight 15-year-old Chinese school children. In this study, urine BPA concentrations were significantly associated with increasing BMI values in all subjects. However, eight studies reported no correlation between obesity and exposure to BPA in children (11, 29-35).

A cross sectional study on 200 subjects showed the placental BPA concentration was greater in low birth weight infants when compared to normal weight infants (11). One study (36) showed a negative correlation between obesity and urinary BPA concentration. In this study, obesity was assessed by fat mass index (FMI) and lean body mass index (LBMI). The results show high urinary BPA concentration may be associated with increased LBM in boys and increased FM in girls. Also, the findings of three studies showed that higher urinary BPA concentrations were associated with lower BMI in girls but not boys (37-39). Studies had reported controversial results about the association of BPA and obesity; however, according to the most studies, positive correlation exists between BPA and obesity. The majority of these studies are accomplished using cross sectional analyses. [Table 1](#) presents the main epidemiologic studies that investigated the associations between BPA and childhood obesity.

6.2. Childhood Obesity and Phthalates Exposure

During the past 10 years, a number of studies (13 papers) have been focused on the association of exposure to phthalates and childhood obesity ([Table 2](#)). Of them, 8 papers reported significant positive associations between PAEs and obesity (40-47). In addition, two studies found no correlation with phthalates and obesity outcomes (33, 48). For example, Boas et al. 2010 (48) reported that most phthalate metabolites did not have any association with height, weight, body surface, and height gain of both genders. Papers, also, showed prenatal exposure to phthalates (MBzP) had positive correlation with birth weight among boys but not in girls (34). In contrary, a cohort study found prenatal exposure to five high-molecular-weight phthalate metabolites (Σ HMWpM) was associated with lower weight z-score difference between birth and 6 and lower BMI z-scores in boys at 4 to 7 years of age (49). They found that Σ HMWpM was associated with higher weight z-score difference and BMI z-scores in girls. In addition, the sum of three low-molecular-weight phthalates (Σ LMWpM) was not significantly associated with any of the growth outcomes. The majority of papers are from cross sectional studies; in general, they reported that PAEs and their metabolites were associated with increased risk of obesity (34).

7. Discussion

The present study assessed the relationship of environmental BPA and PAEs with childhood obesity. The considerable rise in the prevalence of childhood obesity in recent years is the result of complex interactions of changes in individual lifestyle, community structure, and the built

