Endocrine-disrupting chemicals 1

Endocrine-disrupting chemicals: implications for human health

Linda G Kahn, Claire Philippat, Shoji F Nakayama, Rémy Slama, Leonardo Trasande

Since reports published in 2015 and 2016 identified 15 probable exposure–outcome associations, there has been an increase in studies in humans of exposure to endocrine-disrupting chemicals (EDCs) and a deepened understanding of their effects on human health. In this Series paper, we have reviewed subsequent additions to the literature and identified new exposure–outcome associations with substantial human evidence. Evidence is particularly strong for relations between perfluoroalkyl substances and child and adult obesity, impaired glucose tolerance, gestational diabetes, reduced birthweight, reduced semen quality, polycystic ovarian syndrome, endometriosis, and breast cancer. Evidence also exists for relations between bisphenols and adult diabetes, reduced semen quality, and polycystic ovarian syndrome; phthalates and prematurity, reduced anogenital distance in boys, childhood obesity, and impaired glucose tolerance; organophosphate pesticides and reduced semen quality; and occupational exposure to pesticides and prostate cancer. Greater evidence has accumulated than was previously identified for cognitive deficits and attention-deficit disorder in children following prenatal exposure to bisphenol A, organophosphate pesticides, and polybrominated flame retardants. Although systematic evaluation is needed of the probability and strength of these exposure–outcome relations, the growing evidence supports urgent action to reduce exposure to EDCs.

Lancet Diabetes Endocrinol 2020; 8: 703–18

This is the first in a **Series** of two papers about endocrine-disrupting chemicals

Department of Pediatrics (L G Kahn PhD, Prof L Trasande MD), **Department of Environmental Medicine, and Department of Population Health, New York University Grossman School of Medicine and New York University School of Global Public Health, New York University, New York, NY, USA** (Prof L Trasande); **University Grenoble Alpes, Inserm, CNRS, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Institute for Advanced Biosciences, Grenoble, France** (C Philippat PhD, R Slama PhD); **and Center for Health and Environmental Risk Research, National Institute for Environmental Studies, Tsukuba, Japan** (S F Nakayama PhD)

Correspondence to: Prof Leonardo Trasande, Department of Pediatrics, New York University Grossman School of Medicine, New York University, New York, NY 10016, USA
leonardo.trasande@nyulangone.org

Introduction

In 1962, Rachel Carson described the effects of dichlorodiphenyltrichloroethane (DDT) on sexual development and reproduction.[1] Less than a decade later, Herbst and colleagues[2] documented a cluster of patients in Boston (MA, USA) with vaginal adenocarcinoma resulting from prenatal use of the medication diethylstilbestrol. During this time, two assumptions were common: the Paracelsian notion that "Solely the dose determines that a thing is not a poison", and the belief that only rarely could synthetic chemicals disrupt hormonal and homoeostatic responses and thereby contribute to disease and dysfunction.

Over the past 50 years, these two assumptions have proven flawed. Many studies have identified effects of various exogenous chemicals on endocrine processes and functions, exposing the important need for a shift in scientific theory. Many of these dose–response relations have been non-monotonic.[3] Mechanistic studies explain these unconventional associations at the molecular level. These endocrine-disrupting chemicals (EDCs) are not rogue pharmaceuticals or rare contaminants. One examination by the US Food and Drug Administration identified more than 1800 chemicals that disrupt at least one of three endocrine pathways (oestrogen, androgen, and thyroid).[4] 320 of 575 chemicals screened at the instruction of the European Commission showed evidence or potential evidence for endocrine disruption.[5]

EDCs are now recognised as serious and urgent threats to public health, potentially emerging as one of the leading environmental risks globally. Among the non-governmental organisations and governmental agencies documenting the rapidly accelerating evidence and implications for human health are the Endocrine Society,[6] the International Federation of Gynecology and Obstetrics,[7] WHO and the UN Environment Programme (UNEP),[8] and the American Academy of Pediatrics.[9] Reports by these organisations describe the serious adverse effects of EDCs on endocrine processes during susceptible periods of human development and the long latency period between exposure and disease as a result of early-life exposure to chemicals such as DDT, which has been associated with breast cancer incidence half a century later in life.[10]

This Series paper seeks to update the 2015 findings of an expert panel commissioned by the Endocrine Society that led to the identification of 15 exposure–outcome associations with a probability of causation (table 1).[11,12] The paper also aims to expand on the previous report by identifying new exposure–outcome associations of concern, especially with regard to chemicals that were not widely researched several years ago, such as perfluoroalkyl and polyfluoroalkyl substances (PFAS) and polybrominated diphenyl ethers (PBDEs), and by including several outcomes that were not specifically focused on in the WHO and UNEP report, such as anogenital distance and prostate cancer. Because our intention is to inform future research and policy, we have focused on synthetic chemicals that are currently in circulation and not on legacy compounds, such as DDT, other organochlorine pesticides, polychlorinated biphenyls (PCBs), and dioxins and furans. Where possible, we emphasise findings related to newer chemicals that are replacing chemicals that are being phased out or banned.

