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Early-life exposure to endocrine disrupting chemicals associates with childhood obesity

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Increasing prevalence of childhood obesity poses threats to the global health burden. Because this rising prevalence cannot be fully explained by traditional risk factors such as unhealthy diet and physical inactivity, early-life exposure to endocrine disrupting chemicals (EDCs) is recognized as emerging novel risk factors for childhood obesity. EDCs can disrupt the hormone-mediated metabolic pathways, affect children's growth and mediate the development of childhood obesity. Many organic pollutants are recently classified to be EDCs. In this review, we summarized the epidemiological and laboratory evidence related to EDCs and childhood obesity, and discussed the possible mechanisms underpinning childhood obesity and early-life exposure to non-persistent organic pollutants (phthalates, bisphenol A, triclosan) and persistent organic pollutants (dichlorodiphenyltrichloroethane, polychlorinated biphenyls, polybrominated diphenyl ethers, per- and polyfluoroalkyl substances). Understanding the relationship between EDCs and childhood obesity helps to raise public awareness and formulate public health policy to protect the youth from exposure to the harmful effects of EDCs.

Keywords: Endocrine disrupting chemicals, Childhood obesity, Persistent organic pollutants, Early-life exposure

Introduction

Childhood obesity is increasingly recognized as an important health hazard. In addition to the social stigma and psychological consequences, obesity is associated with increased risk of type 2 diabetes mellitus, hypertension, hyperlipidemia, sleep apnea, cardiovascular disease, cancer and arthritis.¹⁾ There is also growing evidence showing that childhood obesity may herald adult obesity.²⁻⁶⁾ The Global Burden of Diseases study recently estimated that nearly 110 million children and adolescents were obese.⁷⁾ Alarming, the prevalence of youth that are overweight and obesity has doubled in the last three decades, with its rate of increase greater than that of adult obesity in most countries.⁷⁾

Unhealthy diet and physical inactivity are traditional risk factors for obesity. Greater energy intake than energy expenditure results in positive energy balance and obesity.⁸⁾ However, lifestyle and genetic factors are unable to fully explain the rising prevalence and incidence of overweight or obese children.^{9,10)} Growing evidence from epidemiological studies indicates that exposure to environmental chemical pollutants may contribute to this global epidemic of childhood obesity.¹¹⁻¹³⁾ Children who have early exposure to these pollutants even during intrauterine period may experience either an increase in body weight at young age or a catch-up increase of body weight in later life.^{14,15)}

Endocrine disrupting chemicals

Endocrine disrupting chemicals (EDCs) are a class of environmental pollutants that affect

the endocrine function and modulate our risk of developing metabolic diseases including obesity.¹⁶⁾ EDCs include organic chemicals (such as nonpersistent organic chemicals and persistent organic pollutants [POPs]) and its analogs (such as alkylphenols). They are mainly man-made chemicals or compounds which are widely found in food, daily use products/materials, and the environment (such as water, indoor air, and dust), that can accumulate in human body through the food chain.¹⁷⁻¹⁹⁾ Intraplacental transfer, breast milk consumption and children's hand to mouth behavior are the common ways that infancy and young children are exposed to EDCs in early-life. Table 1 summarizes the characteristics of some EDCs.

Emerging epidemiological and biological evidence suggests that rapid weight gain during infancy or later childhood might be related to maternal or early-life exposure to EDCs.²⁰⁻²²⁾ In this review, we discuss this interesting relationship and the potential mechanisms.

1. Nonpersistent organic chemicals

Nonpersistent organic chemicals have a short half-life in the range of less than 24 hours to one week and include phthalates, bisphenol A and triclosan.

Phthalates

Phthalates (phthalate esters) are a family of esters of phthalic acid and are mainly used as plasticizers to soften polyvinyl chloride or increase the durability and longevity of consumer products (such as containers and plastics) (Table 1). Phthalates can be found in food, pharmaceutical, cosmetic²³⁾ and baby caring products.^{24,25)} Ingestion, respiration or dermal absorption are the routes for phthalates exposure.^{26,27)} Compared to high molecular weight (HMW) congeners (such as DEHP [di-2-ethylhexyl phthalate], DnOP [di-n-octyl phthalate]),²⁸⁾ low

molecular weight (LMW) phthalates (such as DEP [diethyl phthalate], DnBP [di-n-butyl phthalate], and DiBP [di-isobutyl phthalate]) have higher bioaccumulation factors, which may lead to high concentration within the body and increase the health risk.²⁹⁾ In many developed countries, LMW phthalates have been gradually replaced by HMW phthalates or nonphthalates plasticizers for health concerns.³⁰⁾ However, LMW phthalates (such as DEP, a common solvent for fragrance) are still frequently detected in consumer products.³¹⁾

