Early-life exposure to EDCs: role in childhood obesity and neurodevelopment

Joseph M. Braun

Abstract | Endocrine-disrupting chemicals (EDCs) might increase the risk of childhood diseases by disrupting hormone-mediated processes that are critical for growth and development during gestation, infancy and childhood. The fetus, infant and child might have enhanced sensitivity to environmental stressors such as EDCs due to their rapid development and increased exposure to some EDCs as a consequence of development-specific behaviour, anatomy and physiology. In this Review, I discuss epidemiological studies examining the relationship between early-life exposure to bisphenol A (BPA), phthalates, triclosan and perfluoroalkyl substances (PFAS) with childhood neurobehavioural disorders and obesity. The available epidemiological evidence suggest that prenatal exposure to several of these ubiquitous EDCs is associated with adverse neurobehaviour (BPA and phthalates) and excess adiposity or increased risk of obesity and/or overweight (PFAS). Quantifying the effects of EDC mixtures, improving EDC exposure assessment, reducing bias from confounding, identifying periods of heightened vulnerability and elucidating the presence and nature of sexually dimorphic EDC effects would enable stronger inferences to be made from epidemiological studies than currently possible. Ultimately, improved estimates of the causal effects of EDC exposures on child health could help identify susceptible subpopulations and lead to public health interventions to reduce these exposures.

Numerous studies indicate that exposure to environmental stressors during gestation, infancy and early childhood is a risk factor for diseases in childhood and adulthood[1,2]. These studies demonstrate that perturbation of sensitive biological processes during distinct periods of development can increase the risk of adverse health outcomes years or decades after exposure to the stressor. For example, exposure to environmental chemicals, pharmaceuticals, tobacco smoke, alcohol and stress increase the risk of obesity, type 2 diabetes mellitus, reproductive disorders, neurodevelopmental disorders and/or deficits, and cancer[3–9]. Well-established examples include the increased risk of vaginal clear cell carcinoma following prenatal exposure to diethylstilbestrol, cognitive decrements among children exposed to lead or mercury during the prenatal period or in childhood, and childhood obesity among offspring born to smokers, despite their reduced birth weight[3–5,10].

Environmental chemical exposures are one stressor that might adversely affect normal human development. Endocrine-disrupting chemicals (EDCs) are a class of chemical that could increase the risk of disease across the lifespan by altering the homeostasis or action of endogenous hormones or other signalling components of the endocrine system[11]. EDCs might increase the risk of disease by altering the production, release, transport, metabolism, binding, action or elimination of endogenous hormones that program or maintain normal growth and development. Particular concern exists that the fetus, infant or child might have greater exposure to some EDCs or be more vulnerable to their effects than adult individuals.

Concern also exists about the health effects of EDC mixtures[12]. Despite biomonitoring studies documenting that humans are exposed to dozens of potential EDCs across the lifespan and that some EDC exposures are correlated with each other[13,14], most epidemiological studies have examined the health effects of EDCs as if they occur in isolation from one another. Without accounting for EDC mixtures, the available literature might fail to quantify synergistic or cumulative health effects of EDCs, as well as confounding due to correlated co-pollutants.

In this Review, I discuss epidemiological studies examining associations between early-life exposure to several EDCs and childhood neurodevelopmental

Department of Epidemiology, Brown University, Box G-S121(2), Providence, Rhode Island 02912, USA.
joseph_braun_1@brown.edu

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Key points

- Endocrine-disrupting chemicals (EDCs) might increase the risk of childhood neurodevelopmental disorders or obesity by disrupting hormone-mediated processes during critical periods of development
- The developing fetus, infant and child might have enhanced sensitivity to environmental stressors such as EDCs and increased exposure to some EDCs due to developmentally appropriate behaviour, anatomy and physiology
- The available epidemiological evidence suggest that prenatal bisphenol A and phthalate exposure is associated with adverse neurobehavioural outcomes in children, but not excess adiposity or risk of obesity or being overweight
- Epidemiological studies show that prenatal PFAS exposure is associated with reduced fetal growth, excess adiposity and risk of being overweight or obese, but not neurobehavioural outcomes
- Improving EDC exposure measurement, reducing confounding bias, identifying discrete periods of vulnerability and sexually dimorphic associations, and quantifying the effects of EDC mixtures will enhance inferences made from epidemiological studies

disorders and obesity, focusing on select EDCs for which widespread general population exposure exists, specifically phthalates, bisphenol A (BPA), perfluoroalkyl substances (PFAS) and triclosan. For reviews on chemicals with declining exposure that have been banned or phased out of production (for example, organochlorine compounds), the reader is directed elsewhere[15]. I also describe some limitations in making stronger inferences from epidemiological studies about the impact of EDC exposures on child health and propose how researchers might address these limitations through improved study design and methods. Finally, I provide some guidance for clinicians on how to address patients' concerns about reducing EDC exposures.

Early-life exposure to EDCs

Increased exposure to some EDCs in the fetus, infant or child might result from developmentally appropriate differences in diet, behaviour, physiology, anatomy and toxicokinetics[16]. For instance, infants and children might have higher exposure to some EDCs than adult individuals as they consume more water and greater quantities of specific foods, and have higher ventilation rates, intestinal absorption, surface area to volume ratios, and hand-to-mouth activity[17]. In addition, breastfed infants might have higher serum concentrations of some persistent EDCs than their mothers owing to lactational exposure[18].

In addition to increased exposure to some EDCs, the fetus, infant or child could be more sensitive to the effects of EDCs than adult individuals for two reasons. First, differences in toxicokinetics can result in increased circulating or tissue concentrations of an EDC for a given dose. For example, compared with adult individuals, the fetus has lower levels of several cytochrome P450 enzymes that metabolize environmental chemicals and pharmaceuticals[19,20]. Second, many time-dependent and synchronized processes that are programmed during early development could increase the risk of childhood disease if perturbed. For instance, disruption of neurulation, neuronal differentiation, proliferation or migration, gliogenesis, synaptogenesis, dendritic growth, myelination, apoptosis, synaptic pruning or neurotransmitter systems could increase the risk of behavioural disorders or cognitive deficits[21,22]. Furthermore, epigenetic mechanisms, some of which are hormonally regulated, might mediate some of the effects of early-life EDC exposures on long-term health outcomes[23]. Consequently, concern exists that early-life exposure to EDCs could increase the risk of childhood diseases, including neurodevelopmental disorders and obesity[24,25].