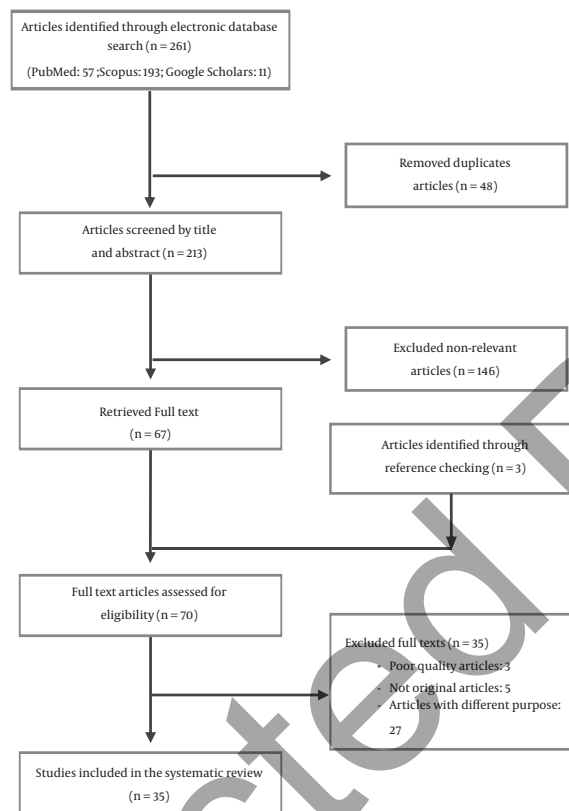


Figure 1. Papers Search and Flowchart of Study Selection

environment, as well as the exposure to certain synthetic chemicals including EDCs (50, 51). In recent years, there has been an increase in the number of publications examining the relationship between exposure to BPA and phthalates with childhood obesity. Two recent systematic reviews focused on the association of BPA with indicators of obesity and BPA with the risk of cardiometabolic disorders in adults (52, 53). Another review considered the epidemiologic studies examining the impacts of maternal exposure to synthetic chemicals (eg, BPA and phthalates) and obesity in the offspring (5). BPA is used in a variety of products including medical equipment, food can linings, food/beverage storage containers, toys, etc. Monomers of this chemical can hydrolyze and leach from polycarbonate plastics and epoxy resins into food and liquids in contact with the container. In general, we found that the results of the studies on BPA were consistent in showing positive associations between BPA concentrations and childhood obesity. Children have higher urinary BPA levels than adults, this is suggested to be because of their higher

food intake per kilogram of body mass. However, it is not known whether metabolic differences between children and adults partially account for the differences in urinary BPA concentrations or not (54). Results of two longitudinal studies showed that exposure to BPA during pregnancy may increase the risk of obesity in childhood (21, 26). Animal studies have reported that BPA affects glucose transport in fat cells and, also, disrupts glucagon secretion in intact Langerhans cells at nanomolar levels (51). Thus, the findings of the current review shows that this chemical could be a risk factor for the development of obesity. There is some argument about exposure to high levels of BPA and childhood obesity, BPA has been shown to have a negative association with childhood obesity in epidemiological studies. Troisi et al. reported a negative association between calculated birth weight and placental BPA level. In their study, placental BPA level was greater in low birth weight infants when compared to normal weight infants. They also reported major route to human exposure will help reduce the potential risk of BPA at all stages of

human life (11). Xue et al. determined urinary levels of 26 EDCs such as BPA in 49 obese and 27 non-obese Indian children. They, also, reported negative associations between childhood obesity and BPA (32). As for different results of epidemiological studies, additional research with a larger sample size is needed.

In children, exposure to PAEs occurs through food and water intake, dental sealants, inhalation of house dust, and dermal absorption (55). Phthalates are used in a wide range of consumer products including cosmetics, personal care products, and plastics (5). Because of increasing scientific research and public concern about the toxicity of PAEs, various regulatory actions are directed at restricting the use of certain phthalates in consumer products, particularly those concerning infants and children. Furthermore, the European Commission has prohibited the use of certain phthalates such as DEHP, DBP, and BBzP for food-contact applications, childcare articles, toys, and cosmetics (56). These chemicals interfere with lipid and weight homeostasis by various mechanisms related to the activity of the sympathetic nervous system, weight-controlling hormones, and sensitivity to neurotransmitters. In addition, it is assumed that exposure to different doses of these contaminants from fetal to adult period may interact with some endocrine signaling mechanisms and in turn can lead to obesity. The difference in the results of two studies (34, 49) may be due to the fact that children with higher weights compared with children with lower weights at birth may tend to grow more slowly in the first years of life, and they could be at a lower risk of obesity. The majority of studies show a positive correlation between phthalates exposure and obesity in children, however, a few studies reported no association. For example, the study result of Boas et al. showed negative associations between urinary phthalate levels and growth in children. In support, animal studies have shown similar results (48).

In general, our findings suggest that these two EDCs are associated with childhood obesity. EDCs including BPA and phthalates disrupt some functional, structural, and epigenetic mechanisms that control energy homeostasis, appetite regulation, lipid metabolism, and adipogenesis. Moreover, exposure to BPA and PAEs may change serum levels of metabolic hormones or may influence the steroid hormone receptors or may influence nuclear receptor signaling pathways in preadipocytes (57). Overall, the reviewed studies have some limitations. Differences between the results of studies are suggested to be due to different methods, timing of BPA and phthalate exposure, and confounding factors. BPA and phthalates exposure misclassification and differences in distributions of outcome measure modifiers are the important limitations of the studies. Also, residual sources of selection bias or in-