Subsequent sections describe evidence that supports previously identified or increasingly likely associations of EDCs with perinatal, neurodevelopmental, metabolic, and reproductive outcomes. More equivocal results and

See Online for appendix

tables summarising all studies reviewed that reported significant or epidemiologically meaningful associations can be found in the appendix. We conclude with an overview of knowledge gaps and opportunities to address those gaps in future studies in humans.

Birth outcomes

Fetal growth and length of gestation, especially low birthweight and preterm birth, are important predictors of health in later life.[13] Increased understanding now exists that environmental exposures (especially EDCs) can induce the so-called thrifty phenotype that was first described by Barker and colleagues,[14] in which a fetal metabolism that is conservatively programmed is maladapted to the ex utero environment, resulting in increased adiposity beginning in childhood and cardiovascular risks later in life. EDCs are increasingly shown to shorten gestation, alter intrauterine growth, and disrupt metabolic programming in laboratory studies.[15] Additionally, measures of anogenital distance obtained at birth are known to track through adulthood[16] and predict infertility and reduced sperm count.[17] Associations between prenatal exposure to EDCs and birth outcomes were not previously assessed in terms of probable evidence for causation. This Series paper identified three associations of note: PFAS and reduced birthweight, phthalates and preterm birth, and phthalates and reduced anogenital distance in male offspring (table 2).

	Outcome	Strength of human evidence	Probability of causation, %
Prenatal PBDEs	IQ loss and intellectual disability	Moderate to high	70–100%
Prenatal organophosphate pesticides	IQ loss and intellectual disability	Moderate to high	70–100%
Multiple prenatal exposures	Attention-deficit disorder	Low to moderate	20–69%
Multiple prenatal exposures	Autism spectrum disorder	Low	20–39%
Prenatal DDE	Childhood obesity	Moderate	40–69%
Prenatal BPA	Childhood obesity	Very low to low	20–69%
Adult DEHP	Adult obesity	Low	40–69%
Adult DEHP	Adult diabetes	Low	40–69%
Prenatal DDE	Adult diabetes	Low	20–39%
Prenatal PBDEs	Cryptorchidism	Low	40–69%
Prenatal PBDEs	Testicular cancer	Very low to low	0–19%
Adult phthalates	Low testosterone, resulting in increased early mortality	Low	40–69%
Adult benzyl and butyl phthalates	Male infertility, resulting in increased use of assisted reproductive technology	Low	40–69%
Adult DEHP	Endometriosis	Low	20–39%
Lifetime DDE	Fibroids	Low	20–39%

Adapted from the data first reported in Trasande et al (2015)[11] and updated in Trasande et al (2016).[12] PBDE=polybrominated diphenyl ether. IQ=intelligence quotient. DDE=dichlorodiphenyldichloroethylene. BPA=bisphenol A. DEHP=di-2-ethylhexyl phthalate.

Table 1: **Exposure–outcome associations with a probability of evidence for causation identified up to 2015**

Birthweight

Human studies have rightly given substantial attention to associations of prenatal exposure to EDCs with fetal growth and birthweight. Previous research that identified decreases in birthweight in relation to maternal prenatal concentrations of PFAS has been further corroborated by a study published in 2017,[18] which suggested that changes in concentrations of maternal glucose act as a mediator. Measurement of PFAS in the blood spots of neonates has not yielded the same findings, perhaps because of temporality and imprecision in measuring exposure.[19] A meta-analysis[20] of 24 studies reported a change in birthweight of –10·5 g (95% CI –16·7 to –4·4) per ng/mL increase in perfluorooctanoic acid (PFOA) concentration in maternal blood or umbilical cord blood, with a greater effect size in studies that measured exposure in late pregnancy (ie, the second or third trimester) compared with those that measured exposure preconceptionally or during early pregnancy (ie, predominantly in the first trimester). The increased effect size is notable given the potential for confounding or reverse causation, or both, in studies that rely on assessment of exposure in late pregnancy.

Evidence for associations of PBDEs, phenols, and phthalates with birthweight is not as strong, including various studies that did not show significant results and, in the case of the non-persistent chemicals, studies that did not have repeated measures of exposure (appendix pp 2–4, 7).

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal PFAS	Low birthweight	Not assessed	Not assessed	Large body of evidence; no significant association at highest levels of (modelled) exposure; weaker associations with exposure measurements in early pregnancy
Prenatal phthalates	Preterm birth	Not assessed	Not assessed	Multiple studies identify associations with DEHP metabolites
Prenatal phthalates	Reduced anogenital distance in male offspring	Not assessed	Not assessed	Five studies show reduced anogenital distance or anogenital index score; two studies show increased anogenital distance; three studies show no association

Adapted from the data first reported in Trasande et al (2015)[11] and updated in Trasande et al (2016).[12] See appendix for full list of studies mentioned here that have updated the literature (appendix pp 2–6). PFAS=perfluoroalkyl and polyfluroalkyl substances. DEHP=di-2-ethylhexyl phthalate.

Table 2: **Updates to assessment of probable associations between prenatal exposures and birth outcomes**

Preterm birth

Preterm birth is a multifactorial condition that can sometimes lead to severe consequences in the long term.[21] Studying preterm birth raises many specific challenges. In particular, studies in humans generally do not distinguish between preterm births on the basis of different proximal causes or clinical contexts,[22] potentially reducing the ability to discern effects related to EDCs that might act along specific biological pathways.