Urinary or serum phthalates and their metabolites have been found to be significantly associated with body size and body mass index (BMI) in children and adolescents based on epidemiology studies³²⁻³⁶⁾ (Table 2). A 4-year prospective study involving 1,239 girls in the United States (US) showed that early exposure to high concentration of LMW phthalates (MEP [monoethyl], MBP [mono-n-butyl], MiBP [mono-isobutyl]) at age 6–8 years were positively associated with weight gain ($\beta=1.2$, 95% confidence interval [CI], 0.41–2.1 kg/m²) and increased waist circumference ($\beta=3.9$, 95% CI, 1.3–6.5 cm) than later exposure at age 7–13 years.³⁷⁾ Furthermore, MEHP (mono-(2-ethylhexyl) phthalate), the urinary metabolites of DEHP, were positively correlated with fasting glucose to insulin ratio (FGIR) (Spearman's correlation coefficient, 0.341; $P=0.039$).³⁸⁾ DEHP exposure in female mice was associated with increased abdominal visceral fat accumulation in the offspring.³⁹⁾ However, another Spanish birth cohort study reported that high maternal urine HMW phthalates (including MBzP [mono-benzyl phthalate], MEHP, MEHHP [mono(2-ethyl-5-hydroxyhexyl) phthalate], MEOHP [mono(2-ethyl-5-oxohexyl) phthalate], and MECPP [mono(2-ethyl-5-carboxypentyl) phthalate]) was negatively associated with body weight z-score in infants aged 0–6 months ($\beta=-0.41$, 95% CI, -0.75 to -0.06).⁴⁰⁾ Therefore, more studies are needed to delineate the potential effects of phthalates on childhood obesity taking sex

Table 1. Characteristics of endocrine disrupting chemicals (EDCs) related to childhood obesity

EDCs	Biological half-life	Usage	Route of exposure
Phthalates	<24 hours	PVC plastics, food package, synthetic leather, toys, scent retainer, personal care products, adhesives	Ingestion, respiration, dermal absorption, placenta transfer
BPA	~6 hours	Consumer plastics and polycarbonate products (such as water bottles, plastic food containers and cans), and medical materials (such as dental fillings)	Oral absorption, placenta transfer
Triclosan	<24 hours	Antimicrobial soaps, personal care products, toothpaste, cleaning products	Oral and dermal absorption; placenta transfer
DDT	~20–30 years	Organochlorine pesticides	Diet ingestion and respiration, dermal absorption, placenta and breastfeeding transfer
PCBs	~10 years	Industrial production (such as transformers and large capacitors), nominally closed systems (such as hydraulic fluids and lubricants) and open applications (such as carbon-less copy paper)	Diet ingestion and respiration, dermal absorption, placenta and breastfeeding transfer
PBDEs	1.8–11.7 years	Used as flame retardant in many products, such as building materials, electronics, furnishings, motor vehicles, airplanes, plastics, polyurethane foams, and textiles	Diet ingestion, respiration and dermal absorption, placenta and breastfeeding transfer
PFASs	3.8–7.3 years	Stain- or oil-resistant coating materials for textiles, carpet, food containers, fire-fighting foams and industrial surfactants	Age-related behavioral contact and diet ingestion, placenta and breastfeeding transfer

BPA, bisphenol A; DDT, dichlorodiphenyltrichloroethane; PCB, polychlorinated biphenyl; PBDE, polybrominated diphenyl ether; PFAS, Per- and polyfluoroalkyl substance.

into consideration.

Bisphenol A

Bisphenol A (BPA) belongs to bisphenols, a group of chemical compounds with 2 hydroxyphenyl functionalities. BPA is commonly used in consumer plastics and polycarbonate products (such as water bottles, plastic food containers, and cans), as well as medical materials (such as dental fillings) (Table 1). Oral absorption is the major exposure pathway because BPA can leak into food and beverage from containers.⁴¹⁻⁴³ Its short biological half-life (about 6 hours) allows for easy detection of BPA and its conjugates in urine.⁴⁴

Table 2 summarizes the cross-sectional and prospective cohort studies that have examined the relationship between exposure to BPA and risk of childhood obesity. In the Columbia Center for Children’s Environmental Health birth cohort study, increased exposure to BPA in children aged 7 years was associated with high fat mass index, body fat and waist circumference⁴⁵ (Table 2). Maternal BPA concentration was shown to be associated with increased plasma leptin levels in boys.⁴⁶ Some cross-sectional studies has found that early-life

exposure to BPA is positively associated with obesity in children and adolescents (Table 2).^{47,48}

In rats, perinatal exposure to BPA promotes adipogenesis and weight gain.^{49,50} Results from a mouse study also revealed that exposure to BPA during fetal period led to age-related increase in body weight due to an increase in adipose tissue mass and volume.⁵¹

Several BPA substituents such as bisphenol F (BPF) and bisphenol S (BPS) are currently available. However, these substituents have a wide spectrum of toxicities with potential endocrine-disrupting effects, particularly BPS which has been shown to be as hormonally active as BPA.^{52,53} However, a study of 1,521 participants aged 20 years or older in the US reported that only urinary BPA was significantly associated with obesity, but not BPF or BPS.⁵⁴ Continued biomonitoring of bisphenols and evaluation of their health effects in human are warranted.