correct model specification may explain the discrepancies across epidemiological studies. One of other limitations is that participants in cohort studies are from a higher socioeconomic class than those excluded from the study. In fact, higher urine concentrations of BPA and phthalates in populations are associated to lower socioeconomic class and lower education. Thus, highly exposed and susceptible women could have been excluded from the study. Sex-specific differences in some studies have not been evaluated. One of the limitations of several studies is that the exact sources of DEHP exposure are not known since the data use of personal care products and daily activity were not available for the population of mothers (34, 49, 58, 59). In the present review, among the epidemiological studies, the majority of studies were cross sectional and case-control. However, cohort studies are very important because they demonstrate the full impact of gestational exposure to BPA and phthalates by measuring the maternal urinary levels of BPA and phthalate metabolites. Also, prenatal period risk factors including maternal and paternal ages, the socio-economic status, smoking status, nutrient deficiencies, and physical activity should also be taken into consideration in future studies. One of the suggestions is that exposure to BPA and phthalates be assessed at several time points of pregnancy than only one time point exposure measurement. In this study, we had no significant search limitations. However, the deficiency of cohort studies and inconsistent results were the main limitations.

7.1. Conclusions

This systematic review shows that exposure to environmental chemical including BPA and PAEs during developmental phases of life, particularly in childhood or fetal period, could increase the risk of excess weight or obesity. The amount of literature is increasing about the association of EDCs, notably BPA and phthalates, with childhood obesity. However, because of the higher susceptibility of child to environmental chemical exposures and for identifying mechanisms of the obesogenic effects of BPA and PAEs, additional studies are needed to determine the relationship between early life EDCs exposure and childhood health outcomes including obesity. Simultaneous efforts should continue to replace these compounds with other plasticizers and to reduce the exposure to these chemicals.

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Footnote

Conflicts of Interest: Nothing to declare.

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Table 1. Summary of Studies Examining the Association Between BPA and Childhood Obesity

First Author and Publication Year	Study Type	Population	Participants' Age, y	Outcome	Main Results
Padmanabhan et al. (2008) (30)	Cross sectional study	40 pregnant mothers	-	Weight, height, weight at time of delivery, gestational length and birth weight	Maternal levels of unconjugated BPA ranged between 0.5 and 22.3 ng mL ⁻¹ in southeastern Michigan mothers. There was no correlation between BPA concentrations and gestational length or birth weight of offspring.
Maserejian et al. (2012) (23)	Cross sectional study	218 boys and 256 girls	6 - 10	BMI-z-score and BF	Children with more treatment on primary teeth had greater increases in BF% regardless of material type.
Trasande et al. (2012) (25)	Cross sectional study	2 838 participants	6 - 19	BMI and BMI-z-score	Median urinary BPA concentration was 2.8 ng/mL. Of the participants, 1,047 (34.1% [SE, 1.5%]) were overweight and 590 (17.8% [SE, 1.3%]) were obese. Similar patterns of association were found in multivariable analyses examining the association between quartiled urinary BPA concentration and BMI z score and in analyses that examined the logarithm of urinary BPA concentration and the prevalence of obesity.
Wang et al. (2012) (27)	Cross sectional study	20 obese, 10 overweight, and 30 normal weight children	8 - 15	BMI	Urine BPA concentrations were significantly associated with increasing BMI values in all subjects after adjustment for age and sex.
Bhandari et al. (2013) (18)	Cross sectional study	2 664 children	6 - 18	BMI	Positive association between increasing levels of urinary BPA and obesity.

