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Early Life Exposure to Endocrine Disrupting Chemicals and Childhood Obesity and Neurodevelopment

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Abstract

Endocrine disrupting chemicals (EDCs) may increase the risk of childhood diseases by disrupting hormonally mediated processes critical for growth and development during gestation, infancy, or childhood. The fetus, infant, and child may have enhanced sensitivity to environmental stressors like EDCs due to rapid development and greater exposure to some EDCs that results from their developmentally appropriate behavior, anatomy, and physiology. This review summarizes epidemiological studies examining the relations of early-life exposure to bisphenol A (BPA), phthalates, triclosan, and perfluoroalkyl substance (PFAS) with childhood neurobehavioral disorders and obesity. The available epidemiological evidence suggests that prenatal exposure to several of these ubiquitous EDCs is associated with adverse neurobehavior (BPA and phthalates) and excess adiposity or increased risk of obesity/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 result in stronger inferences from epidemiological studies. Ultimately, better estimates of the causal effects of EDC exposures on child health could help identify susceptible sub-populations and lead to public health interventions to reduce these exposures.

Introduction

Accumulating research shows that environmental stressors during gestation, infancy, and early childhood are risk factors 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, reproductive disorders, neurodevelopmental disorders/deficits, and cancer.[3–9] Well-established examples include the increased risk of vaginal clear cell carcinoma following prenatal diethylstilbestrol exposure; cognitive decrements among children with prenatal or childhood exposure to lead or mercury; and childhood obesity among offspring born to smokers, despite lower birth weight.[3–5,10]

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Environmental chemical exposures are one stressor that may adversely affect normal human development. Endocrine disrupting chemicals (EDCs) are a class of chemicals that could increase the risk of disease across the lifespan by altering the homeostasis or action of endogenous hormones or other signalling chemicals of the endocrine system.[11] EDCs may 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 (Figure 1). There is particular concern that the fetus, infant, or child may have higher exposure to some EDCs or be more vulnerable compared to adults.

The fetus, infant, and child may have higher exposure to some EDCs than adults. because of developmentally appropriate differences in diet, behavior, physiology, anatomy, and toxicokinetics.[12] For instance, infants and children may have higher exposure to some EDCs than adults because 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.[13] In addition, breastfed infants may have higher serum concentrations of some peristent EDCs than their mothers becaues of lactational exposure.[14]

In addition to higher exposure to some EDCs, the fetus, infant, and child may be more sensitive to the effects of EDCs than adults for two reasons. First, differences in toxicokinetics can result in higher circulating or tissue concentrations of an EDC for a given dose. For example, compared to adults, the fetus has lower levels of several cytochrome P450 enzymes that metabolize environmental chemicals and pharmaceuticals.[15,16] Second, there are many time-dependent and synchronized processes that are programmed during early development that could increase the risk of childhood disease if perturbed. For instance, disruption of neurulation, neuronal differentiation/proliferation/migration, gliogenesis, synaptogenesis, dendritic growth, myelination, apoptosis, synaptic pruning, or neurotransmitter systems could increase the risk of behavioral disorders or cognitive deficits.[17,18] In addition, epigenetic mechanisms, some of which are hormonally regulated, may mediate some of the effects of early life EDCs exposures on long term health outcomes.[19] Thus, there is concern that early life exposure to EDCs may increase the risk of childhood diseases, including neurodevelopmental disorders and obesity. [20,21]

EDCs may increase the risk of childhood neurodevelopmental disorders by interfering with early life thyroid hormone signaling or metabolism. Thyroid hormones play a critical role in neuronal migration, synaptogenesis, and myelination during gestation and childhood.[22] Even clinically non-significant variations in maternal thyroxine or thyroid stimultaing hormone (TSH) levels during pregnancy are associated with reduced cognitive abilities, [23] attention-deficit hyperactivity disorder (ADHD) symptoms,[24] and increased autism risk.[23–26] Studies show that the timing of thyroid hormone availability influences the neurobehavioral phenotype. Gestational thyroxine reductions are associated with deficits in visual processing, visuomotor abilities, and motor skills, while postnatal reductions are associated with deficits in language, fine motor skills, attention, and memory.[27–30] That both pre- 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 may perturb neuroendocrine systems involved in growth, energy metabolism, appetite, adipogenesis, and glucose-insulin homeostasis to promote childhood obesity, cardiometabolic dysfunction, and liver dysfunction.[31–34] These perturbations may lead to a 'thrifty phenotype' that promotes more efficient energy storage, rapid early life weight gain, and excess adipose mass.[35–41] Rapid growth and excess adiposity lead to increased circulating levels of free fatty acids, in turn causing a cascade of metabolic changes that reduce the capacity for liver and muscle to absorb, store, and metabolize glucose,[42–44] which in turn casues 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 the liver vacuoles, and hepatic steatosis (i.e., non-alcoholic fatty liver disease).[45]