EDCs might increase the risk of childhood neurodevelopmental disorders by interfering with thyroid hormone signalling or metabolism in early life (BOX 1). Thyroid hormones have a critical role in neuronal migration, synaptogenesis and myelination during gestation and childhood[26]. Even clinically nonsignificant variations in maternal levels of thyroxine or thyroid-stimulating hormone (TSH) during pregnancy are associated with reduced cognitive abilities[27], attention-deficit hyperactivity disorder (ADHD) symptoms[28] and increased autism risk[27–30]. Studies have shown that the timing of thyroid hormone availability influences the neurobehavioural phenotype. Gestational thyroxine reductions are associated with deficits in visual processing, visuomotor abilities and motor skills, whereas postnatal reductions are associated with deficits in language, fine motor skills, attention and memory[31–34]. That both prenatal and postnatal thyroid hormones are necessary for different aspects of neurodevelopment illustrates the potential time-dependent sensitivity of the developing brain to thyroid hormone disruptions.

Early-life EDC exposures might perturb neuroendocrine systems involved in growth, energy metabolism, appetite, adipogenesis and glucose–insulin homeostasis to promote childhood obesity, cardiometabolic dysfunction and liver dysfunction[35–38] (BOX 2). These perturbations could lead to a 'thrifty phenotype' that promotes more efficient energy storage, rapid early-life weight gain and excess adipose mass[39–45]. Rapid growth and excess adiposity lead to increased circulating levels of free fatty acids, causing a cascade of metabolic changes that reduce the capacity of the liver and muscle to absorb, store and metabolize glucose[46–48], which in turn causes increased pancreatic insulin secretion and resistance. In the setting of insulin resistance, excess adipose tissue lipolysis contributes to increased delivery of free fatty acids to the liver, *de novo* hepatic lipogenesis, accumulation of triglycerides in liver vacuoles and hepatic steatosis (that is, nonalcoholic fatty liver disease)[49].

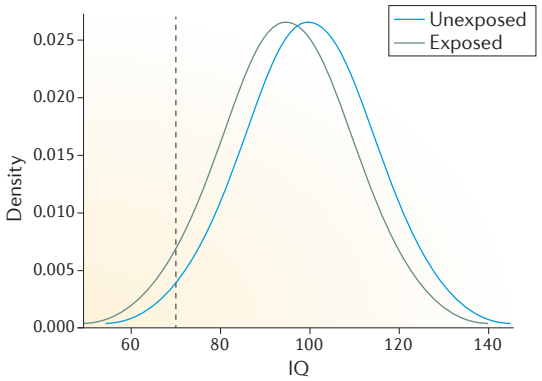
Despite their seemingly unrelated nature, shared neuroendocrine pathways could be disrupted by EDC exposures to influence the risk of both childhood obesity and neurodevelopmental disorders[50–52] (FIG. 1). Indeed, the prevalence of excess adiposity is increased among children with behavioural disorders such as ADHD, and children with obesity have lower academic achievement, impaired attention and working memory, and reduced cortical thickness and white matter integrity compared with lean children[53–55]. Moreover, up to 30% of the genes associated with adiposity are also associated with processing speed[56]. Finally, increased impulsiveness, a key

Box 1 | **Neurodevelopmental disorders of childhood**

Many neurodevelopmental disorders develop during childhood, with prevalence in the USA of 1.5% for autism spectrum disorders (ASD), 6.7% for attention-deficit hyperactivity disorder (ADHD) and 7.7% for specific learning disabilities[215,216]. The clinical presentation of these disorders varies between and within a diagnosis. For ASD, children have deficits in social communication and interactions, as well as repetitive, restricted and stereotypic behaviours. Within the ASD diagnosis, deficits can be mild or severe and accompanied by intellectual disabilities (IQ <70) and substantial comorbidities[217]. For ADHD, children present with hyperactivity, inattention and poor impulse control, and display deficits in executive function (for example, inhibition, behavioural regulation and planning or organizing). Diagnosis of ADHD is classified into hyperactive or impulsive, or inattentive subtypes[218]. Learning disabilities are characterized by difficulties mastering and using specific academic skills (for example, reading and mathematics) and are distinct from intellectual disability, which is defined by global impairments in cognitive function.

Many epidemiological studies assess continuously distributed measures of functional domains related to clinical phenotypes instead of clinical diagnoses[219,220]. For instance, global measures of cognition (that is, IQ) and academic performance can be used to study whether EDC exposures affect intellectual abilities and specific academic skills, respectively. Continuous outcomes are advantageous as they provide a relative ranking of an individual's ability and/or behaviour, which enhances statistical power. Moreover, clinical diagnosis could misclassify individuals as they might fail to detect earlier manifestations of disease and diagnostic thresholds are often set at arbitrary levels that change over time. By examining continuous neurobehavioral measures, epidemiological studies can determine if EDC exposures are associated with shifts in these traits at the population level, which could result in an increased prevalence and/or incidence of clinical disorders.

To illustrate, the density distribution of IQ in EDC exposed and unexposed populations (1 million individuals each) can be calculated (see the figure to the right). The dashed vertical line signifies the threshold for IQ scores consistent with intellectual disabilities (IQ <70). In the unexposed population, the mean IQ is 100 (SD = 15), whereas in the exposed population the mean IQ is 95 (SD = 15). This five-point shift in IQ results in nearly a doubling in the proportion of people with IQ scores consistent with intellectual disabilities in the exposed population compared with the unexposed population (4.48% and 2.27%, respectively; J. M. Braun, unpublished work).



feature of ADHD, is related to food responsiveness in adolescents[57] and administration of the adipocytokine ghrelin to rodents increases impulsive behaviours[58].