Strong evidence exists for a relation between di-2-ethylhexyl phthalate (DEHP) and preterm birth,[23–25] with associations observed in several studies of high quality, including some studies relying on repeated samples taken during pregnancy to assess exposures. In the LIFECODES study,[26] several phthalates were shown to be associated with oxidative stress markers in pregnancy, which mediated part of the associations observed between DEHP metabolites and preterm birth observed in this population. Adverse effects of dibutyl phthalate (DBP) were reported in at least two studies that used biomarkers of exposure.[24,27] Another study noted an increased rate of preterm birth in women with high exposure to DBP from taking mesalazine during pregnancy.[28] Other phthalate compounds, such as diisobutyl phthalate and diethyl phthalate, have also been associated with an increased risk of preterm birth, but in fewer studies of high quality.

Studies of associations of PFAS and phenols with preterm birth were inconsistent, and there was not enough evidence regarding organophosphate pesticides, pyrethroids, PBDEs, or organophosphorus flame retardants (OPFRs) to draw conclusions (appendix pp 4–5, 7–8).

Anogenital distance

Many studies have examined the relation between EDCs and anogenital distance, the distance between the anus and genitals (scrotum or penis in boys, clitoris or fourchette in girls), which is hypothesised to reflect the androgenicity of the in utero environment. In boys, most studies of phthalates of both high and low molecular weight measured in prenatal urine (n=8) or umbilical cord blood (n=1) reported associations with shorter anogenital distance (a feminising effect) or lower anogenital index (a measure that takes the child's weight into account).[29–33] Additionally, one study showed an association between longer anogenital distance and exposure to phthalates of low molecular weight,[34] one study noted associations between shorter anogenital distance and exposure to mono-2-ethylhexyl phthalate (MEHP; a metabolite of DEHP) and between longer anogenital distance and the summed metabolites of DBP (low molecular weight),[35] and one study found no associations.[36] Results for bisphenol A (BPA) were inconsistent, and there was too little evidence regarding triclosan, PFAS, PBDEs, or other EDCs to discern any significant associations (appendix pp 5–6, 8–9). In girls, anogenital distance and anogenital index were not clearly associated with in utero exposure to EDCs.

Neurodevelopment

Prenatal exposure to EDCs can affect fetal neurodevelopment via at least two distinct hormonal pathways. Because the fetus relies on transplacental supply of thyroid hormone until the second trimester, maternal thyroid imbalance can result in permanent and lifelong neurodevelopmental consequences for children, including attention-deficit disorder, autism spectrum disorder, and cognitive and behavioural dysfunction.[37] Disruption of the function of sex hormones can also induce dimorphic effects on brain development.[38] Epidemiological studies have built on a substantial amount of toxicological literature documenting EDCs that affect these key pathways in animals, and have generally yielded similar findings in humans. This Series paper identified additional evidence to support associations of prenatal exposure to PBDEs and organophosphate pesticides with decreases in intelligence quotient (IQ); PBDEs, BPA, organophosphate pesticides, and pyrethroids with behavioural outcomes; and organophosphate pesticides, and pyrethroid pesticides with autism spectrum disorder (table 3).

Prenatal and perinatal exposure and child cognition

Evidence in humans for the cognitive effects of prenatal and perinatal exposure to EDCs is strongest for

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal PBDEs	IQ loss and intellectual disability	Moderate to high	70–100%	Additional longitudinal evidence supporting high probability of causation
Prenatal organophosphate pesticides	IQ loss and intellectual disability	Moderate to high	70–100%	Additional longitudinal evidence supporting high probability of causation
Multiple prenatal exposures	Attention-deficit disorder and behaviour problems	Low to moderate	20–69%	Multiple longitudinal studies identify associations with BPA, PBDEs, organophosphate pesticides, and pyrethroids; results not uniform
Multiple prenatal exposures	Autism spectrum disorder	Low	20–39%	Evidence for organophosphate and pyrethroid pesticides; other exposures show more inconsistent associations

Adapted from the data first reported in Trasande et al (2015)[33] and updated in Trasande et al (2016).[12] See appendix for full list of studies mentioned here that have updated the literature (appendix pp 10–21). PBDE=polybrominated diphenyl ether. IQ=intelligence quotient. BPA=bisphenol A.

Table 3: **Updates to assessment of probable associations between prenatal exposures and neurodevelopmental outcomes**

organophosphate pesticides and PBDEs. Although one longitudinal study of prenatal exposure to organophosphate pesticide did not find an association with child cognition,[39] six studies showed decreases in IQ[40–43] or IQ subscales,[44,45] and one of these studies also noted parietal and cortical changes matching the neuropsychological deficits found.[46] Organophosphate pesticides have increasingly been replaced by pyrethroids, for which one longitudinal study reported an adverse association between prenatal exposure and child cognition,[43] whereas another study did not.[47] With respect to PBDEs, except for two small studies (n<70),[48,49] all studies showed consistent negative associations with IQ.[50–54] PBDEs are increasingly being replaced by OPFRs, which have already raised concerns, with two studies showing decreases in IQ in relation to prenatal exposure.[43,55] Overall, studies of environmental phenols and PFAS have yielded discordant findings with respect to measures of cognition (appendix pp 10–13, 22).