Triclosan

Triclosan (2,4,4'-trichloro-2'-hydroxy-diphenyl ether) is an antibacterial reagent commonly found in pharmaceuticals

Table 2. Epidemiological evidence for the association among EDCs and childhood obesity

Author/Year	Population/study design	Location	Objects	Measured EDCs	Outcome (IDR/aOR; 95% CI)
Buser ³² /2014	NA/cross-sectional study	United States	6–19 years old	Phthalates: MnBP, MEP, MiBP, MECPP, MEHHP, MEOHP, MEHP, MBzP, MCNP, MCOP	LMP (MnBP, MEP, and MiBP) are significantly associated with higher odds for obesity in male children in second, third and highest quartiles (aOR, 2.96; 95% CI, 1.66–5.30; aOR, 2.80; 95% CI, 1.60–4.90; aOR, 2.84; 95% CI, 1.40–5.78) and adolescents in second, third and highest quartiles (aOR, 3.97; 95% CI, 2.23–7.08; aOR, 3.13; 95% CI, 1.69–5.81; aOR, 5.39; 95% CI, 1.87–15.53).
Zhang ³³ /2014	593/cross-sectional study	Shanghai, China	School-aged children	Phthalates: MEP, MBP, MMP, MEHP, MEOHP, MEHHP	Urinary concentrations of MBP and sum of LMP was positively associated with obesity in boys (OR, 5.768; 95% CI, 1.622–20.515; OR, 6.841; 95% CI, 2.073–22.575), while concentrations of MEOHP (OR, 0.092; 95% CI, 0.009–0.958), MEHHP (OR, 0.084; 95% CI, 0.008–0.910), and sum of DEHP metabolites (gMEHP) (OR, 0.078; 95% CI, 0.008–0.791) were negatively associated with girls' obesity.
Kim ³⁴ /2015	128/cohort study	Republic of Korea	Healthy pregnant women and newborns	DEHP metabolites: MEHHP, MEOHP	MEHHP and MEOHP were positively associated with triglyceride levels ($\beta=0.15$, 95% CI, 0.024–0.267; $\beta=0.13$, 95% CI, 0.009–0.256); total urinary DEHP was positively associated with triglyceride ($\beta=0.14$, 95% CI, 0.020–0.267); besides, urinary DEHPs were positively associated with the BMI z-scores of new born (first 3 month) (OR, 4.35; 95% CI, 1.20–15.72). Both MEHHP and MEOHP showed increased OR for body mass increase over the 50th centile (OR, 4.43; 95% CI, 1.22–16.04; OR, 3.91; 95% CI, 1.12–13.65).
Hatch ³⁵ /2008	4,369/cohort study	United States	2–59 years old	Phthalates: MEP, MEHP, MBP, MBzP, MEHHP, MEOHP	MEHP was inversely related to BMI in adolescent girls (adjusted mean BMI=25.4, 23.8; 95% CI, 23.4–22.9)

Table 2. Epidemiological evidence for the association among EDCs and childhood obesity (continued)