Despite their seemingly unrelated nature, shared neuroendocrine pathways could be disrupted by EDC exposures to influence the risk of both childhood obesity and neurodevelopment disorders (Figure 1).[46–48] Indeed, the prevalence of excess adiposity is higher among children with behavioral disorders, like attention-deficit hyperactivity disorder (ADHD), and obese children have lower academic achievement, impaired attention and working memory, and reduced cortical thickness and white matter integrity compared to lean children.[49–51] Moreover, up to 30% of the genes associated with adiposity are the same as those associated with processing speed.[52] Finally, increased impulsivity, a key feature of ADHD, is related to food responsivity in adolescents[53] and administration of the adipocytokine ghrelin to rodents increases impulsive behaviors.[54]

There is concern over the health effects of EDC mixtures.[55] 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,[56,57] 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 may fail to quanitfy the synergistic or cumulative healht effects of EDCs, as well as confounding due to correlated co-pollutants.

Given the above, this narrative review has three objectives. First, this review will discuss epidemiological studies examining associations between early-life exposure to several EDCs and childhood neurodevelopmental disorders and obesity. It will focus on select EDCs for which there is widespread general population exposure, specifically phthalates, bisphenol A (BPA), perfluoroalkyl substances (PFAS), and triclosan (Table 1). There are other excellent reviews for readers interested in chemicals with declining exposure that have been banned or phased out of production (e.g., organochlorine compounds).[58] As a second objective, this review will describe some limitations to making stronger inferences from epidemiological studies about the impact of EDC exposures on child health and propose how researchers might address these limitations through better study designs and methods. Finally, this review closes with some guidance for clinicians to address patients' concerns about EDC exposure reduction.

Phthalates

Phthalate Uses, Exposure, and Measurement

Phthalates are a class of EDCs used in a multitude of consumer products, including personal care products, medications, and plastics (Table 1). Biomonitoring studies from around the world indicate that there is universal phthalate exposure 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, resulting in exposure to the fetus.[77]

After entering the body, phthalates are rapidly hydrolyzed to their respective monoester metabolites (Table 1).[78] Low molecular weight phthalates (di-ethyl phthalate [DEP], di-n-butyl phthalate, and di-iso-butyl phthalate) are excreted in the urine as glucuronide or sulfate conjugated hydrolytic monoesters, while 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 hours), there is repeated, episodic, and long-term exposure. Phthalate exposure is assessed using urine biospecimens since phthalates are predominately excreted in the urine and blood levels, which are considerably lower, may be subject to exogenous contamination during sample collection, storage, or processing.[79]

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

Biological Mechanisms of Phthalate Action

Phthalates may 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 may reduce thyroxine and triiodothyronine concentration in pregnant women and children,[83–85] antagonize T3 binding to thyroid receptor-β,[86] reduce cellular T3 uptake,[87] and affect transcription of the sodium-iodine transporter.[88] Phthalates can also inhibit 11-β-hydroxysteroid dehydrogenase-2, which deactivates cortisol.[89] In addition, phthalate exposure may affect offspring health by causing oxidative stress[90] or via epigenetic re-programming of the fetus and placenta.[91]

There is concern about the health effects of phthalate mixtures since humans are exposed to multiple phthalates at once and rodent studies demonstrate that phthalates have concentration additive effects on fetal androgen production.[82,92] Thus, the aggregate of individual phthalate exposures may have an additive impact on human health since individual phthalates share a common mechanism of action.

Phthalates and Neurodevelopment

Six publications from four prospective cohort studies report that prenatal exposure to several different phthalates is associated with ADHD behaviors,[59,60,93,94] autistic behaviors,[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 as or larger than the cognitive decrements observed with childhood lead exposure (5^{th} vs. 1^{st} quintile: 7-points; 95% confidence interval [CI]: 2, 11).[3,63] It is important to note that three other publications did not find associations between prenatal phthalate exposure and child neurobehavior.[64–66]

Three publications report that childhood exposure to some phthalates is associated with reduced cognitive abilities[65] and behavioral problems.[67,68] However, these studies were cross-sectional and reverse causality may explain these findings.

In summary, the epidemiological literature to date suggests that prenatal phthalate exposure may be associated with behavioral problems and cognitive decrements in children. Inconsistencies across studies may be due to differences in the timing of when phthalate exposure was assessed (e.g., early vs. late gestation), misclassification of phthalate exposure from studies using a single urine sample to assess exposure, or differences in child age at neurodevelopment assessment.