Prenatal exposure and autism spectrum disorder

Studies of prenatal exposure to EDCs and clinical outcomes such as attention-deficit disorder and autism spectrum disorder have been limited in part by the relative infrequency of these conditions. For autism spectrum disorder, the strongest evidence exists for a relation with organophosphate pesticides. Studies from California,[56–59] New York State,[60] and Cincinnati (OH, USA)[61] have reported an association between exposure to organophosphate pesticides, as estimated by pesticide-use registries or urinary concentrations of pesticide metabolites, and increased risk of autism spectrum disorder or increased scores on the Social Responsiveness Scale, a parental questionnaire used to evaluate signs of autism spectrum disorder. One study identified effect modification by paraoxonase genotype, suggesting differential effects in relation to detoxification of organophosphate pesticides.[61] Three studies of pyrethroids have suggested an increased risk of autism spectrum disorder in Californian children living near areas with higher pyrethroid use estimated by pesticide registries.[56,58,59]Altogether, studies of other EDCs have not yielded much clarity with respect to autism spectrum disorder (appendix pp 13–14, 22).

Prenatal exposure and child behavioural outcomes

Scales used to measure attention-deficit disorder and related behavioural outcomes have shown more consistent evidence for association with prenatal exposure to EDCs than have scales used for autism spectrum disorder. Adverse associations were identified with prenatal exposure to PBDEs in the Salinas Valley (CA, USA)[52] Cincinnati (OH, USA)[62] and New York City (NY, USA).[63] Dutch[49] and Spanish[64] studies did not identify associations, although the difference in results could be explained by the higher prevalence of exposure to PBDEs in the USA compared with in Europe. A South Korean study[65] reported increased scores for children on scales for attention-deficit disorder in mothers who had been exposed to higher concentrations of PBDEs, and a Norwegian study[66] noted divergent associations with different PBDE congeners in breastmilk. In utero exposure to organophosphate pesticides has been associated with higher scores on the Child Behavior Checklist in California[67] and New York State (USA),[42] supported by evidence in Mexican boys,[68] although a Danish longitudinal study did not identify any association.[69] Cohorts from France, USA, and Denmark reported that increases in attention-deficit hyperactivity disorder scores,[69] internalising symptoms (eg, anxiety, depression, and somatisation),[60,70] and externalising symptoms (eg, aggression, hyperactivity, and conduct problems)[60] were related to concentrations of urinary pyrethroids. Among 16 analyses of the relations between prenatal exposure to BPA and child behaviour, 13 articles (representing seven different cohorts) reported deleterious associations.[62,71–82] A randomised trial of bisphenol-based dental amalgam versus mercury amalgam in children showed higher self-reported Behaviour Assessment System for Children scores on emotional symptoms and clinical maladjustment and lower scores on personal adjustment, which indicates worse functioning in the bisphenol group.[83] Cohorts that have examined sex-specific associations with prenatal exposure to BPA have noted either increased externalising behaviours[77,78,82] or other behavioural effects in boys,[76,79] whereas few studies have reported effects in girls.[62] Overall, evidence for associations between OPFRs and behavioural problems is sparse but consistent, whereas numerous studies of phthalates and behaviour have reported diverse findings (appendix pp 14–21, 23).

Obesity and metabolism

EDCs have been shown to disrupt peroxisome proliferator-activated receptors, oestrogen receptors, and thyroid hormone receptors, among other metabolic signalling pathways, in prospective studies with measurements of exposure in utero and in cross-sectional studies in adults. Additionally, EDCs might produce a maladaptive so-called thrifty phenotype, which increases cardiometabolic risk in later life. New data reinforce previous evidence of a link between prenatal exposure to BPA and childhood obesity, and suggest associations of prenatal exposure to PFAS and phthalates with child adiposity. Evidence is increasing that exposure to PFAS and phthalates in adulthood might be associated with gestational diabetes, impaired glucose tolerance, and obesity, and that these chemicals, as well as bisphenols, could be linked to type 2 diabetes (table 4).

Prenatal exposure and child adiposity

Among the studies that we reviewed, prenatal exposure to PFAS was associated with increases in child adiposity in multiple birth cohorts, although frequently with sexual dimorphism.[84–89] Longer-chain PFAS have increasingly been replaced in consumer products by shorter-chain PFAS, such as perfluorobutane sulfonic acid, although