Phthalates

Uses, exposure and measurement. Phthalates are a class of EDC used in a multitude of consumer products, including personal care products, medications and plastics (TABLE 1). Biomonitoring studies from around the world indicate that universal phthalate exposure exists among pregnant women, infants and children[59–72]. Phthalate exposure occurs through ingestion, inhalation or dermal absorption[73–76]. Additionally, phthalates can cross the placenta, which results in exposure to the fetus[77].

After entering the body, phthalates are rapidly hydrolysed to their respective monoester metabolites[78] (TABLE 1). Low molecular weight phthalates (such as diethyl phthalate (DEP), di-n-butyl phthalate and di-iso-butyl phthalate) are excreted in the urine as glucuronide or sulfate-conjugated hydrolytic monoesters, whereas mono-2-ethylhexyl phthalate, the hydrolytic metabolite of di-2-ethylhexyl phthalate (DEHP), undergoes additional enzymatic oxidation before being conjugated and excreted. Although phthalates do not persist in the body and have short biological half-lives (<24 h), repeated, episodic and long-term exposure occurs. Phthalate exposure is assessed using urine biospecimens as phthalates are predominately excreted in the urine; blood levels are considerably lower and might be subject to exogenous contamination during sample collection, storage or processing[79].

Misclassification of phthalate exposure is a concern in epidemiological studies owing to their short biological half-lives and the episodic nature of phthalate exposures from diet (for example, DEHP) or personal care products (such as DEP). To address this concern, accurate phthalate exposure assessment necessitates the collection and analysis of multiple urine samples[80].

Mechanisms of action. Phthalates might interfere with the action or metabolism of androgens, thyroid hormones and glucocorticoids. Some phthalates are anti-androgenic and reduce testicular testosterone production by decreasing the expression of genes involved in steroidogenesis and steroid trafficking[81,82]. Animal and human studies show that some phthalates can reduce thyroxine and T_3 concentrations in pregnant women and children[83–85], antagonize T_3 binding to thyroid hormone receptor β[86], reduce cellular T_3 uptake[87] and affect transcription of the sodium–iodine cotransporter[88]. Phthalates can also inhibit 11-β-hydroxysteroid dehydrogenase 2, which deactivates cortisol[89]. In addition, phthalate exposure might affect offspring health by causing oxidative stress[90] or via epigenetic reprogramming of the fetus and placenta[91].

Box 2 | **Prevalence and origins of childhood obesity**

Childhood obesity is a major threat to public health in the USA, with the prevalence rising from 7% in 1980 to 17% in 2012 (REF. 221). Obesity is also a major public health problem globally; 10–14% of adult individuals worldwide were overweight or obese in 2008 (REF. 222). Childhood obesity increases the risk of type 2 diabetes mellitus, cardiovascular disease and the metabolic syndrome, and has adverse effects on pulmonary, musculoskeletal and psychosocial functioning[223].

The principal cause of obesity is caloric imbalance from excess calorie intake and insufficient physical activity. However, considerable evidence exists that the *in utero* and neonatal environments program the developing fetus and infant for obesity risk[1,2]. A non-optimal fetal or infant environment can lead to enduring functional and structural changes to the body that increase obesity risk by reprogramming neuroendocrine systems involved in growth, energy metabolism, appetite, adipogenesis and glucose–insulin homeostasis[36–38]. These environmental stressors might program the fetus or infant towards a 'thrifty phenotype' that efficiently stores excess calories in a postnatal environment with abundant calories and reduced physical activity. Thus, children with this phenotype will efficiently store excess calories as fat, have altered insulin homeostasis and ultimately develop a cardiometabolic disease profile.

Concern exists about the health effects of phthalate mixtures as humans are exposed to multiple phthalates simultaneously and rodent studies demonstrate that phthalates have concentration-additive effects on fetal androgen production[82,92]. Thus, the aggregate of individual phthalate exposures might have an additive impact on human health as individual phthalates share a common mechanism of action.

Role in neurodevelopment. Prospective cohort studies have found that prenatal exposure to several different phthalates is associated with ADHD behaviours[59,60,93,94], autistic behaviours[61], reduced mental and psychomotor development[60,62], emotional problems[60] and reduced IQ[63]. In a prospective cohort of 328 mothers, the reductions in child IQ associated with increasing maternal urinary phthalate concentrations were as large or larger than the cognitive decrements observed with childhood lead exposure (5th versus 1st quintile: 7 points; 95% CI 2–11)[3,63]. Importantly, three other studies found no association between prenatal phthalate exposure and child neurobehaviour[64–66]. Childhood exposure to some phthalates has also been reported to be associated with reduced cognitive abilities[65] and behavioural problems[67,68]. However, these findings were obtained from cross-sectional studies, in which reverse causality could explain the findings.

Overall, the epidemiological literature to date suggests that prenatal phthalate exposure might be associated with behavioural problems and cognitive decrements in children. Inconsistencies across studies might be due to differences in the timing of when phthalate exposure was assessed (for example, early versus late gestation), misclassification of phthalate exposure from studies using a single urine sample to assess exposure, or differences in child age at the time of neurodevelopment assessment.

Role in adiposity and obesity. Prospective cohort studies have examined prenatal phthalate exposure and childhood adiposity[70–72]. Prenatal exposure to DEHP has been reported to be associated with decreased BMI in boys and increased BMI in girls[70], whereas non-DEHP phthalate exposures have been shown to be associated with decreased BMI in boys, but not in girls[71]. A further study did not find any association between prenatal phthalate exposure and childhood adiposity[72]. In a pooled cohort study that included participants from the USA from two cohorts[70,71], increasing maternal urinary mono-3-carboxypropyl phthalate concentrations during pregnancy were found to be associated with a doubling in the risk of being overweight or obese (95% CI 1.2, 4.0)[95].