Phthalates and Adiposity/Obesity

Three publications from prospective cohorts examined prenatal phthalate exposure and childhood adiposity.[70–72] One publication reported that prenatal DEHP exposure is associated with decreased body mass index (BMI) in boys and increased BMI in girls,[70] whereas another publication found that non-DEHP phthalate exposures were associated with decreased BMI in boys, but not girls.[71] A third publication did not report any association between prenatal phthalate exposure and childhood adiposity.[72] In a pooled cohort including US participants from two of the previously mentioned cohort studies, increasing maternal urinary mono-3-carboxypropyl phthalate concentrations during pregnancy were associated with a doubling in the risk of being overweight or obese (95% CI: 1.2, 4.0).[95]

Four publications have examined childhood phthalate exposure and adiposity.[71,96–98] Three of these reported that childhood exposure to DEP was associated with excess adiposity and increased prevalence of obesity or excess adiposity,[98] but another did not.[71] In a prospective cohort of over 1,000 US girls, higher DEP exposure at 6–8 years of age was associated with increased BMI scores and waist circumference at 7–13 years of age.[97] In a cross-sectional study of US children, increasing urine concentrations of low molecular weight phthalates was associated with a 22% increase in the prevalence of obesity.[99]

In summary, 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 to this was the association between childhood DEP exposure and child adiposity or obesity prevalence. However, this association may be due to children with higher adiposity also having greater 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 MEP concentrations.[99]

BPA

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 since BPA can leach into food and beverage containers; however, dermal absorption and inhalation may be additional routes of exposure among persons working with BPA-containing receipts.[100–102] BPA is excreted in the urine as glucuronide/sulfate conjugates, does not persist in the body, and has an estimated biological half-life of ~6 hours.[103] BPA exposure is assessed by measuring urine concentrations of free and conjugated BPA. Urine is used since BPA is almost exclusively excreted in the urine, and blood levels are considerably lower and subject to exogenous contamination.[79] Biomonitoring studies around the world indicate nearly universal BPA exposure among pregnant women, infants, and children.[56,64,104–120] Much like some phthalates, urinary BPA concentrations have considerable within-person variation due to diet being the predominant source of exposure. Thus, it is essential to collect multiple urine samples to ensure accurate exposure assessment.

Biological Mechanisms of BPA Action

BPA may interact with a variety of hormonal systems that affect growth, metabolism, and neurodevelopment. Dodds and Lawson recognized BPA as a weak estrogen in 1936.[121] BPA is a weak agonist of the nuclear estrogen receptors α and β compared to estradiol.[122] However, BPA may also act on plasma protein bound estrogen receptors allowing BPA to interfere with estrogenic signaling at nanomolar and picomolar levels.[123,124] *In vitro* studies show that BPA may affect androgen/estrogen concentrations by inhibiting key enzymes involved in gonadal hormone synthesis and metabolism,[125] but results from human studies are not consistent.[126–128] Rodent studies have found that prenatal BPA exposure is associated with higher T4 levels in offspring[129] and thyroid-specific gene expression.[130] Some epidemiological studies show that BPA exposure is associated with altered maternal, neonatal, or adolescent thyroid parameters.[131–133]

BPA and Neurodevelopment

In 2008, the National Toxicology Program concluded that there was “some concern” over the effect of BPA on neurobehavioral endpoints based on findings in animal studies.[134] Since then, there have been eight studies from five prospective cohorts examining prenatal BPA exposure and child neurobehavior.[64,110–116] Four publications from three of these prospective cohorts reported that prenatal BPA exposure was associated with more internalizing behaviors in children, with stronger associations in boys than girls.[110,113–115] Two publications from another cohort reported that prenatal BPA exposure was associated with more internalizing and externalizing behaviors in girls, but not boys.[111,112] One publication reported that prenatal BPA concentrations were associated with increased risk of ADHD-related behaviors at 4 years of age, with stronger associations in boys.[116] Two other publications have reported that prenatal urinary BPA concentrations were not associated

with parent-reported reciprocal social behaviors.[61,64] The association between prenatal BPA exposures and children's cognitive abilities has not been thoroughly examined, with one study reporting that prenatal urinary BPA concentrations were associated with parent-reported executive function in 3-year old girls.[112]

Seven publications have examined the relation between childhood BPA exposures and behavior problems or ADHD-related behaviors.[67,110,112–114,135,136] Generally, the results are inconsistent. Some report that childhood BPA exposures were associated with ADHD behaviors in boys,[135] ADHD behaviors in both boys and girls,[135] anxious/depressive/aggressive behaviors in girls,[110,113,114] or learning problems.[137] Some publications report null associations between childhood BPA exposures and neurobehavior.[67,112]

In summary, these studies suggest that both prenatal and postnatal BPA exposure is associated with parent-reported behavior problems in children, but there are inconsistencies across these studies with regard to the period of life with the greatest vulnerability to exposure (prenatal vs. infancy vs. childhood) and sex-specific effects. The heterogeneity of these findings could be due to the substantial within-person variation of urinary BPA concentrations that results in BPA exposure misclassification.