Author/Year	Population/ study design	Location	Objects	Measured EDCs	Outcome (IDR/aOR; CI)
Teitelbaum ³⁶ / /2012	521/cohort study	New York	6–8 years old children	Phthalates: low MWP: MEP, MBP and MiBP; high MWP: MECPP, MEHHP, MEOHP, MEHP and MBzP	MEP (67,131,235,948 µg/g creatinine) has a dose relationship with quartiles girls adjusted BMI ($\beta=21.3$, 95% CI, 20.5–22.2; $\beta=21.7$, 95% CI, 20.7–22.8; $\beta=23.8$, 95% CI, 22.7–24.8; $\beta=23.5$, 95% CI, 22.5–24.3); adjusted waist circumference ($\beta=73.4$, 95% CI, 71.0–75.7; $\beta=73.5$, 95% CI, 70.7–76.4; $\beta=79.2$, 95% CI, 76.3–82.0; $\beta=78.8$, 95% CI, 76.3–81.3)
Hoepner ⁴⁵ / /2016	375/birth cohort	United States	Pregnant mother and their child (age 3–7 years)	BPA	Prenatal urinary BPA concentrations were positively associated with children fat mass index at age 7 ($\beta=0.31$ kg/m ² ; 95% CI, 0.01–0.60), percent body fat ($\beta=0.79$; 95% CI, 0.03–1.55, $P=0.04$), and waist circumference ($\beta=1.29$ cm; 95% CI, 0.29–2.30)
Volberg ⁴⁶ / /2013	188/longitudinal cohort study	California, United States	Pregnant women >18 years of age, <20 weeks gestation and their child	BPA	Late pregnancy urinary BPA concentrations were positively associated with 9-year leptin levels ($\beta=0.06$, 95% CI, 0.01–0.11) in boys. But in girls, early pregnancy BPA concentrations were positively associated with 9-year adiponectin levels ($\beta=3.71$, 95% CI, 0.38–7.04).
Trasande ⁴⁷ / /2012	2,838/ cross sectional study	United States	Age 6–19 years	BPA	In 4 quartiles, the correlation between urinary BPA and obesity are (OR, 2.22; 95% CI, 1.53–3.23) in quartiles 2, 3 (OR, 2.09; 95% CI, 1.48–4.95), 4 (OR, 2.53; 95% CI, 1.72–3.74).
Wang ⁴⁸ / /2012	2,921/cross- sectional study	Shanghai, China	Age 8–15 years	BPA	BPA was detected in 84.9% of urine samples with a median concentration of 0.60 ng/mL. Urinary BPA was positively associated with children BMI ($\beta=0.02$, 95% CI, 0.001–0.038) aged 8–11 years old.
Li ⁶¹ / /2015	2,898 /cohort study	United States	Children (6–19 years old)	Triclosan	Urinary triclosan was associated with aOR 0.34 (95% CI, 0.05–0.64) kg/m ² lower level of BMI and 0.92 (95% CI, 0.09–1.74) cm smaller waist circumference in boys, and a 0.62 (95% CI, 0.31–0.94) kg/m ² lower level of BMI and 1.32 (95% CI, 0.54–2.09) cm smaller waist circumference in girls.
Tang- Péronard ⁷² / /2014	640/prospective cohort study	Faroe Islands	Pregnant women who gave birth between November 1997 to March 2000	PCBs (138, 153, and 180) and DDE	Serum PCBs was positively associated with increased BMI ($\beta=2.07$; 95% CI, 0.59–1.65) of 7-year-old girls with overweight mothers, and PCBs and DDE were also associated with an increased change in BMI from 5 to 7 years of age (PCB: $\beta=1.23$, 95% CI, 0.42–2.05; DDE: $\beta=1.11$, 95% CI, 0.30–1.92). PCBs was associated with increased waist circumference in girls with overweight mothers ($\beta=2.48$, 95% CI, 1.10–3.85) and normalweight mothers ($\beta=1.25$, 95% CI, 0.04–2.45); DDE was associated with increased waist circumference only in girls with overweight mothers ($\beta=2.21$, 95% CI, 0.84–3.56).
Valvi ⁷³ / /2014	2,150/birth cohort study	Spanish	Pregnant women (>16 years)	DDT, DDE, HCB, β -hexachlorocyclohexane, and PCB congeners 28, 52, 101, 118, 138, 153, and 180	The serum concentration (ng/g lipid) of DDE in pregnancy is about 132±2.4. Serum DDE was positively associated with the rapid growth in the total populations ($\beta=1.13$; 95% CI, 1.01–1.26), and overweight at 14 months age ($\beta=1.15$; 95% CI, 1.03–1.28).
Warner ⁷⁴ / /2014	601/longitudinal birth cohort study	California, United States	Pregnant women (>18 years), their newborns (1–7 years)	<i>o,p'</i> -DDT, <i>p,p'</i> -DDT, <i>p,p'</i> -DDE	Among boys, 10-fold increases in prenatal DDT and DDE concentrations were associated with increased odds of becoming overweight or obese (for <i>o,p'</i> -DDT: aOR, 2.5; 95% CI, 1.0–6.3; for <i>p,p'</i> -DDT: aOR, 2.1; 95% CI, 1.0–4.5). The odds ratios for girls were not significant.

Table 2. Epidemiological evidence for the association among EDCs and childhood obesity (continued)