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal DDE	Childhood obesity	Moderate	40–69%	Not reassessed
Prenatal PFAS	Childhood obesity	Not assessed	Not assessed	Multiple cohorts report positive findings consistent with Barker hypothesis[14] and possible mechanism of impaired glucose tolerance; less consistent associations than with birthweight
Prenatal BPA	Childhood obesity	Very low to low	20–69%	Increases in body fat measures (more consistent results than BMI); highly variable approaches to exposure assessment complicate interpretation; pattern of sexual dimorphism not consistent
Prenatal and peripubertal phthalates	Childhood obesity	Not assessed	Not assessed	Pattern of association across studies with increases in BMI and fat mass measures; one longitudinal study showed associations with peripubertal exposure
Pregnancy PFAS	Impaired glucose tolerance	Not assessed	Not assessed	Multiple studies with consistent associations; others with gestational diabetes
Prenatal phthalates	Impaired glucose tolerance	Not assessed	Not assessed	Multiple studies with consistent associations; others with gestational diabetes
Adult DEHP	Adult obesity	Low	40–69%	Positive findings strengthen existing evidence
Adult PFAS	Adult obesity	Not assessed	Not assessed	No significant association at highest levels of (modelled) exposure; associations with lower levels of exposure in multiple cohorts with mechanistic insight and effect modification by diet
Adult DEHP	Adult diabetes	Low	40–69%	One study in adults modestly supports existing evidence of association
Prenatal DDE	Adult diabetes	Low	20–39%	Not reassessed
Pregnancy PFAS	Adult diabetes	Not assessed	Not assessed	Two longitudinal studies of low exposures show associations with indices of insulin resistance; inverse association in higher range of exposure noted in one study
Adult BPA and BPS	Adult diabetes	Not assessed	Not assessed	Case-control, small-scale intervention, and longitudinal studies all consistent with associations found in laboratory studies

Adapted from the data first reported in Trasande et al (2015)[11] and updated in Trasande et al (2016).[12] See appendix for full list of studies mentioned here that have updated the literature (appendix pp 24–29). DDE=dichlorodiphenyltrichloroethane. PFAS=perfluoroalkyl substances. BPA=bisphenol A. DEHP=di-2-ethylhexyl phthalate. BPS=bisphenol S.

Table 4: **Updates to assessment of probable associations between exposures and metabolic outcomes**

evidence from a birth cohort in Shanghai, China, suggests that short-chain PFAS are obesogens and thus are a regrettable substitute.[90] A meta-analysis[91] of ten cohort studies found an overall 25·0% increase in children who are overweight (95% CI 4·0–50·0; I^2=40·5%) and 0·10 unit increase in BMI Z score per ng/mL of PFOA in maternal blood (95% CI 0·03–0·15; I^2=27·9%).

Compared with studies of prenatal exposure to PFAS, studies of prenatal exposure to phthalates and bisphenols have not shown as consistent associations with measurements of child adiposity. The links for phthalates appear to be strongest in girls, with three studies noting associations between prenatal exposure to phthalates and BMI Z score,[92–94] and another cohort study of young girls reporting associations between childhood exposure to phthalates at age 6–8 years and increased BMI and waist circumference over the subsequent years of follow-up.[95] Two other studies identified associations between prenatal exposure to phthalates and increases in adiposity that do not appear to differ by sex.[96,97] The phthalates that induce effects on adiposity vary across studies, emphasising the complexity of this chemical category, which is known to contain molecules with different antiandrogenic and oestrogenic properties[15] and differential peroxisome proliferator-activated receptor activity.[98] Four cohorts reported increased childhood adiposity in relation to prenatal exposure to BPA,[93,99–101] whereas two studies of childhood exposure did not report significant findings.[102,103] Few studies have examined longitudinal effects of prenatal exposure to other chemicals on postnatal growth (appendix pp 24–25).

Pregnancy exposure and gestational diabetes

Six cohort studies and two case-control studies have raised compelling concerns about exposure to PFAS during pregnancy, including short-chain replacements,[104] contributing to gestational diabetes and impaired glucose tolerance in pregnant women from China,[104–106] USA,[107,108] Canada,[109] Denmark,[110] or Spain.[111] Four studies identified impairments in glucose tolerance, changes in glucose concentrations, or gestational diabetes associated with phthalate exposure during pregnancy,[112–115] but one well designed Canadian cohort study did not identify any association with gestational diabetes.[116] Bisphenols and parabens have also been identified as chemicals that might cause gestational diabetes, but the evidence for this association is sparse (appendix pp 25–26, 30).

Adult exposure and adult weight gain

Over the past 5 years, evidence has increased to suggest that exposure to phthalates contributes to weight gain in adults, with most studies done in women. Findings from

the Women's Health Initiative[117] have identified an association between urinary concentrations of some metabolites of phthalates, of both high and low molecular weight, and weight gain, supporting previous concerns raised by the Nurses' Health Study[118] in the USA and the PIVUS cohort in Sweden.[119] One study examined exposures during pregnancy and identified possible divergent effects of different phthalates in relation to post-partum weight gain.[120]

Two American studies have identified an association between weight gain and serum concentrations of PFAS across both sexes. In the Diabetes Prevention Program lifestyle intervention trial,[121] concentrations of total PFAS were associated with increased weight gain exclusively in the control group, whose members did not receive a lifestyle intervention. Follow-up of the POUNDS LOST trial[122] of an energy-restricted diet gave mechanistic insights: PFAS, in particular perfluorooctane sulfonate (PFOS) and perfluorononanoic acid, were associated with reductions in resting metabolic rate. In communities surrounding a chemical plant in Washington (WV, USA) that were continuously exposed to high concentrations of PFAS, no association was reported between exposure to PFAS and weight gain in adults. However, exposure imprecision due to modelled rather than measured concentrations of PFAS, different coexposures, and different participant characteristics could explain the absence of significant findings (appendix pp 27, 30).[123]