BPA and Adiposity/Obesity

Seven publications from prospective cohort studies have examined whether early-life BPA exposure is obesogenic.[104–107,117,118,138] Three publications report that higher prenatal BPA exposure was associated with lower BMI and that these associations were stronger in girls.[104–106] Two other publications reported that prenatal BPA exposure was associated with increased waist circumference, BMI, and risk of being overweight or obese.[107,117] Two other publications reported no association between prenatal BPA exposure and child adiposity measures.[118,138]

Some of the aforementioned studies have prospectively examined the relation between infant or childhood BPA exposure and subsequent adiposity,[104–107] and several cross-sectional studies have been conducted.[119,120] Among publications with prospective measures of BPA exposure during infancy or childhood, there is little evidence to suggest that BPA exposure is associated with excess adiposity.[104–107] However, cross-sectional studies 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 US children, children in the top 3 quartiles of urinary BPA concentrations were ~25% more likely to be overweight and >2-fold more likely to be obese compared to children in the lowest quartile.[119] However, the strength of this association did not monotonically increase across quartiles of BPA exposure, suggesting a threshold effect or potential residual confounding. Still, other publications report no association between infant or childhood BPA exposure and childhood obesity.[104,107]

The available epidemiological literature is equivocal about the obesogenic effects of early-life BPA exposure, with studies showing both increases and decreases in adiposity or risk of being overweight or obese with higher 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 persons with excess adiposity have different dietary patterns that increase their exposure to BPA.

Triclosan

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 (Table 1).[139] Exposure is predominately through oral and dermal routes.[139] Triclosan is not persistent, has a biological half-life <24 hours, and is predominately 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.[56,108,141] While triclosan has a short biological half-life similar to that of BPA and some phthalates, unlike BPA and some phthalates, urinary triclosan concentrations are relatively stable over time within a person.

Biological Mechanisms of Triclosan 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 may reduce thyroxine concentrations by activating nuclear receptors to increase hepatic catabolism of thyroxine.[145] Results from epidemiological studies of triclosan and thyroid function are not consistent.[146,147] However, there are no prospective epidemiological studies examining the relation between triclosan and thyroid hormone biomarkers during gestation, infancy, or childhood. Finally, given its antimicrobial activity, triclosan may be capable of altering the composition or function of the microbiota, but there is little research examining this hypothesis.[148]

Triclosan and Neurodevelopment

Currently, there are no animal or epidemiological studies directly examining the neurotoxicity of early-life triclosan exposure. As noted, triclosan exposure may reduce serum thyroxine concentrations during pregnancy and this could cause adverse neurodevelopment given the important role that thyroxine plays in fetal brain development.[23] Three epidemiological studies report suggestive inverse associations between prenatal triclosan exposure and neonatal anthropometry.[118,149,150] Thus, given that head circumference is positively correlated with later life IQ, early-life triclosan exposure could adversely impact neurodevelopment.[151]

Triclosan and Adiposity/Obesity

Four publications have reported on the relation between triclosan exposure and childhood obesity or excess adiposity.[152,153] Two cross-sectional studies using 6–19 year old children from the National Health and Nutrition Examination Survey report conflicting results. One

publication (years: 2007–2010), found no association between urinary triclosan concentrations and BMI z-score, waist circumference, or prevalence of being overweight or obese.[154] In the second publication (years: 2003–2010), urinary triclosan concentrations were associated with a monotonic decrease BMI and waist circumference.[153] Another publication a reported that urinary triclosan concentrations were similar in lean and overweight/obese children.[155] In a prospective cohort study, prenatal triclosan exposure was not associated with child adiposity at 4 to 9 years of age.[138]

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

Perfluoroalkyl Substances

PFAS Uses, Exposure, and Measurement

PFAS are a class of man-made fluorinated chemicals used in stain/water resistant coatings for textiles, non-stick cookware, food container coatings, floor polish, fire-fighting foam, and industrial surfactants (Table 1).[156] 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.[157] 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, indicating that exposure is ubiquitous and these chemicals can cross the placenta.[56,64,158–176]