Childhood phthalate exposure and adiposity has also been examined[71,96–98]. Although three studies found that childhood exposure to DEP was associated with excess adiposity and an increased prevalence of obesity[96–98], another study found no association[71]. A prospective cohort of >1,000 girls in the USA found that increased DEP exposure at 6–8 years of age was associated with increased BMI and waist circumference at 7–13 years of age[97], whereas a cross-sectional study of children in the USA found that increasing urinary concentrations of low molecular weight phthalates were associated with a 22% increase in the prevalence of obesity[99].

Overall, the associations between early-life phthalate exposure and child adiposity or obesity risk have been inconsistent and do not support the hypothesis that phthalates are chemical obesogens. The one exception is the association between childhood DEP exposure and child adiposity or obesity prevalence. However, this association could be due to children with increased adiposity also having increased surface area, leading to the application of greater amounts of phthalate-containing personal care products to their skin, which in turn results in higher urinary monoethyl phthalate (MEP) concentrations[99].

BPA

Uses, exposure and measurement. BPA is used to produce polycarbonate plastics and resins that are used in a wide range of consumer products (TABLE 1). Oral ingestion is the predominant exposure route as BPA can leach into food and beverage containers; however, dermal absorption and inhalation can be additional routes of exposure among individuals working with BPA-containing merchandise receipts[100–102]. BPA is excreted in the urine as glucuronide or sulfate conjugates, does not persist in the body and has an estimated biological half-life of ~6 h (REF. 103). BPA exposure is assessed by measuring urinary concentrations of free and conjugated BPA. Urine samples are used as BPA is almost exclusively excreted in the urine; blood levels of BPA are considerably lower and are subject to exogenous contamination[79]. Biomonitoring studies around the world indicate nearly universal BPA exposure among pregnant women, infants and children[13,64,104–120]. Much like some phthalates, urinary BPA concentrations have considerable within-person variation due to diet being the predominant source of exposure. Collecting multiple urine samples is, thus, essential to ensure accurate exposure assessment.

Mechanisms of action. BPA might interact with a variety of hormone systems that affect growth, metabolism and neurodevelopment. Dodds and Lawson recognized BPA

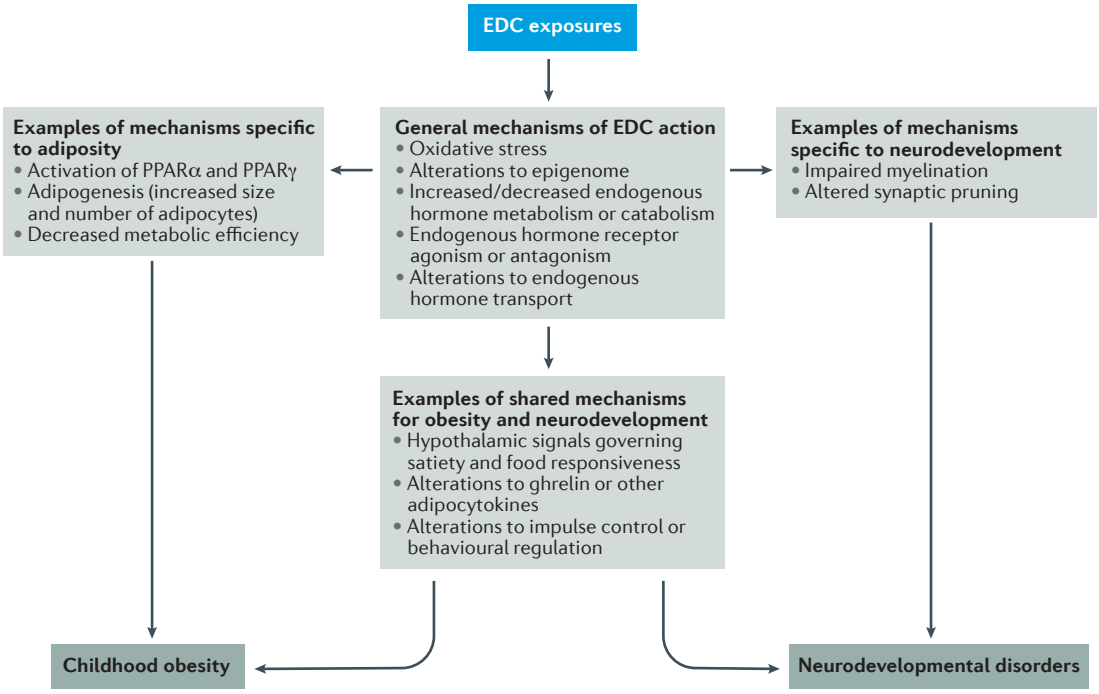


Figure 1 | **EDC mechanisms of action and biological targets.** Conceptual representation of general mechanisms of endocrine-disrupting chemical (EDC) action and examples of specific biological targets relevant to childhood neurodevelopmental disorders and obesity. PPAR, peroxisome proliferator-activated receptor

as a weak oestrogen in 1936 (REF. 121). BPA is a weak agonist of the nuclear oestrogen receptors α and β compared with oestradiol[122]. However, BPA can also act on oestrogen receptors bound to plasma proteins, thereby allowing BPA to interfere with oestrogenic signalling at nanomolar and picomolar levels[123,124]. *In vitro* studies have shown that BPA can affect androgen and/or oestrogen concentrations by inhibiting key enzymes involved in gonadal hormone synthesis and metabolism[125], however, results from human studies have been inconsistent[126–128]. In rodents, prenatal BPA exposure is associated with increased T_4 levels in offspring[129] and thyroid-specific gene expression[130]. Some epidemiological studies have found that BPA exposure is associated with altered maternal, neonatal or adolescent thyroid parameters[131–133].

Role in neurodevelopment. In 2008, the National Toxicology Program acknowledged concern about the effect of BPA on neurobehavioural endpoints used in animal studies[134]. Since that time, numerous studies using prospective cohorts have examined prenatal BPA exposure and child neurobehaviour[64,110–116]. Prenatal BPA exposure has been reported to be associated with more internalizing behaviours in children, with stronger associations in boys than girls[110,113–115]; with more internalizing and externalizing behaviours in girls but not boys[111,112]; and with increased risk of ADHD-related behaviours at 4 years of age, with stronger associations in boys than girls[116]. No association between prenatal urinary BPA concentrations and parent-reported reciprocal social behaviours has also been reported[61,64]. The association between prenatal BPA exposures and the cognitive abilities of children has been examined in one study; prenatal urinary BPA concentrations were associated with parent-reported executive function in girls aged 3 years[112].