Eng et al. (2013) (20)	Cross sectional study	Pregnant women (n = 27); with self-reported diabetes (n = 24), those taking insulin (n = 15), and those taking oral medications (n = 2)	6 -18	BMI, and waist circumference-to-height ratio	Higher odds of obesity (BMI \geq 95th percentile) with increasing quartiles of BPA for quartiles 2 vs 1 (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.17 - 2.60, P = .008), 3 vs 1 (OR 1.64, 95% CI 1.09 - 2.47, P = .02), and 4 vs 1 (OR 2.01, 95% CI 1.36 - 2.98, P = .001). Higher odds of having an abnormal waist circumference-to-height ratio (quartiles 2 vs 1 [OR 1.37, 95% CI 0.98 - 1.93, P = 0.07], 3 vs 1 [OR 1.41, 95% CI 1.07-1.87, P = .02], and 4 vs 1 [OR 1.55, 95% CI 1.12-2.15, P = .01]).
Li et al. (2013) (22)	Cross sectional study	1326 children	4 -12	Age- and gender-specific weight	The association showed a dose-response relationship with increasing urine BPA level associated with further increased risk of overweight (p = 0.006 for trend test). Other anthropometric measures of obesity showed similar results.
Valvi et al. (2013) (26)	Cohort study	424 pregnant women	-	BMI and WC	26 percent of children were rapid growers; 25% were overweight at 14 months and 21% at 4 years. At 4 years, BPA exposure was associated with increased WC (β per log ₁₀ μ g/g = 0.28 [95% confidence interval = 0.01 to 0.57]) and BMI (β = 0.28 [-0.06 to 0.63]).
Harley et al. (2013) (38)	Cohort study	311 children	5 - 9	BMI, WC, BF%, overweight	Prenatal urinary BPA concentrations were associated with decreased BMI at 9 years of age in girls but not boys. BPA concentrations at 9 years were positively associated with BMI, WC, fat mass, and overweight/obesity at 9 years in boys and girls.
Lee et al. (2014) (21)	Cohort study	757 pregnant women	-	Birth weight and birth length	Significant association between BPA levels and birth weight.
Wells et al. (2014) (28)	Cross-sectional study	2 836 children	6 - 18	WHR	In adjusted models, greater BPA was associated with increased WHR. Children in the second, third, and fourth quartiles of BPA had 0.011 (95% CI 0.001e0.020); 0.010 (95% CI 0.001e0.019), and 0.016 (95% CI 0.007e0.026) increase in WHR, respectively, compared with children in the first quartile.

Braun et al. (2014) (39)	Cohort study	297 mother-child pairs	2 - 5	BMI	After confounder adjustment, each 10-fold increase in prenatal ($\beta = -0.1$; 95% CI: -0.5, 0.3) or early-childhood ($\beta = -0.2$; 95% CI: -0.6, 0.1) BPA concentrations was associated with a modest and non-significant reduction in child BMI. These inverse associations were suggestively stronger in girls than in boys.
Durmaz et al. (2014) (29)	Case-control study	28 Non-obese girls, controls: 25 healthy age matched girls	4 - 8	BMI	No correlation between urinary BPA levels and body mass index in either group.
Troisi et al. (2014) (11)	Cross sectional study	Infant	-	Birth weight	No correlation between calculated birth weight centile and levels of placental BPA ($P < 0.05$).
Wang et al. (2014) (31)	Cross sectional study	666 school children	9 - 12	BMI	BPA was detected in 98.9% of urine samples with their unadjusted concentrations ranging from 0.1 to 326.0 ng/ml (LOD = 0.06 ng/ml). No significant difference in urinary BPA concentrations between overweight or obese children and those with normal weight ($P = 0.26$).
D'Aniello et al. (2015) (19)	Case-control study	31 overweight/obese children; controls: 23 normal weight	Mean 9.8	BMI	Free and total BPA levels increased paralleling the BMI increase ($r > 0.8$).
Pornkunwilai et al. (2015) (24)	Cross sectional study	376 children and adolescents	3 - 18	BMI z-score	BPA was detected in 283 of 376 urine samples (75.3%) with a median adjusted BPA 0.53 $\mu\text{g/g}$ creatinine (range 0.04 - 1.12). Thirty-one participants (9%) were overweight and 39 (11%) were obese. The BPA detection rate was significantly higher in obese children (OR 3.42, 95% confidence interval (CI) 1.18 - 9.95, $P = 0.02$) compared with children of normal weight.
Xue et al. (2015) (32)	Case-control study	49 obese and 27 non-obese children	2 - 14	BMI	Eleven EDCs, such as BPA were found in 470% of urine samples. No correlation between BPA levels and body mass index.