Unlike phthalates, BPA, and triclosan, PFAS have long biological half-lives in humans, ranging from 3.8 to 7.3 years.[177] Thus, a single serum or plasma concentration is sufficient to characterize exposure for epidemiological studies. The sources and relative contributions of different PFAS to human exposure vary according to age-related behavioral factors and dietary patterns, and PFAS exposures during infancy can equal or exceed prenatal exposures derived from the mother.[156,178] For instance, breast milk and formula may contribute almost exclusively to infant's exposure since PFAS are found in breast milk and water, and infants consume up to 6 times as much fluid as adults (150 vs. 26 ml/kg/day).[179–181]

Biological Mechanisms of PFAS Action

PFAS may 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 lower global DNA cytosine methylation, higher Long Interspersed Nuclear Element-1 methylation, and changes in the expression of genes involved in cholesterol metabolism.[182–184] PFOA and PFOS can bind to and activate the peroxisome proliferator activated receptor (PPAR)-α/γ to increase adipocyte differentiation and increase body fat.[185–187] 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 show that PFAS are capable of inducing changes in thyroid function,[188] but results from human studies are not consistent.[189]

PFAS and Neurodevelopment

Eleven publications from prospective cohorts have examined the relations between prenatal PFAS exposure and cognitive abilities,[165,166] attainment of developmental milestones,[167] parent or teacher reported behaviors and executive function,[64,167–170] psychomotor development,[169] academic achievement,[171] or risk of autism spectrum disorders, ADHD, or cerebral palsy.[172–174] With regard to the most commonly detected PFAS (PFOA, PFOS, PFNA, and PFHxS), these publications report inconsistent results. In a prospective birth cohort of 218 mother-child pairs, higher prenatal PFOS exposure was associated with worse parent-reported executive function.[170] 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.[172] Several studies report protective or null associations between prenatal PFAS exposure and child neurobehavior.[64,165–167,169,173]

Four publications have examined the relations between childhood PFAS exposure and neurodevelopment.[165,168,175,176] Two publications from cross-sectional studies report that children's serum PFAS concentrations were associated with increased prevalence of parent-reported ADHD or ADHD medication use.[168,175] However, in a prospective cohort study with exceptionally high PFOA exposure, children's serum PFOA concentrations were not consistently associated with parent- or teacher-reported ADHD-related behaviors or other neuropsychological measurements.[165,172]

The available body of evidence does not consistently suggest that early-life PFAS exposures are associated with neurodevelopment. While some studies suggest adverse neurobehavioral outcomes among children with elevated prenatal or childhood PFAS exposures, there are inconsistencies regarding which individual PFAS exposures may be associated with neurobehavior and whether there are heightened periods of vulnerability to PFAS exposures. The protective associations between early-life PFAS exposure and neurodevelopment is biologically plausible because *in vitro* studies report that PFOA and PFOS are agonists of PPAR-γ and activation of this receptor may be neuroprotective.[190] Additional studies with longitudinal measures of exposure and comprehensive assessment of neurodevelopment are warranted given the ubiquity and persistence of PFAS exposure.

PFAS and Adiposity/Obesity

There is a compelling body of evidence suggesting that prenatal PFAS exposure 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, increasing prenatal PFOA exposure was associated with a 19 gram decrease in birth weight (95% CI: −30, −8).[158] These results in humans are similar to those observed in 21 rodent studies where each 1 mg/kg/d increase in PFOA exposure was associated with a 0.023 gram decrease in pup birth weight (95% CI: −0.029, −0.016).[191] Altered fetal growth patterns related to PFAS exposure may increase the risk of subsequent obesity and cardiometabolic disorders as prior studies

show that fetal growth deceleration and infancy growth acceleration are associated with increased adiposity and cardiometabolic risk markers in later childhood.[39,192,193]

Consistent with this hypothesis, five publications from prospective cohort studies report that prenatal PFAS exposure is associated with alterations in infant or child growth,[160,163] increased adiposity during childhood and adulthood,[159–161] and higher waist-to-height ratio.[162] Two publications from other prospective cohort studies, including one with exceptionally high PFOA exposure, did not observe an association between prenatal PFAS exposure and child or adult adiposity or risk of being overweight or obese.[164,194] These two studies used self- or parent-reported anthropometry, which could be responsible for the null results since there are well-documented errors in self- and parent-reported anthropometry that could misclassify adiposity and attenuate associations towards the null.[195,196]

Two studies have examined childhood PFAS exposure and adiposity. In a cross-sectional study of US adolescents, PFOS exposure was associated with decreased BMI and waist circumference, while other PFAS were not associated with BMI or waist circumference.[197] 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.[198]