The relationship between childhood BPA exposures and behaviour problems or ADHD-related behaviours has been investigated[67,110,112–114,135,136], although results are inconsistent. Childhood BPA exposures have been found to be associated with ADHD behaviours in boys[135], ADHD behaviours in both boys and girls[135], anxious, depressive or aggressive behaviours in girls[110,113,114] and learning problems[137]; null associations between childhood BPA exposures and neurobehaviour have also been reported[67,112].

Overall, the available evidence suggest that both prenatal and postnatal BPA exposure is associated with parent-reported behaviour problems in children; however, inconsistencies exist across these studies with regard to the period of life with the greatest vulnerability to exposure (that is, prenatal versus infancy versus childhood) and sex-specific effects. The heterogeneity of the findings could be due to the substantial within-person variation in urinary BPA concentrations that results in BPA exposure misclassification.

Role in adiposity and obesity. Prospective cohort studies have examined whether early-life BPA exposure is obesogenic[104–107,117,118,138]. Prenatal BPA exposure has been reported to be associated with reduced BMI, with stronger associations in girls than in boys[104–106], and with increased waist circumference, BMI and risk of being overweight or obese[107,117]; no association between prenatal BPA exposure and child adiposity measures has also been reported[118,138].

Table 1 | **Epidemiological exposure assessment and commercial uses of EDCs***

EDC	Exposure assessment	Uses in commerce or industry
Di-2-ethylhexyl phthalate (DEHP)	Urine concentrations of mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) and mono-2-ethyl-5-oxohexyl phthalate (MEOHP)	PVC plastics, food packaging, plastic medical tubing and plastic bags
Butylbenzyl phthalate (BBzP)	Urine concentrations of monobenzyl phthalate (MBzP)	Vinyl flooring, adhesives, food packaging, synthetic leather and toys
Diethyl phthalate (DEP)	Urine concentrations of monoethyl phthalate (MEP)	Scent retainer in personal care products and medication excipient
Di-n/i-butyl phthalate (DnBP/DiBP)	Urine concentrations of mono-n/i-butyl phthalates (MnBP/MiBP)	Scent retainer in personal care products, medication excipients, cellulose plastics and adhesives
Bisphenol A (BPA)	Urine concentrations of BPA	Polycarbonate plastics, resins, thermal merchandise receipts, food cans, dental fillings and medical equipment
Triclosan	Urine concentrations of triclosan	Antimicrobial soaps, personal care products, toothpaste, kitchen utensils, clothes and cleaning products
Perfluoroalkyl substances (PFAS)	Serum concentrations of individual perfluoroalkyl or perfluorinated chemicals	Stain and water-resistant coatings, nonstick cookware, food container coatings, floor polish, fire-fighting foam and industrial surfactants

*Phthalates, bisphenol A, polybrominated diphenyl ethers and PFAS. EDC, endocrine-disrupting chemical; PVC, polyvinyl chloride.

Some of the aforementioned studies prospectively examined the relationship between infant or childhood BPA exposure and subsequent adiposity[104–107]; several cross-sectional studies have also been conducted[119,120]. Among reports of prospective measures of BPA exposure during infancy or childhood, little evidence exists to suggest that BPA exposure is associated with excess adiposity[104–107]. However, cross-sectional data show that BPA exposure is positively correlated with adiposity or the prevalence of being overweight or obese[105,106,120]. For instance, in a nationally representative sample of children in the USA, children in the top three quartiles of urinary BPA concentrations were ~25% more likely to be overweight and greater than twofold more likely to be obese than children in the lowest quartile[119]. However, the strength of this association did not monotonically increase across quartiles of BPA exposure, which suggests a threshold effect or potential residual confounding. Other studies have found no association between infant or childhood BPA exposure and childhood obesity[104,107].

The available epidemiological evidence is equivocal about the obesogenic effects of early-life BPA exposure; both increases and decreases in adiposity or risk of being overweight or obese have been reported with increased early-life BPA exposure. Cross-sectional associations between urinary BPA concentrations and childhood adiposity could be due to residual confounding from dietary factors that are associated with both BPA exposure and adiposity. In addition, reverse causality could be responsible for these correlations if individuals with excess adiposity have different dietary patterns that increase their exposure to BPA.

Triclosan

Uses, exposure and measurement. Triclosan is an antimicrobial chemical that disrupts bacterial lipid synthesis and cell membrane integrity and is used in numerous consumer products[139] (TABLE 1). Exposure is predominantly through oral and dermal routes[139]. Triclosan does not persist, has a biological half-life of <24 h and is primarily excreted in the urine as a glucuronide or sulfate conjugate[140]. Triclosan exposure is measured using urine biospecimens for the same reasons BPA and phthalates are measured using urine biospecimens[79]. Biomonitoring studies indicate nearly universal triclosan exposure among pregnant women and children[13,108,141]. Whereas triclosan has a short biological half-life similar to that of BPA and some phthalates, unlike these EDCs, urinary triclosan concentrations are relatively stable over time within an individual.

Mechanisms of action. Triclosan can disrupt gonadal and thyroid hormone homeostasis. In rodents, triclosan reduces testosterone production by disrupting cholesterol biosynthesis in Leydig cells[142,143]. In a systematic review and meta-analysis of eight rodent studies, triclosan exposure reduced thyroxine concentrations in the fetus, dam, neonate and juvenile[144]. Triclosan might reduce thyroxine concentrations by activating nuclear receptors to increase hepatic catabolism of thyroxine[145]. Although results from epidemiological studies of triclosan and thyroid function are inconsistent[146,147], no prospective epidemiological study has examined the relationship between triclosan and thyroid hormone biomarkers during gestation, infancy or childhood. Finally, given its antimicrobial activity, triclosan might be capable of altering the composition or function of the gut microbiota; however, little research has examined this hypothesis[148].