Li et al. (2015) (36)	Cross sectional study	1860 children	8 - 19	Fat mass index (FMI) and lean body mass index (LBMI)	Higher quartiles and log-transformed urinary BPA levels were significantly associated with elevated lean body mass index (LBMI) z-scores in boys ($P < 0.05$), and significantly associated with elevated fat mass index (FMI) z-scores in girls ($P < 0.05$). Lower urinary BPA concentration was associated with lower percentage of trunk fat in girls (compared to 1st quartile; 2nd-quartile: $b \%$ 2.85, 95% CI, 0.92e4.78; 3rd-quartile: $b \%$ 2.57, 95% CI, 0.28e4.85; 4thquartile: $b \%$ 2.79, 95% CI, 0.44e5.14; all $P < 0.05$).
Agay-Shay et al. (2015) (33)	Cohort study	470 children	7	Weight, height, BMI z-score	BPA exposures did not confound this association.
Vafeiadi et al. (2015) (37)	Cohort study	500 mother-child pairs	6 months-4 years of children	Birth weight, BMI from 6 months to 4 years of age, WC, skinfold thickness, blood pressure, serum lipids, C-reactive protein, and adipokines at 4 years of age.	They found that higher BPA concentrations in children's urine were associated with increased BMI z-score, waist circumference, and the sum of skin fold thickness at 4 years of age. Prenatal BPA was negatively associated with BMI and adiposity measures in girls and positively in boys
Pinney et al. (2016) (60)	Cross sectional study	second trimester amniotic fluid (AF)	Infant	BW	The mean BW of infants with AF BPA 0.40 - 2.0 ng/mL was 241.8 g less than infants with AF BPA less than the LOQ after controlling for covariates ($P = 0.049$). No effect was seen outside this range indicating a non-monotonic effect. This study results suggest that low level BPA exposure in utero decreases BW and needs further study.
Casas et al. (2016) (34)	Cohort study	488 mother-child pairs	Infant	Weight, birth length, HC at birth, and placental weight.	Results did not support the associations of exposure to BPA during pregnancy with fetal growth parameters.
Buckley et al. (2016) (35)	Cohort study	404 healthy women and infants	4 - 9	BMI, CDC SASMacro	Results did not show associations of bisphenol A with childhood percent fat mass.

Table 2. Summary of Studies Examining the Association Between PAEs and Childhood Obesity

First Author and Publication Year	Study Type	Population Studied	Participants' Age, y	Phthalate Type	Outcome	Main Results
Hatch et al. (2008) (42)	Cross sectional study	4369 participants	6 - 8	Monoethyl phthalate (MEP), mono(2-ethylhexyl) phthalate (MEHP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP)	BMI, WC	Positive associations were found for MEOHP, MEHHP, MEP, and MBP in females, BMI and WC increased with MEP quartile in adolescent girls.
Boas et al. (2010) (48)	Cross sectional study	845 children	4 - 9	MEP; MBP; monobenzyl phthalate (MBzP); mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); mono-n-octyl phthalate (MOP) and monoisononyl phthalate (MiNP) and monocarboxyisooctyl phthalate (MCiOP)	height, weight, body surface, and height gain	Most phthalate metabolites were negatively associated with height, weight, body surface, and height gain in both sexes.
Teitelbaum et al. (2012) (45)	Cohort study	387 children	6 - 8	MEP; MBP; mono-(3-carboxypropyl) phthalate (MCPP); MBzP; mono-isobutyl phthalate (MiBP); mono-(2-ethyl-hexyl) (MEHP); mono-(2-ethyl-5-oxohexyl) (MEOHP); mono-(2-ethyl-5-carboxypentyl) (MECPP); and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	BMI, BMI z-score, and WC	Dose response relationships were seen with MEP and the sum of low molecular-weight phthalates and BMI and WC among overweight children; for increasing MEP concentration quartiles among girls.

Trasande et al. (2013) (46)	Cross sectional study	2,884 children	6 -19	Diethylhexyl phthalate (DEHP)	BMI z-score	In stratified, multivariable models, each log unit (roughly 3-fold) increase in low-molecular-weight metabolites was associated with 21% and 22% increases in odds (95% CI: 1.05 - 1.39 and 1.07 - 1.39, respectively) of overweight and obesity, and a 0.090-SD unit increase in BMI z-score (95% CI: 0.003 - 0.18), among non-Hispanic blacks.
Wang et al. (2013) (47)	Cross sectional study	124 normal weight, 53 overweight, and 82 obese students	8 -15	MEHP, MEOHP, MECPP, MEHHP, MBP, MiBP, MEP, mono[(2-carboxymethyl)hexyl] phthalate (MCMHP), mono(4-hydroxybutyl) phthalate (MHBP), monomethyl phthalate (MMP), monocyclohexyl phthalate (MCHP), MBzP, monoisononyl phthalate (MiNP), and monoethyl phthalate (MOP).	BMI, WC	The urine specific gravity-corrected concentrations of nine urine phthalate metabolites and five molar sums were positively associated with BMI or WC in children after adjustment for age and sex.
Saravanabhavan et al. (2014) (44)	Cross sectional study	5,604 population	children (6 -11), adolescents (12 -19), and adults (20 -49)	MEP and diethyl phthalate (DEP)	Body weight	They observed that body weight affects the trends in the MEP concentrations significantly among children and adolescents.
Choi et al. (2014) (41)	Case-control study	young girls	6 -14	MEP, Dibutyl phthalate (DBP), MBP, DEHP, MEHP, phthalic anhydride (PA) and MBzP	BMI	PA in urine and MEP, DBP and PA in serum showed statistically significant differences between the control and obese groups; those compounds were considered to be associated with obesity. In addition, DHEA in serum showed a statistically significant difference between obese and control groups.