Challenges to Making Stronger Inferences about EDCs and Child Health

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

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.[199] First, given the large number of environmental agents to which humans are exposed, there is a need to identify those most strongly associated with adverse child health outcomes, particularly when little data are available about the toxicity of individual exposures. Second, multiple EDCs may have a synergistic association with health outcomes by disrupting the homeostasis of compensatory mechanisms. Finally, cumulative exposure to certain classes of EDCs (e.g., phthalates) could adversely impact 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.[200,201] Several methods showed promise in addressing

questions related to EDC mixtures. For instance, Least Absolute Shrinkage and 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, non-linear dose-response functions, and co-pollutant confounding.[202]

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.[203,204] 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 (e.g., toxic equivalency factors for dioxins),[205] or quantifying the biological activity in biospecimens.[206] These summation methods of examining cumulative exposures are likely too simplistic since they assume a single mechanism of EDC action. Thus, there is a need to develop methods that incorporate the potency of EDCs on multiple biological pathways.

By implementing methods that account for chemical mixtures, we are likely to identify previously undocumented chemical risk factors for childhood disease, 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, there may be a high rate of false positives. [207]

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, where the misclassification results in a less precise estimate of an individual's exposure and this makes 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, then 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 may 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 (e.g., 2nd trimester) 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 the 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.[208]

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, then this suggests that observed associations may be attenuated towards the null and true associations may be much stronger. However, non-causal explanations should not be ruled out, including confounding by traditional risk factors for adverse neurodevelopment or correlated co-pollutants.

Confounding

As is the case for all observational studies, there is the potential for confounding factors associated with both early-life EDC exposures and child health to 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 (e.g., diet) are correlated with lifestyle factors (e.g., maternal diet) that may also be associated with EDC exposures (Figure 2). Thus, to determine if a given EDC has obesogenic effects independent of other predictors of obesity, it is necessary to measure and control for factors like diet, physical activity, breast feeding, etc. When examining neurotoxic EDCs, many socioeconomic factors associated with exposure are also associated with parental IQ or behavior and the quality of caregiving environment, which are important determinants of child IQ and behavior. Finally, it is necessary to consider potential confounding from other EDC exposures since the effect of one EDC may 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 (For an example, see the directed acyclic graphs and change in estimate approach development by Weng and colleagues).[209] It is imperative to note that it is not appropriate to adjust for variables that are caused by EDC exposure and causes of poor childhood health (i.e., causal intermediates) since this ‘over-adjustment bias’ may mask causal associations.[210] For instance, prenatal PFAS exposures are associated with lower birth weight and increased risk of childhood obesity. Moreover, birth weight is a determinant of childhood obesity risk.[211] 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 (e.g., neurulation) and postnatal (e.g., synaptic pruning) neurodevelopmental processes.[18] This could be a reason for some of the heterogeneity in the results of the studies discussed above. This highlights the need for prospective studies with serial measures of EDC exposure across the lifespan, as well as appropriate statistical methods to identify periods of heightened vulnerability.[199]

Sexually Dimorphic Associations

Some associations between EDC exposures and childhood health are sexually dimorphic and EDCs may be capable of acting in a sex-specific manner given the important role that gonadal hormones play 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 behavior in boys, but not girls.[69] The identification of sex-specific effects in epidemiological studies will require larger sample sizes than most studies conducted to date.

Advice for Clinicians and Concerned Patients

Presently, there are no evidence-based methods for reducing EDC exposures, but there are some general recommendations that clinicians could give to concerned patients. For EDCs found in the diet (e.g., BPA, DEHP, and PFAS), eating a balanced diet may be one way to avoid exposure from any one foodstuff, but 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 study showed that handling BPA-containing thermal receipts was an important route of exposure and that wearing gloves could reduce BPA exposure from this route.[102] Another study found some evidence that children who have handle thermal receipts may have higher BPA exposure.[109]

Individuals may be able to reduce their exposure to DEP and DnBP by reducing or eliminating the use of some lotions, cosmetics, and colognes/perfumes.[76,212] However, there are no requirements for personal care products to include these phthalates in their ingredient list, making it difficult to avoid this source of exposure. Individuals can reduce triclosan exposure by avoiding triclosan-containing toothpastes. However, because triclosan-containing toothpastes are clinically indicated for some individuals, the benefits and risk of continued use should consider the specific conditions and susceptibilities of the individual (e.g., pregnancy). Finally, granular activated carbon water filtration systems may be effective at reducing PFAS exposure when consuming PFAS contaminated water,[213] but this may have a minimal effect on total PFAS body burden when diet is the predominant source of PFAS exposure.[214]

Conclusions

Exposure to BPA, phthalates, triclosan, and PFAS is ubiquitous and occurs during potentially sensitive periods of development that are important in the etiology of childhood neurodevelopmental disorders and obesity. The available research suggests that prenatal BPA and phthalate exposures are related to adverse neurobehavioral outcomes in children. Furthermore, prenatal PFAS exposure is related to reduced fetal growth and excess childhood adiposity. While this review did not compare the findings of animal or laboratory studies to the results of epidemiological ones, future reviews or risk assessments of these chemicals should include this important feature of establishing causality.[215]

We can make stronger inferences about the role of EDCs in the etiology 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 sub-populations and reduction of EDC exposures via public health interventions.