Adult exposure and type 2 diabetes

Occupational studies of persistent EDCs provided the first human evidence of diabetogenicity, when PFAS were identified as contributors to type 2 diabetes in a sample that was exposed to these chemicals at work.[124] Although measured exposure was not associated with diabetes in a population near Washington (WV, USA) that was consistently exposed to drinking water that was contaminated with PFAS,[125,126] concentrations of total PFAS measured in blood samples have been associated with diabetes in Swedish[127] and American cohorts.[128,129] A dietary intervention appeared to modify the risk of diabetes associated with PFAS in one American study.[129]

The strongest associations with diabetogenicity in adults relate to bisphenols and other non-persistent chemicals. Case-control studies have associated BPA with increased risk of diabetes,[130–132] as has the prospective Nurses' Health Study.[133] Two small-scale (n<25) intervention studies have identified effects of BPA on glucose, insulin, and C-peptide, suggesting that concentrations that are considered safe by US regulators alter the glucose-stimulated insulin response in humans.[134,135] A meta-analysis[136] estimated the pooled relative risk of type 2 diabetes to be 1·45 (95% CI 1·13–1·87) for BPA and 1·48 (95% CI 0·98–2·25) for phthalates. Since then, a French case-cohort study[137] identified a near doubling of type 2 diabetes risk in relation to measured BPA glucuronide and bisphenol S (BPS) glucuronide, adding to concerns that BPS and other replacements of BPA, which are widely used in aluminium cans and thermal paper receipts, might be regrettable substitutes. Two case-control[131,138] and two cohort studies[133,139] have also identified exposure to phthalates as a risk factor for type 2 diabetes. Data have suggested that PBDEs, some non-persistent pesticides and herbicides, parabens, and benzophenones could be associated with type 2 diabetes, but more research is needed in these areas (appendix pp 27–29, 30).

Male reproductive health

Testicular dysgenesis syndrome is the prevailing hypothesis linking prenatal exposure to EDCs with male reproductive health outcomes across the life course. Testicular dysgenesis syndrome posits that prenatal exposure to EDCs interferes with healthy testicular development, including differentiation and proliferation of fetal germ cells that give rise to spermatogonia, Sertoli cells that aid in the transformation of those spermatogonia to functional sperm, and Leydig cells that produce the testosterone necessary for testis descent and overall masculinisation.[140] In this section, we review associations of EDCs with outcomes that might result from perturbations in this developmental trajectory, including hypospadias, cryptorchidism, testicular cancer, prostate cancer, low testosterone, and poor semen quality. Studies reinforced previous findings of links between PBDEs and cryptorchidism and between phthalates of high molecular weight and reduced testosterone. Additionally, evidence is accumulating of associations of occupational exposure to persistent pesticides with prostate cancer, and of exposure to bisphenols, PFAS, phthalates, and organophosphate pesticides with reduced semen quality (table 5).

Prenatal and perinatal exposure and genital malformations

A large Canadian study that measured PBDEs in hair samples obtained from mothers 3–18 months post partum reported a positive association with cryptorchidism.[141] Evidence for associations of prenatal and perinatal exposure to numerous other persistent and non-persistent chemicals with hypospadias and cryptorchidism was either sparse or inconsistent (appendix pp 31–32, 41).

Testicular cancer

Although much still needs to be understood about the environmental origins of testicular cancer, a condition that has increased in many countries since the middle of the 20th century,[142] no new biomarker studies have been published since 2015. The few studies published since 2015 were ecological studies or were based on pesticide-use registries, and examined exposure to only PFAS and pesticides (appendix pp 32, 41–42). The scarcity of research on other chemicals included in this Series paper emphasises the need for biomarker studies that collect samples during relevant windows of

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal PBDEs	Cryptorchidism	Low	40–69%	One study reports a positive association
Prenatal PBDEs	Testicular cancer	Very low to low	0–19%	No new evidence
Occupational pesticides	Prostate cancer	Not assessed	Not assessed	Evidence for increased risk with exposure to persistent pesticides from studies in diverse geographical regions
Adult phthalates	Low testosterone (resulting in increased early mortality)	Low	40–69%	Increased evidence for negative association with testosterone in cross-sectional studies (n=13; all but one for DEHP and MEHP, two for MiBP); association of prenatal exposure and testosterone in children, adolescents, and young men was not as consistent
Adult BPA and BPS	Semen quality	Not assessed	Not assessed	Six studies show negative associations with concentration of sperm and total sperm count; negative associations with motility (n=3), morphology (n=2), and reduced semen quality (n=1); two studies found no associations, one study found positive association for motility and concentration; one study of BPS shows negative associations with total sperm count, concentration, motility, and normal morphology
Adult PFAS	Semen quality	Not assessed	Not assessed	Four studies consistently associated higher concentrations of PFAS with lower semen quality (three of morphology, one of motility)
Organophosphate pesticides	Semen quality	Not assessed	Not assessed	Three studies consistently associated higher concentrations of organophosphate pesticides with lower semen quality (sperm concentration, motility, and morphology)
Adult benzyl and butyl phthalates	Male infertility (resulting in increased use of assisted reproductive technology)	Low	40–69%	22 more studies linked higher phthalate concentrations to lower sperm concentration, motility, or normal morphology; three studies had increases in these measures; three studies showed no significant association