Author/Year	Population/ study design	Location	Objects	Measured EDCs	Outcome (IDR/aOR; CI)
Wang ⁴⁸⁾ /2012	2,921/cross-sectional study	Shanghai, China	Age 8–15 years	BPA	BPA was detected in 84.9% of urine samples with a median concentration of 0.60 ng/mL. Urinary BPA was positively associated with children BMI ($\beta=0.02$, 95% CI, 0.001–0.038) aged 8–11 years old.
Li ⁶¹⁾ /2015	2,898 /cohort study	United States	Children (6–19 years old)	Triclosan	Urinary triclosan was associated with aOR 0.34 (95% CI, 0.05–0.64) kg/m ² lower level of BMI and 0.92 (95% CI, 0.09–1.74) cm smaller waist circumference in boys, and a 0.62 (95% CI, 0.31–0.94) kg/m ² lower level of BMI and 1.32 (95% CI, 0.54–2.09) cm smaller waist circumference in girls.
Tang-Péronard ⁷²⁾ /2014	640/prospective cohort study	Faroe Islands	Pregnant women who gave birth between November 1997 to March 2000	PCBs (138, 153, and 180) and DDE	Serum PCBs was positively associated with increased BMI ($\beta=2.07$; 95% CI, 0.59–1.65) of 7-year-old girls with overweight mothers, and PCBs and DDE were also associated with an increased change in BMI from 5 to 7 years of age (PCB: $\beta=1.23$, 95% CI, 0.42–2.05; DDE: $\beta=1.11$, 95% CI, 0.30–1.92). PCBs was associated with increased waist circumference in girls with overweight mothers ($\beta=2.48$, 95% CI, 1.10–3.85) and normalweight mothers ($\beta=1.25$, 95% CI, 0.04–2.45); DDE was associated with increased waist circumference only in girls with overweight mothers ($\beta=2.21$, 95% CI, 0.84–3.56).
Valvi ⁷³⁾ /2014	2,150/birth cohort study	Spanish	Pregnant women (>16 years)	DDT, DDE, HCB, β -hexachlorocyclohexane, and PCB congeners 28, 52, 101, 118, 138, 153, and 180	The serum concentration (ng/g lipid) of DDE in pregnancy is about 132±2.4. Serum DDE was positively associated with the rapid growth in the total populations ($\beta=1.13$; 95% CI, 1.01–1.26), and overweight at 14 months age ($\beta=1.15$; 95% CI, 1.03–1.28).
Warner ⁷⁴⁾ /2014	601/longitudinal birth cohort study	California, United States	Pregnant women (>18 years), their newborns (1–7 years)	<i>o,p'</i> -DDT, <i>p,p'</i> -DDT, <i>p,p'</i> -DDE	Among boys, 10-fold increases in prenatal DDT and DDE concentrations were associated with increased odds of becoming overweight or obese (for <i>o,p'</i> -DDT: aOR, 2.5; 95% CI, 1.0–6.3; for <i>p,p'</i> -DDT: aOR, 2.1; 95% CI, 1.0–4.5). The odds ratios for girls were not significant.
Lignell ⁸⁷⁾ /2013	413/cross-sectional study	Swedish	Pregnant women and newborns	PCB (138, 153 and 180) PBDE- (-47, -99, -100, -153)	Di-ortho PCBs in breast milk was positively associated with birth weight ($\beta=143$, $P=0.03$); the total di-ortho PCBs in breast milk from the mothers was 103±54 ng/g lipid.
Dallaire ⁸⁹⁾ /2014	548/prospective cohort study	Inuit	Children (8-14 years)	PCB 153	Children blood PCB-153 concentrations were associated with reduced weight ($\beta=-0.15$, $P\leq 0.01$), height ($\beta=-0.39$, $P\leq 0.001$) and head circumference ($\beta=-0.28$, $P\leq 0.001$) during childhood.
Erkin-Cakmak ⁹⁶⁾ /2015	224/longitudinal birth cohort study	California, United States	Pregnant women (>18 years) and their children	PBDEs (-17, -28, -47, -66, -85, -99, -100, -153, -154, and -183)	The sum of four penta BDEs (-47, -99, -100, -153) concentration (log ₁₀) in child serum was positively associated with overweight (aOR, 0.36; 95% CI, 0.14–0.94), while inversely associated with BMI ($\beta=0.44$, 95% CI, -0.83 to -0.06) as well as waist circumference ($\beta=-0.35$, 95% CI, -0.66 to -0.04) at 7 years age; Besides, BDE -100 and BDE -153 was significantly associated with children overweight at age of 7 years with aOR 0.40 (95% CI, 0.16–1.03) and 0.08 (95% CI, 1.03–0.27) respectively.

Table 2. Epidemiological evidence for the association among EDCs and childhood obesity (continued)

Author/Year	Population/study design	Location	Objects	Measured EDCs	Outcome (IDR/aOR; CI)
Vuong ⁹⁷ / /2016	318/birth cohort study	Ohio, United States	Pregnant women (>18 years) and their children	BDEs -17, -28, -47, -66, -85, -99, -100, -153, -154, and -183.	No statistically significant associations between prenatal PBDEs and height or weight z-score. A 10-fold increase in maternal serum BDE-153 was associated with lower BMI z-score ($\beta=-0.36$, 95% CI, -0.60 to -0.13) at 2–8 years, smaller waist circumference ($\beta=-1.81$ cm; 95% CI, -3.13 to -0.50) at 4–8 years, and lower percent body fat ($\beta=-2.37$; 95% CI, -4.21 to -0.53) at 8 years.
Braun ¹⁰⁸ / /2016	468/prospective cohort study	Ohio, United States	Pregnant women: 16 \pm 3 weeks gestation; >18 years old; living in a home built before 1978; no history of HIV infection; not taking any medications for seizure or thyroid disorders.	PFOA, PFOS, PFNA, and PFHxS	Children born to women in the top two PFOA tertiles had greater adiposity at 8 years than children in the 1st tertile. Waist circumference (cm) was higher among children in the 2nd (PFOA, 5.3 ng/mL) ($\beta=4.3$; 95% CI, 1.7–6.9) and 3rd tertile (PFOA, 9.4 ng/mL) ($\beta=2.2$; 95% CI, 20.5–4.9) compared to children in the 1st tertile (PFOA, 3.3 ng/mL). Children in the top 2 PFOA tertiles also had greater BMI gains from 2 to 8 years compared to children in the 1st tertile ($P<0.05$). No significantly association observed between PFOS, PFNA, and PFHxS with adiposity in children.
Manzano-Salgado ¹¹⁰ / /2017	2,150/birth cohort study	Gipuzkoa, Sabadell, and Valencia, Spanish	Pregnant women (16 years or older)	PFHxS, PFOS, PFOA, and PFNA	The most abundant compounds are PFOS and PFOA with geometric mean concentrations are 5.80 and 2.32 ng/mL, respectively. Prenatal serum PFHxS was positively associated with children serum triglycerides z-score ($\beta=0.11$, 95% CI, 0.01–0.21).