Buser et al. (2014) (40)	Cross sectional study	population	6 - 19	MnBP, MEP, mono-isobutyl phthalate (MiBP), MECPP, MEHHP, MEOHP, MEHP, MBzP, mono-(carboxynonyl) phthalate (MCNP), and mono-(carboxyoctyl) phthalate (MCOP)	BMI z-score	MnBP, MEP and MiBP are significantly ($P < 0.05$) associated with higher odds for obesity in male children and adolescents.
Hou et al. (2015) (43)	Cross sectional study	270 adolescents and 38 complainants	6.5 - 15 and 6.5 - 8.5	Dimethyl phthalate (DMP), DEP, DnBP, DiBP, BBzP, and DEHP	weight, height, WC, HC, and skin fold thickness	They found that urinary PAE metabolite concentrations (specifically, metabolites of DEP, DnBP, DiBP, and DEHP) were positively associated with the anthropometric indices for abdominal obesity.
Valvi et al. (2015) (49)	Cohort study	657 women in the first trimester	4 - 7	five high-molecular-weight phthalate metabolites (Σ HMWPm) and three low-molecular-weight phthalates (Σ LMWPm): including MBzP, MEHP, MEHHP, MEOHP, MECPP, MEP, MiBP, and MnBP	age- and sex-specific z-scores, BMI, waist-to-height ratio	The sum of five HMWPm was associated with lower weight z-score difference between birth and 6 months (β per doubling of exposure = -0.41; 95% CI: -0.75, -0.06) and BMI z-scores at later ages in boys (β = -0.28; 95% CI: -0.60, 0.03) and with higher weight z-score difference (β = 0.24; 95% CI: -0.16, 0.65) and BMI z-scores in girls (β = 0.30; 95% CI: -0.04, 0.64) (p for sex interaction = 0.01 and 0.05, respectively). The sum of three LMWPm was not significantly associated with any of the growth outcomes.
Agay-Shay et al. (2015) (33)	Cohort study	470 children	7	MBzP, MEHP, MEHHP, MEOHP, MECPP, MEP, MiBP, and MnBP	Weight, height, BMI z-score	Phthalates exposures did not confound this association.
Casas et al. (2016) (34)	Cohort study	488 mother-child pairs	infant	Eight phthalates [four DEHPm, MBzP, and three low-molecular-weight phthalate metabolites (LMWPm) including MEP, MiBP, MnBP	Birth weight, birth length, HC at birth, and placental weight.	MBzP was positively associated with birth weight among boys (48 g; 95% CI: 6, 90) but not in girls (-27 g; 95% CI: -79, 25) (interaction P value = 0.04).

Buckley et al. (2016) (35)	Cohort study	707 children	4-7	MEP, MnBP, MiBP, MCP, MBzP, MEHP, MEHHP, MEOHP, and MECPP.	BMI z scores	MECPP concentrations were positively associated with overweight/obese status in children (odds ratio [95% credible interval] = 2.1 [1.2, 4.0]) but not with BMI z scores (β = -0.02 [-0.15, 0.11]). We did not observe evidence of obesogenic effects for other metabolites. However, MEP and Σ DEHP concentrations were inversely associated with BMI z scores among girls (MEP beta = -0.14 [-0.28, 0.00]; Σ DEHP beta = -0.12 [-0.27, 0.02]).
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