Adapted from the data first reported in Trasande et al (2015)[21] and updated in Trasande et al (2016).[12] See appendix for full list of studies mentioned here that have updated the literature (appendix pp 31–40). PBDE=polybrominated diphenyl ethers. DEHP=di-2-ethylhexyl phthalate. MEHP=mono-2-ethylhexyl phthalate. MiBP=monoisobutyl phthalate. BPA=bisphenol A. BPS=bisphenol S. PFAS=perfluoroalkyl substances.

Table 5: **Updates to assessment of probable associations between exposures and outcomes in male reproductive health**

biological susceptibility for testicular cancer, and the need for development of relevant animal models.

Prostate cancer

Overall, occupational exposure to pesticides was consistently associated with prostate cancer in the American Agricultural Health Study[143] and other studies from Canada, France, and elsewhere in the USA.[144–146] Only one study, from the Netherlands, reported an inverse relation with self-reported occupational use of pesticides,[147] whereas another study from Australia did not find a significant association.[148]

Findings for self-reported exposure to exclusively non-persistent pesticides were less consistent and results were sparse for other chemicals, including phthalates, BPA, PBDEs, polycyclic aromatic hydrocarbons (PAHs), and PFAS (appendix pp 32–33, 42). None of these studies were able to directly test the testicular dysgenesis syndrome hypothesis, as they were mostly cross-sectional and exposure was not measured during the prenatal period.

Testosterone

The testicular dysgenesis syndrome theory postulates that prenatal exposure to EDCs impairs proliferation and development of fetal Leydig cells, leading to lifelong reduced production of testosterone. Most evidence from cross-sectional studies of boys and men across the life course supports a negative association of DEHP or its main metabolite MEHP, or both, with testosterone.[149–160] Studies of prenatal exposure were less consistent. Although two studies noted negative associations of DEHP or MEHP with free testosterone at birth[161] and at age 8–14 years,[162] four studies did not find associations with testosterone in adulthood.[160,163–165] The longitudinal Raine study[166] from Australia reported a positive association between prenatal exposure to DEHP, MEHP, the replacement chemical diisononyl phthalate, and monoisononyl phthalate (the main metabolite of diisononyl phthalate) with total testosterone at ages 20–22 years. However, phthalates were measured in stored maternal serum in this study, which is less reliable than measures in urine. Results were weaker for phthalates of low molecular weight, BPA, organophosphate pesticides, PFAS, and parabens, and data were sparse for benzophenones, PAHs, PBDEs, triclosan, pyrethroids, and carbamates (appendix pp 34–36, 43).

Semen quality

Most studies of semen quality are cross-sectional and do not contain information on exposure in utero and in

early life, so they cannot provide evidence to support the testicular dysgenesis syndrome hypothesis. The results of these studies are still relevant to the question of how EDCs affect sperm production, which occurs continuously beginning in puberty and affects male fecundity.

Most studies investigating phthalates reported negative associations with at least one, but often multiple, semen quality parameters, including sperm concentration, motility, and morphology. In contrast to testosterone, however, phthalates of both low and high molecular weight were implicated. Evidence is also mounting for a negative association between BPA and semen quality, including results from the Raine birth cohort, in which BPA was measured in prenatal serum;[166] a Chinese occupational cohort;[167] cohorts of young men from Denmark[168] and Spain;[169] and five studies done in men recruited from fertility clinics,[170–174] in which BPA was measured cross-sectionally. The Boston-based Environment And Reproductive Health study[175] was the only one to analyse BPS, a widely prevalent replacement for BPA that shares its obesogenic properties, and reported negative associations with sperm concentration, motility, and morphology, but only in men who had overweight or obesity.

Three studies that examined organophosphate pesticides and semen quality all reported negative associations,[176–178] as did four studies that examined PFAS.[179–182] Results were more variable for benzophenones, triclosan, parabens, and PBDEs, and sparse for pyrethroids, carbamates, and OPFRs. Many of these studies recruited men who were part of couples seeking fertility treatment, so results might not be generalisable (appendix pp 36–40).

Female reproductive health

Paralleling the testicular dysgenesis syndrome hypothesis linking prenatal endocrine disruption to adverse outcomes in male reproductive health, the ovarian dysgenesis syndrome hypothesis suggests that prenatal exposure to EDCs could lead to pathophysiological reproductive conditions in women, including polycystic ovarian syndrome, endometriosis, uterine fibroids, and cancers at reproductive sites.[183] Few studies have had the data for prenatal exposure that would be necessary to test this hypothesis; however, substantial evidence exists to implicate exposure to EDCs closer to the time of diagnosis. In particular, studies identified an increased risk of polycystic ovarian syndrome in association with exposure to BPA and PFAS; reinforced links between phthalates and endometriosis; and suggested associations of PFAS with endometriosis and of organophosphate pesticides and PFAS with breast cancer (table 6; appendix p 47). Similar to outcomes in male reproductive health, most epidemiological studies of female reproductive health are cross-sectional and cannot be interpreted to support causal associations, especially when participants had pre-existing conditions.