EDC, endocrine disrupting chemical; IDR, incidence density ratio; aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; β , regression coefficient; MWP, molecular-weight phthalates; LMP, low molecular-weight phthalate; MEP, monoethyl phthalate; MBP, mono-n-butyl phthalate; MCPP, mono-(3-carboxypropyl); MBzP, mono-benzyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MECPP, mono(2-ethyl-5-carboxy-pentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; DEHP, di-2-ethylhexyl phthalate; MMP, monomethyl phthalates; MnBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MCNP, mono-(carboxynonyl) phthalate; MCOP, mono-(carboxyoctyl) phthalate; BPA, bisphenol A; HCB, hexachlorobenzene; PCB, polychlorinated biphenyl; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; PBDE, Polybrominated diphenyl ether; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexanesulfonic acid; *p,p'*-DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane; *o,p'*-DDT, 1,1,1-trichloro-2-(*p*-chlorophenyl)-2-(*o*-chlorophenyl)-ethane.

and personal care products such as toothpastes, cosmetics, soaps, surgical cleaning treatment reagents and toys (Table 1).⁵⁵ Similar to BPA, its biological half-life is very short (<24 hours), and the majority (24%–83%) was excreted in urine after 4 days exposure.⁵⁶ An individual can also be exposed to triclosan via skin contact.⁵⁷

Recent studies have suggested triclosan may be toxic to humans in addition to having antibacterial activity.⁵⁸ Pregnant rats exposed to triclosan from 8 days before mating to lactation day 21 developed primary hypothyroidism with decreased total serum T4 and T3 level. Pups also had a lower body weight on postnatal day 20 than that were not exposed to triclosan.⁵⁹ Although intrauterine exposure to triclosan was associated with reduced body weight in offspring, male triclosan-exposed rats were 12.5% heavier at 4 months ($P<0.001$) than their unexposed counterparts, while females were 19% heavier for at 8 months than their unexposed counterparts ($P=0.01$).⁶⁰

In a cross-sectional analysis of the US National Health and Nutritional Examination Surveys involving 7,964 participants, there was an inverse association between urinary triclosan level

and obesity in children aged 6–19 years ($\beta=-0.47$, 95% CI, -0.69 to -0.26) (Table 2).⁶¹ This finding was replicated in other cohort studies with possible gender difference; girls with a high urine triclosan level (>13.83 $\mu\text{g/mL}$) had a reduced plasma leptin level ($\beta=0.4$, 95% CI, 0.2–1.1).^{62,63} Taken together, these data indicate an inconsistent relationship between triclosan exposure and childhood obesity, perhaps due to variations in study design and/or participants' characteristics.

1. Persistent organic pollutants

POPs are EDCs that persist in the environment and tend to bioaccumulate through food chain.⁶⁴ Due to their lipophilicity, most POPs can accumulate in adipose tissue, which then act as a toxicity pool.⁶⁵

Dichlorodiphenyltrichloroethane

Dichlorodiphenyltrichloroethane (DDT) belongs to the

organochlorine pesticides group and refers to a mixture of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)-ethane (*p,p'*-DDT) and 1,1,1-trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)-ethane (*o,p'*-DDT). Although the usage of DDT has been banned worldwide since the last century, it is still commonly used in malaria-endemic countries such as sub-Saharan Africa and India.⁶⁶⁾ Of note, its half-life in the atmosphere and soil can be as long as 2.5 years and 20–30 years, respectively (Table 1).⁶⁷⁾ Previous studies revealed that DDT posed negative effects on the reproductive system by altering endometrial function through kinase transduction pathway via an estrogen receptor-independent mechanism.^{68,69)} DDT could increase the gene expressions regulating adipogenesis such as peroxisome-proliferator activated receptor- γ (PPAR γ) and CCAAT/enhancer-binding protein α (C/EBP α), enhance adipocyte differentiation from preadipocytes and adipogenic stem cells, which resulted in increased cellular uptake of fatty acids.^{70,71)}

Several studies have demonstrated that prenatal exposure to DDT and dichlorodiphenyldichloroethylene (DDE) is associated with childhood obesity,^{20,72,73)} with possible gender differences. Every 10-fold increase in prenatal DDT and DDE concentrations was positively associated with increased odds of becoming overweight or obesity in boys (for *o,p'*-DDT, adjusted odds ratio [aOR], 2.5; 95% CI, 1.0–6.3; for *p,p'*-DDT, aOR, 2.1; 95% CI, 1.0–4.5), but not reported in girls.⁷⁴⁾ This obesogenic effect was evident in the first 6 months after birth and might persist until teenage or adulthood.^{20,74,75)} However, isomers of DDT may have different effects. Every unit increase in *p,p'*-DDT was associated with increased birth weight $\beta=274$ g (95% CI, 122–425), while exposure to either *o,p'*-DDT was associated with decreased birth weight $\beta=-153$ g (95% CI, -296 to -10).⁷⁶⁾ Given the similarity in molecular structure between DDT and thyroid hormones, it has been postulated that DDT may promote obesity via disruption of thyroid homeostasis, although this requires confirmation in future mechanistic studies.^{77,78)}