Role in neurodevelopment. Currently, no animal or epidemiological studies have directly examined the neurotoxicity of early-life triclosan exposure. Triclosan exposure might reduce serum thyroxine concentrations during pregnancy and this could cause adverse neurodevelopment given the important role that thyroxine has in fetal brain development[27]. An inverse association between prenatal triclosan exposure and neonatal anthropometry has been suggested by some

epidemiological studies[118,149,150]. As head circumference is positively correlated with later-life IQ, early-life triclosan exposure could adversely affect neurodevelopment[151].

Role in adiposity and obesity. Triclosan exposure has been reported to be associated with childhood obesity or excess adiposity[152,153]. Two cross-sectional studies involving children aged 6–19 years from the National Health and Nutrition Examination Survey (NHANES) yielded conflicting results. One study (years: 2007–2010) found no association between urinary triclosan concentrations and BMI z-score, waist circumference or prevalence of overweight or obesity[154], whereas the second study (years: 2003–2010) found urinary triclosan concentrations were associated with a monotonic decrease in BMI and waist circumference[153]. Urinary triclosan concentrations have also been reported to be similar in lean and overweight or obese children[152]. Furthermore, in a prospective cohort study, prenatal triclosan exposure was not associated with child adiposity at 4–9 years of age[138].

In summary, insufficient evidence exists to determine if early-life triclosan exposure is associated with childhood obesity. The inconsistent results between studies that used the NHANES highlights the importance of replication when examining the potential health effects of EDCs.

PFAS

Uses, exposure and measurement. PFAS are a class of man-made fluorinated chemicals used in stain-resistant and water-resistant coatings for textiles, non-stick cookware, food containers, floor polish, fire-fighting foam and industrial surfactants[155] (TABLE 1). The strong C–F chemical bond makes PFAS extremely resistant to thermal, chemical and biological degradation, which results in bioaccumulation and persistence in human tissues for years[156]. Four perfluoroalkyl acids — perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonate (PFHxS) — are almost universally detected in the serum of pregnant women, neonates and children worldwide, which indicates that exposure is ubiquitous and that these chemicals can cross the placenta[13,64,157–175].

Unlike phthalates, BPA and triclosan, PFAS have long biological half-lives in humans, which range from 3.8 to 7.3 years[176]. A single serum or plasma concentration is, thus, sufficient to characterize exposure for epidemiological studies. The sources and relative contributions of different PFAS to human exposure vary according to age-related behavioural factors and dietary patterns; PFAS exposures during infancy can equal or exceed prenatal exposures derived from the mother[155,177]. For instance, breast milk and formula might contribute almost exclusively to an infant's exposure as PFAS are found in breast milk and water, and infants consume up to sixfold more fluid than adults (150 versus 26 ml/kg/d)[178–180].

Mechanisms of action. PFAS might act on a number of endocrine pathways to affect the risk of neurodevelopmental disorders and obesity. In epidemiological studies, PFOA and PFOS exposures are associated with reduced global DNA cytosine methylation, increased long interspersed nuclear element 1 methylation and changes in the expression of genes involved in cholesterol metabolism[181–183]. PFOA and PFOS can bind to and activate peroxisome proliferator-activated receptor α (PPARα) or PPARγ to increase adipocyte differentiation and increase body fat[184–186]. In addition, PFOA, PFOS and PFHxS inhibit 11-β-hydroxysteroid dehydrogenase 2 to increase glucocorticoid concentrations in rodents, which might affect growth and brain development[89]. Animal studies have shown that PFAS are capable of inducing changes in thyroid function[187]; however, results from human studies are inconsistent[188].

Role in neurodevelopment. Prospective cohort studies have examined the relationship between prenatal PFAS exposure and cognitive abilities[164,165], attainment of developmental milestones[166], parent or teacher reported behaviours and executive function[64,166–169], psychomotor development[168], academic achievement[170] and risk of autism spectrum disorders, ADHD or cerebral palsy[171–173]. With regard to the most commonly detected PFAS (PFOA, PFOS, PFNA and PFHxS), studies have produced inconsistent results. In a prospective birth cohort of 218 mother–child pairs, increased prenatal PFOS exposure was associated with worse parent-reported executive function[169]. In another prospective birth cohort, increasing prenatal PFOS and PFOA exposures were associated with 70% (95% CI: 1.0, 2.8) and 110% (95% CI: 1.2, 3.6) increased risk of cerebral palsy, respectively[171]. Several studies have reported protective or null associations between prenatal PFAS exposure and child neurobehaviour[64,164–166,168,172].

The relationship between childhood PFAS exposure and neurodevelopment has been investigated[164,167,174,175]. While cross-sectional data indicate that serum PFAS concentrations in children are associated with increased prevalence of parent-reported ADHD or ADHD medication use[167,174], prospective cohort data (based on exceptionally high PFOA exposure) show that serum PFOA concentrations in children are not consistently associated with parent or teacher-reported ADHD-related behaviours or other neuropsychological measurements[164,171].

The available body of evidence does not consistently suggest that early-life PFAS exposures are associated with neurodevelopment. While some studies suggest adverse neurobehavioural outcomes among children with elevated prenatal or childhood PFAS exposures, inconsistencies regarding which individual PFAS exposures might be associated with neurobehaviour and whether heightened periods of vulnerability to PFAS exposures exist. The protective associations between early-life PFAS exposure and neurodevelopment is biologically plausible as *in vitro* studies report that PFOA and PFOS are agonists of PPARγ and activation of this receptor might be neuroprotective[189]. Additional studies with longitudinal measures of exposure and comprehensive assessment of neurodevelopment are warranted given the ubiquity and persistence of PFAS exposure.