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Biography

Dr. Joseph M. Braun is an Assistant Professor in the Department of Epidemiology at the Brown University School of Public Health. He was formerly a school nurse in Milwaukee, WI before receiving his master's and doctoral degrees in Epidemiology from the University of North Carolina-Chapel Hill. Dr. Braun studies the patterns, determinants, and health consequences of early-life chemical exposures in pregnant women, infants, and children. His research focuses primarily on childhood obesity, neurobehavioral disorders, and cardiometabolic outcomes.

Box 1

Neurodevelopmental Disorders of Childhood

Many neurodevelopmental disorders develop during childhood, with prevalence in the United States of 1.5% for autism spectrum disorders (ASD), 6.7% for attention-deficit hyperactivity disorder (ADHD), 7.7% for specific learning disabilities (LD).[216,217] 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 behaviors. Within the ASD diagnosis, deficits can be mild or severe and accompanied by intellectual disabilities (IQ<70) and substantial comorbidities.[218] For ADHD, children present with hyperactivity, inattention, and poor impulse control, and display deficits in executive function (e.g., inhibition, behavioral regulation, and planning/organizing). ADHD diagnosis is classified into hyperactive/impulsive or inattentive subtypes.[219] LD is characterized by difficulties learning and using specific academic skills (e.g., reading and mathematics) and is 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.[220,221] For instance, global measures of cognition (i.e., IQ) and academic performance can be used to study whether EDC exposures affect intellectual abilities and specific academic skills, respectively. Continuous outcomes are advantageous since they provide a relative ranking of an individual's ability/behavior, which enhances statistical power. Moreover, clinical diagnosis could misclassify individuals since they may 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 increased prevalence/incidence of clinical disorders (Figure B1).

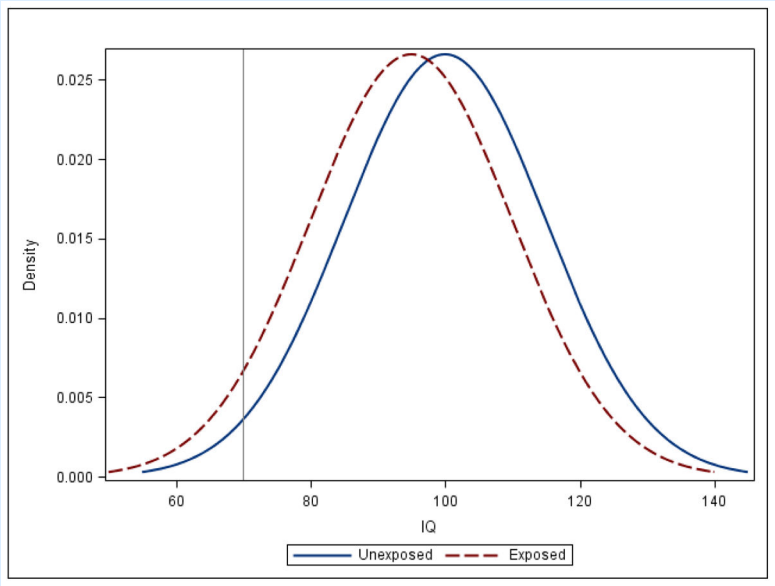

Figure B1.

Density Distribution of IQ in EDC Unexposed and Exposed Populations

Figure B1 represents the distribution of IQ in two populations of one million individuals each. The grey line signifies the threshold for IQ scores consistent with intellectual disabilities (IQ<70).

In the unexposed population, the mean IQ is 100 (standard deviation=15), while in the exposed population the mean IQ is 95 (standard deviation=15). This 5-point shift in IQ results in nearly a doubling in the proportion of people with IQ scores consistent with intellectual disabilities (IQ<70) in the exposed population (4.48%) compared to the unexposed population (2.27%).

Box 2

Prevalence and Origins of Childhood Obesity

Childhood obesity is a major threat to public health in the United States, with the prevalence rising from 7% in 1980 to 17% in 2012.[222] Obesity is also a major public health problem globally, with 10–14% of adults worldwide being overweight or obese in 2008.[223] Childhood obesity increases the risk of type-2 diabetes, cardiovascular disease, and metabolic syndrome, and has adverse effects on pulmonary, musculoskeletal, and psychosocial functioning.[224]

The principal cause of obesity is caloric imbalance from excess calorie intake and insufficient physical activity. However, there is considerable evidence 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 re-programming neuroendocrine systems involved in growth, energy metabolism, appetite, adipogenesis, and glucose-insulin homeostasis.[32–34] These environmental stressors may 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.