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are derived from biphenyl, where the hydrogen atoms of biphenyl are replaced by chlorine atoms to form 209 different congeners. PCBs are widely employed in industrial production (transformers and large capacitors), nominally closed systems (hydraulic fluids and lubricants) and open applications (carbonless copy paper) (Table 1).⁷⁹⁾ PCBs have been banned since 2001, after the Stockholm Convention.⁸⁰⁾ They have long half-lives (0.4–11.4 years in humans and 1–20 years in soil).^{81–84)} Due to their lipophilicity, PCBs tend to accumulate in adipose tissue. Exposure to PCBs could promote adipogenesis and increase the release of inflammatory cytokines and lipid accumulation during adipocytes differentiation.^{64,85,86)}

In a cross-sectional study involving 526 mother-child pairs, prenatal exposure to di-ortho PCBs (including PCB-138, -153, -180) was significantly associated with increased birth weight ($\beta=137$ g; 95% CI, 76–198; $P=0.02$).⁸⁷⁾ This was further

supported by several prospective cohort studies that reported the detrimental effect of prenatal PCBs exposure on the development of obesity during neonatal period, which might persist until childhood (Table 2).^{72,88)} By contrast, in another prospective cohort study in the Inuit population, plasma PCB-153 level was inversely associated with body weight during childhood (Table 2).⁸⁹⁾ A similar trend was found in a pooled analysis of seven European cohort studies; postnatal PCB 153 exposure was associated with a reduced weight-for-age z-score ($\beta=-0.10$; 95% CI, -0.19 to -0.01, for every interquartile range increase of 183 ng/g lipid).⁹⁰⁾

Different PCB congeners could have different effects on childhood obesity. Therefore, more epidemiological studies are needed to clarify the obesogenic effects of different congeners and total effects of PCBs mixture.

Polybrominated diphenyl ethers

Polybrominated diphenyl ethers (PBDEs) are organobromine compounds that have been extensively applied as flame retardants in consumer products including furniture foam, plastics, electronics and textiles (Table 1).⁹¹⁾ Use of PBDEs has been banned since 2004. However, they continue to enter the environment from consumer products and waste.⁹²⁾ Similar to PCBs, replacement of hydrogen atoms by bromine atoms in biphenyl ethers generates 209 congeners of PBDEs. In general, the biological half-life of PBDEs is long, which ranges from 1.8–3 years for BDE-47 to 6.6–11.7 years for BDE-153.⁹³⁾

Infants (73 ± 7 ng/g lipid) and young children (28 ± 8 ng/g lipid) had higher concentration of total PBDEs than adults (15 ± 5 ng/g lipid) after exposure via maternal transfer and breast milk consumption.⁹⁴⁾ BDE-47, -99, -100, and -153 were the most abundantly detected congeners.⁹⁵⁾ In a US longitudinal birth cohort involving 224 mother-child pairs, every 10-fold increase in maternal serum PBDEs (including BDE-47, -99, -100, -153) had an inverse association with BMI z-scores in girls ($\beta=-0.41$; 95% CI, -0.87 to -0.05) (Table 2).⁹⁶⁾ A cohort study involving 413 mothers in Sweden demonstrated that PBDEs (sum of BDE-47, -99, -100, and -153) level in breast milk were inverse associated with birth weight in the multivariate model ($\beta=-106$; 95% CI, -158 to -54).⁸⁷⁾ Another cohort study involving 318 mother-child pairs reported no statistically significant associations observed between prenatal PBDEs (including BDEs-28, -47, -99, -100, -153) and birth weight z-score, whereby a 10-fold increase in maternal serum BDE-153 was associated with a lower BMI z-score at 2–8 years, decreased waist circumference at 4–8 years, and decreased body fat percentage at 8 years (Table 2).⁹⁷⁾

Our research group and others have demonstrated that PBDEs induced *in vitro* adipocytes differentiation by increasing the expressions of genes involved in the adipogenesis and lipid accumulation.^{98–100)} In mice models, prenatal exposure of BDE 47 worsened hepatic steatosis and metabolic profiles in the offspring, possibly via the alteration of gut microbiome and impairment of insulin sensitivity.^{101,102)} In male rats, a low dose of BDE 47 increased plasma insulin-like growth factor

1 level and impaired glucose metabolism.^{103,104} These results suggest that BDE 47 can be an environmental obesogen, while the obesogenic effects of other PBDEs congeners remain to be verified in epidemiological and laboratory studies.