Role in adiposity and obesity. A compelling body of evidence exists suggesting that prenatal exposure to PFAS could affect fetal growth and subsequent risk of childhood obesity. In a systematic review of 18 publications, and subsequent meta-analysis of nine of these papers, increasing prenatal PFOA exposure was associated with a 19 g decrease in birth weight (95% CI −8 to −30)[157]. These results in humans are similar to those observed in 21 rodent studies where each 1 mg/kg per day increase in PFOA exposure was associated with a 0.023 g decrease in pup birth weight (95% CI −0.016 to −0.029)[190]. Altered fetal growth patterns related to PFAS exposure might increase the risk of subsequent obesity and cardiometabolic disorders as earlier studies have shown that fetal growth deceleration and infant growth acceleration are associated with increased adiposity and levels of cardiometabolic risk markers in later childhood[43,191,192].

Consistent with this hypothesis, prospective cohort data show that prenatal PFAS exposure is associated with alterations in infant or child growth[159,162], increased adiposity during childhood and adulthood[158–160], and an increased waist-to-height ratio[161]. Findings from other prospective cohort studies, including one with exceptionally high PFOA exposure, did not confirm an association between prenatal PFAS exposure and child or adult adiposity or risk of being overweight or obese[163,193]. These other studies used self-reported or parent-reported anthropometry, which could be responsible for the null results, as well-documented errors in these forms of anthropometry could misclassify adiposity and attenuate associations towards the null[194,195].

Childhood PFAS exposure and adiposity has also been investigated. In a cross-sectional study of adolescents in the USA, PFOS exposure was associated with decreases in BMI and waist circumference, whereas other PFAS were not[196]. In a prospective cohort study, PFOS exposure at 9 years of age (and to a less precise extent PFOA exposure) was associated with increased adiposity at 15 and 21 years of age[197].

EDCs and child health

Impediments to making stronger inferences

Chemical mixtures, exposure misclassification, confounding, periods of heightened vulnerability and sexually dimorphic associations are challenges to making strong inferences about the causal links between early-life EDC exposures and the risk of childhood diseases. Tractable solutions that, if incorporated into study design or statistical analysis, could improve our confidence in making causal inferences are discussed below.

Chemical mixtures. Exposure to a mixture of EDCs occurs across the lifespan, yet researchers primarily examine exposures as if they occur in isolation from one another. This 'one chemical at a time' approach has left us with insufficient knowledge about the individual, interactive and cumulative health effects of EDC mixtures. Epidemiological studies can address three broad questions related to EDC mixtures[198]. First, given the large number of environmental agents to which humans are exposed, a need exists to identify those most strongly associated with adverse child health outcomes, particularly when few data are available about the toxicity of individual exposures. Second, multiple EDCs might have a synergistic association with health outcomes by disrupting the homeostasis of compensatory mechanisms. Finally, cumulative exposure to certain classes of EDCs (for example, phthalates) could adversely affect child health when individual components of the mixture act via common biological pathways and cumulative exposure to these individual agents is sufficient to induce an adverse effect.

A recent workshop at the National Institute of Environmental Health Sciences brought together leaders in the fields of epidemiology, biostatistics and toxicology to develop, implement and compare different methods of quantifying the health effects of environmental chemical mixtures[199,200]. Several methods showed promise in addressing questions related to EDC mixtures. For instance, least absolute shrinkage, selection operator and elastic net methods can identify individual EDCs associated with health outcomes and their interactions while controlling for co-pollutant confounding. Bayesian kernel machine regression is another method that can estimate the health effects of individual EDCs of concern while also examining potential interactions, nonlinear dose-response functions and co-pollutant confounding[201].

Weighted quantile sum regression is a method that shows promise for quantifying the cumulative effect of EDC exposures while also estimating the relative contribution of individual components of the mixture to the health outcome of interest[202,203]. Other methods of estimating the cumulative effect of EDC mixtures include mathematically weighting the sum of individual components of the mixture by their biological potency (for example, toxic equivalency factors for dioxins)[204] or quantifying biological activity in biospecimens[205]. These summation methods of examining cumulative exposures are probably too simplistic as they assume a single mechanism of EDC action. A need, therefore, exists to develop methods that incorporate the potency of EDCs on multiple biological pathways.

By implementing methods that account for chemical mixtures, we will probably identify previously undocumented chemical risk factors for childhood diseases, susceptible subgroups or aggregate exposures that should be considered in the risk assessment process. However, the performance of these methods has not been fully evaluated and a simulation study showed that some of these methods do not have perfect sensitivity and in some situations, a high rate of false positives might occur[206].

Exposure misclassification. The episodic nature of many EDC exposures and short biological half-lives of their biomarkers can cause exposure misclassification. Exposure misclassification represents a signal-to-noise problem, in which the misclassification results in a less precise estimate of an individual's exposure, making it more difficult to rank their exposure relative to other individuals in the study. If misclassification is not systematically different with respect to childhood health outcomes, the study will have reduced statistical power to detect an association and observed associations will be attenuated towards the null.

A simulation study showed that at least 10 estimates of exposure per individual might be required to ensure adequate statistical power, especially for chemical exposures like BPA and DEHP[80]. One solution is to collect multiple urine samples from the same individual during a specific developmental period (for example, the 2nd trimester of pregnancy) and then create a pooled specimen for each individual using an equal volume of sample from their repeated samples[79,80]. One disadvantage to the pooling method is that it does not allow for examination of discrete periods of heightened vulnerability unless multiple pools are created for different periods of development. When a single measurement of exposure is available, statistical techniques like regression calibration could correct non-differential measurement error[80]. To date, studies have not used regression calibration methods to correct for non-differential EDC exposure misclassification, but studies of air pollutants have successfully used these methods to study a variety of health effects while accounting for exposure measurement error[207].

Despite the potential for non-differential misclassification of BPA and phthalate exposures, several studies have observed that early-life BPA or phthalate exposures are associated with adverse child neurodevelopment. If non-differential misclassification is present, observed associations might be attenuated towards the null and true associations could be much stronger. However, non-causal explanations such as confounding by traditional risk factors for adverse neurodevelopment or correlated co-pollutants should not be ruled out.