Key Points

- Endocrine disrupting chemicals may increase the risk of childhood neurodevelopmental disorders or obesity by disrupting hormonally-mediated processes during critical periods of development.
- The developing fetus, infant, and child may have enhanced sensitivity to environmental stressors like EDCs and greater exposure to some EDCs because of developmentally appropriate behavior, anatomy, and physiology.
- The available epidemiological evidence suggests that prenatal bisphenol A and phthalate exposure is associated with adverse neurobehavioral outcomes in children, but not excess adiposity or risk of obesity/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 neurobehavioral 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.

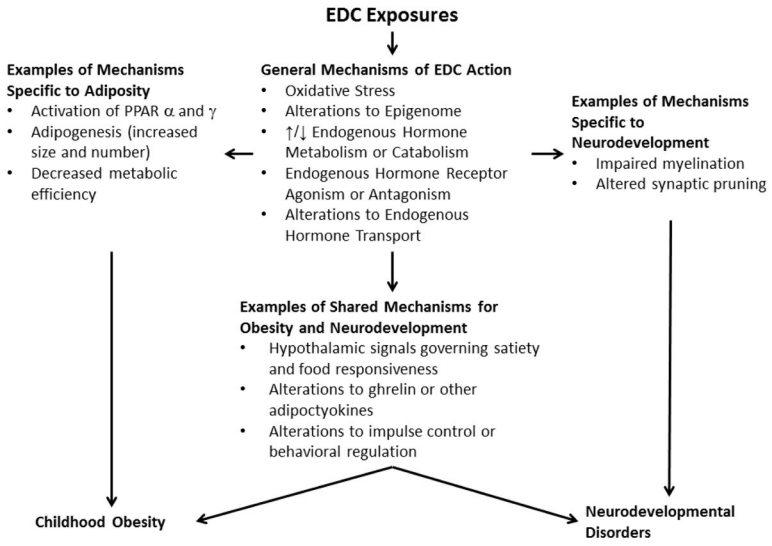

Figure 1.

Conceptual diagram illustrating general mechanisms of endocrine disrupting chemical (EDC) action and examples of specific biological targets relevant to childhood neurodevelopmental disorders and obesity

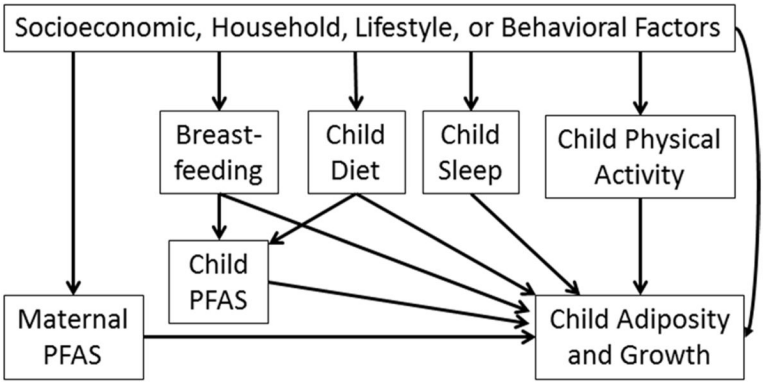

Figure 2.
Directed acyclic graph for the relationship between early life PFAS exposure and child adiposity

Table 1

Epidemiological exposure assessment and commercial/industrial uses of phthalates, bisphenol A, polybrominated diphenyl ethers, and perfluoroalkyl substances

EDC	Exposure Assessment	Uses in Commerce or Industry
Di-2-ethylhexyl phthalate (DEHP)	Urine concentrations of mono-2-ethylhexyl (MEHP), mono-2-ethyl-5-carboxypentyl (MECPP), mono-2-ethyl-5-hydroxyhexyl (MEHHP), and mono-2-ethyl-5-oxohexyl (MEOHP) phthalate	PVC plastics, food packaging, and plastic medical tubing and 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 and DiBP)	Urine concentrations of mono-n/i-butyl phthalates (MnBP and MiBP)	Scent retainer in personal care products, medication excipients, cellulose plastics, & adhesives.
Bisphenol A (BPA)	Urine concentrations of BPA	Polycarbonate plastics, resins, thermal 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/water resistant coatings, non-stick cookware, food container coatings, floor polish, fire-fighting foam, and industrial surfactants.