Per- and polyfluoroalkyl substances

Per- and polyfluoroalkyl substances (PFAS) belong to a class of synthetic fluorinated chemicals that are widely employed as stain- or oil-resistant coating materials for textiles, carpet, food containers and industrial surfactants.¹⁰⁵ The biological half-life of PFAS is more than 4 years. Given their relatively stable structure, PFAS are extremely resistant to chemical and biological degradation, with high bioaccumulation in human body through the food chain.^{105,106} Four types of PFAS including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS), are the most universally detected in the serum of pregnant women and children as well as in general population.¹⁰⁷⁻¹⁰⁹

Compared to health-based guidance of 0.04 µg/L for PFOA in drinking water, PFOS and PFOA are the most frequently detected congeners in the PFAS family and their geometric mean concentrations in pregnant women are 5.80 and 2.32 ng/mL respectively, while the mean concentration of PFNA and PFHxS are 0.66 and 0.61 ng/mL.¹¹⁰ Excess maternal PFOA exposure was associated with increased waist circumference ($\beta=4.3$; 95% CI, 1.7–6.9) in children at 8 years old (Table 2).¹⁰⁸ Furthermore, high prenatal PFAS, PFOA and PFOS levels were associated with increased serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels in children.^{110,111} Interestingly, another prospective cohort study involving 665 mother-child pairs observed inverse associations between PFOS or PFOA and homeostatic model assessment of insulin resistance when children were around 7 years old ($\beta=-10.1$, 95% CI, -16.4 to -3.3; and $\beta=-0.1$, 95% CI, -17.3 to -2.3 for PFOS and PFOA, respectively).¹¹²

In animal models, PFOA, PFOS and perfluoroalkyl acids increase lipid accumulation, promote insulin resistance and induce adipocytes differentiation, resulting in obesity.¹¹³⁻¹¹⁶ However, *in utero* exposure to C57BL/6J-Min/+ (multiple intestinal neoplasia) mice with either PFOS or PFOA did not significantly increase the body weight of offspring.¹¹⁷ Therefore, the obesogenic effects of PFOA and PFOS need to be verified with additional animal studies and epidemiological data.

Possible mechanisms linking POPs, obesity, and diabetes

There are several postulated mechanisms that can explain the effects of EDCs on early-life obesity, including mitochondrial dysfunction and epigenetic regulation.

Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction can induce the development of cardiometabolic diseases including obesity, diabetes and cancer.¹¹⁸ Mitochondrial dysfunction increases the accumulation of diacylglycerol (metabolites of fatty acids metabolism)¹¹⁹ and reactive oxygen species (ROS),¹²⁰ particularly in insulin-resistant tissues (such as liver tissue).¹¹⁸

In obese mice, exposure to a PCB mixture (Aroclor 1260) impaired mitochondrial function and increased adipokines level, which could mediate inflammation and insulin resistance.¹²¹ A study in C57BL/6J mice demonstrated that visceral obesity, insulin resistance and glucose intolerance occurred when mice were fed salmon contaminated with PCBs (PCB-28, -52, -101, -138, -153, -180).¹²² Taken together, these findings suggest that mitochondrial dysfunction is one of the key factors in the development of obesity associated with chronic exposure to POPs.

Oxidative stress also contributes to the development of obesity.^{123,124} Multiple studies showed that ROS such as H₂O₂ can induce adipocyte differentiation and lipid peroxidation, leading to obesity and metabolic syndrome.^{123,125-128} In addition to mitochondrial dysfunction,^{120,129} ROS increases the transcriptional activity of PPAR γ and C/EBP α , which are the key transcriptional factors for adipogenesis.^{100,130,131} Oxidative stress is often correlated with DNA oxidation because obesity causes significant oxidative stress, oxidative DNA damage, and changes of DNA methylation pattern in the tissue.^{126,132} BDE-47 has been reported to increase the intracellular and mitochondrial ROS levels, adipocyte differentiation, lipid peroxidation, and DNA oxidation.^{100,133,134} Importantly, inhibition of mitochondrial ROS production suppressed BDE-47-induced lipid accumulation and insulin resistance.¹⁰⁰ These results were confirmed by a decreased ratio of GSH to GSSG, which are biomarker of oxidative stress.

DNA methylation

DNA methylation, an epigenetic mechanism, involves addition of methyl groups to DNA, thereby modifying the activity of the DNA segment without changing the sequence. This can repress gene transcription, especially when methylation sites are located in a promoter region. Many POPs and BPA can induce DNA methylation.¹³⁵ Among 70 general workers in Arctic Council (which monitored the levels of pollutants in all Arctic environment), high serum POPs levels were associated with global DNA hypomethylation.¹³⁶ An inverse relationship was found between plasma levels of methylation of cytosine residues and many POPs including p,p'-DDT.

In a mouse model with the 3T3-L1 cell line, exposure to BDE-47 and PCB-153 altered DNA methylation levels.^{99,135} Three hypomethylation CpG sites were located in the promoter region of PPAR γ 2, which is the key transcription

factor for adipogenesis.^{99,135} *In vitro* studies had demonstrated that PFOS and PFOA induced adipocyte differentiation via DNA methylation and Nrf2 pathways.^{115,116,135} Thus, DNA methylation may be one of the mechanisms by which organic pollutants predispose animals to obesity.

Conclusions

This is epidemiological and preclinical evidence that perinatal exposure to EDCs has detrimental effects in children. Early-life exposure to EDCs may impose an increased risk of obesity in later life, likely via impaired mitochondrial function and epigenetic dysregulation. Well-designed animal and prospective cohort studies are needed to provide more mechanistic insights on the relationships between EDCs and childhood obesity. Heightened efforts from governments and other stakeholders are warranted to formulate effective health policy and disseminate health education programs to raise public awareness to protect our youth from the detrimental effects of EDCs.

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