Confounding. As is the case for all observational studies, potential confounding factors associated with both early-life EDC exposures and child health can bias study results. Socioeconomic factors are important determinants of childhood health and some chemical exposures. For instance, in the case of obesogens, many strong determinants of adiposity (for example, diet) are correlated with lifestyle factors (such as, maternal diet) that might also be associated with EDC exposures (FIG. 2). Thus, to determine if a given EDC has obesogenic effects independent of other predictors of obesity, factors like diet, physical activity and breast feeding need to be measured and controlled for. When examining neurotoxic EDCs, many socioeconomic factors associated with exposure are also associated with parental IQ or behaviour and the quality of the care-giving environment, which are important determinants of child IQ and behaviour. Finally, potential confounding from other EDC exposures need to be considered as the effect of one EDC might be misattributed to another correlated co-pollutant.

Subject matter knowledge should guide the selection of potential confounders and various approaches can be used to identify a parsimonious statistical model[208]. Imperatively, adjusting for variables that are caused by EDC exposure and causes of poor childhood health (that is, causal intermediates) is not appropriate as this 'over-adjustment bias' might mask causal associations[209]. For instance, prenatal PFAS exposures are associated with reduced birth weight and an increased risk of childhood obesity; moreover, birth weight is a determinant of childhood obesity risk[210]. Thus, adjusting for birth weight might bias associations between PFAS and risk of childhood obesity.

Discrete periods of heightened vulnerability. The potential effects of EDCs could be dependent on the timing of exposure given the possibility of unique periods of vulnerability to environmental stressors. For instance, the effect of EDC exposures on neurodevelopment could depend on different biological mechanisms specific to prenatal (for example, neurulation) and postnatal (for example, synaptic pruning) neurodevelopmental processes[22], which could be a reason for some of the heterogeneity in the results of the studies discussed earlier. This limitation highlights the need to conduct prospective studies with serial measures of EDC exposure across the lifespan, as well as for appropriate statistical methods to identify periods of heightened vulnerability[198].

Sexually dimorphic associations. Some associations between EDC exposures and childhood health are sexually dimorphic and EDCs might be capable of acting in a sex-specific manner given the important role that gonadal hormones have in shaping some sexually dimorphic traits[59,60,69,112,117]. For instance, in a prospective cohort, prenatal exposure to anti-androgenic phthalates was associated with reduced masculine play behaviour in boys but not in girls[69]. The identification of sex-specific effects in epidemiological studies requires larger sample sizes than those of most studies conducted to date.

Advice for clinicians and patients

Currently, no evidence-based methods for reducing EDC exposures exist; however, some general recommendations are available that clinicians could give to concerned patients. For EDCs found in the diet (such as, BPA, DEHP and PFAS), eating a balanced diet could be one way to avoid exposure from any one foodstuff; however, this advice has not been empirically evaluated. Intervention studies show that decreasing or eliminating canned or packaged food consumption is effective at reducing BPA and DEHP exposure[73,100]. An intervention

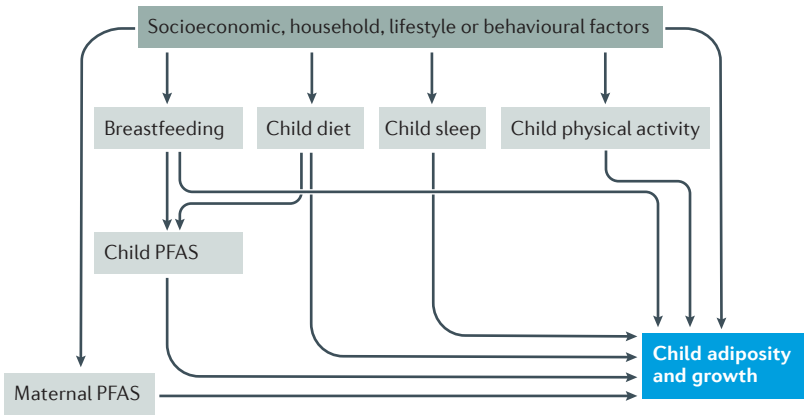


Figure 2 | **Early- life PFAS exposure and child adiposity.** Directed acyclic graph depicting the relationship between early-life perfluoroalkyl substances (PFAS) and childhood adiposity.

study showed that handling BPA-containing thermal merchandise receipts was an important route of exposure and that wearing gloves could reduce BPA exposure from this route[102]. Some evidence also exists that children who handle thermal merchandise receipts might have increased BPA exposure[109].

Individuals might be able to reduce their exposure to DEP and di-n-butyl phthalate (DnBP) by reducing or eliminating the use of some lotions, cosmetics, colognes and/or perfumes[76,211]. However, no requirements are in place for personal care products to include these phthalates in their ingredient list, which makes avoiding this source of exposure difficult. Individuals can reduce triclosan exposure by avoiding triclosan-containing toothpastes. However, because triclosan-containing toothpastes are clinically indicated for some individuals, assessment of the benefits and risks of continued use should take into account the specific conditions and susceptibilities of the individual (for example, pregnancy). Finally, granular activated carbon water filtration systems might be effective at reducing PFAS exposure when consuming PFAS contaminated water[212]; however, this system might have a minimal effect on total PFAS body burden when diet is the predominant source of PFAS exposure[213].

Conclusions

Exposure to BPA, phthalates, triclosan and PFAS is ubiquitous and occurs during potentially sensitive periods of development that are important in the aetiology of childhood neurodevelopmental disorders and obesity. The available research suggests that prenatal BPA and phthalate exposures are related to adverse neurobehavioural outcomes in children. Furthermore, prenatal PFAS exposure is related to reduced fetal growth and excess childhood adiposity. Although this Review did not compare the findings of animal or laboratory studies with those of epidemiological ones, future reviews or risk assessments of these chemicals should include this important feature of establishing causality[214].

We can make stronger inferences about the role of EDCs in the aetiology of childhood disease by quantifying the impact of chemical mixtures, reducing exposure misclassification, identifying sexually-dimorphic associations and periods of enhanced vulnerability, and collecting data on relevant potential confounders in prospective cohort studies. Ultimately, quantifying the impact of EDC exposures on child health could lead to the identification of susceptible subpopulations and a reduction in EDC exposures via public health interventions.

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Competing interests statement
The author declares no competing interests.