Polycystic ovarian syndrome

Among various studies examining associations between EDCs and polycystic ovarian syndrome, the evidence is strongest for an association with PFAS. Three cross-sectional studies of polycystic ovarian syndrome reported positive associations with various PFAS: a study in China with perfluorododecanoic acid,[184] an American study with PFOA and PFOS,[185] and a smaller study in the UK with only PFOS.[186] Evidence is also accumulating of a link between BPA and polycystic ovarian syndrome. Six cross-sectional studies reported positive associations between BPA and polycystic ovarian syndrome,[187–192] although one of these studies identified associations only among women who had overweight or obesity, and three studies reported no associations.[185,193,194] Overall, knowledge about other EDCs, such as PBDEs, phthalates, PAHs, and triclosan, and polycystic ovarian syndrome is just beginning to emerge, but no conclusions can be drawn about these chemicals yet (appendix pp 44–45, 49).

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
BPA	Polycystic ovarian syndrome	Not assessed	Not assessed	Multiple case-control studies identify increased risk
PFAS	Polycystic ovarian syndrome	Not assessed	Not assessed	Case-control studies identify increased risk
Adult DEHP (and metabolites)	Endometriosis	Low	20–39%	Three studies show positive associations; one study shows negative association; one study shows no significant association
PFAS	Endometriosis	Not assessed	Not assessed	Two studies report positive association; one study with mixed associations (positive for PFBS, negative for PFAS)
Lifetime DDE	Fibroids	Low	20–39%	Not reassessed
PFAS	Breast cancer	Not assessed	Not assessed	Multiple studies show positive associations for exposure at different stages of life

Adapted from the data first reported in Trasande et al (2015)[11] and updated in Trasande et al (2016).[12] See appendix for full list of studies mentioned here that have updated the literature (appendix pp 44–48). BPA=bisphenol A. PFAS=perfluoroalkyl and polyfluoroalkyl substances. DEHP=di-2-ethylhexyl phthalate. PFBS=perfluorobutane sulfonate. DDE=dichlorodiphenyldichloroethylene.

Table 6: **Updates to assessment of probable associations between exposures and outcomes in female reproductive health**

Endometriosis and uterine fibroids

Notable additions to the literature on EDCs and endometriosis have been made regarding PFAS, but results are inconsistent. An analysis of 2002–06 US NHANES data[195] and the ENDO study[196] of women recruited from Utah and California (USA) in 2007–09 reported positive associations with PFOS, PFOA, and perfluorononanoic acid. A 2017 Chinese study[197] suggested a positive association with perfluorobutane sulfonate and negative associations with perfluoroheptanoic acid, perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid.

One cross-sectional study showed a positive association between serum DEHP and endometriosis, although this study did not adjust for covariates,[198] and another study reported a positive association between urinary mono-2-ethyl-5-carboxypentyl phthalate[199] (a metabolite of DEHP) and endometriosis. A third study of phthalates and endometriosis found no associations, although this study was smaller and did not adjust for covariates.[200] Other additions to the endometriosis literature examined BPA, benzophenones, and PBDEs, but none of the evidence was conclusive (appendix pp 45, 49).

Studies of EDCs and uterine fibroids have focused on phthalates and phenols, but results have been varied (appendix pp 46, 49–50).

Breast, endometrial, and ovarian cancer

Breast cancer studies have investigated a wide range of EDCs, with several studies reporting positive associations for PFAS and organophosphate pesticides. The evidence for PFAS includes results from the Child Health and Development Studies[201] in Oakland (CA, USA) in which prenatal exposure to N-ethyl-perfluorooctane sulfonamidoacetic acid, a precursor of PFOS, was positively associated with breast cancer in daughters, whereas prenatal exposure to PFOS was protective. Other longitudinal analyses include the French E3N study[202] of women born between 1925 and 1950, which reported a positive association between PFOS and postmenopausal breast cancer, and the Danish National Birth Cohort study,[203] in which perfluorooctane sulfonamide in first-trimester blood samples was positively associated with postnatal development of maternal breast cancer, whereas PFHxS was protective. In a cross-sectional study of Greenland Inuit women, PFOS, PFHxS, and the sum of perfluoroalkyl acids were associated with higher odds of breast cancer.[204] Finally, an ecological study in the Veneto region of Italy reported higher mortality rates from female breast cancer in municipalities with drinking water contaminated with PFAS.[205] The only study of PFAS not to find any associations was a large case-control analysis nested in the longitudinal California Teachers Study.[206]

All four studies that examined organophosphate pesticide exposure and breast cancer reported increased risk, specifically for chlorpyrifos, methyl parathion, terbufos, coumaphos, diazinon, fonofos, and phorate. None of these studies measured chemicals in blood or metabolites in urine; all were studies of agricultural populations that estimated exposure from self-report or geocoded addresses linked to pesticide registries.[143,207–209]

The literature on phthalates and breast cancer is sparse with inconsistent results. Results for studies of PBDEs, phenols, benzophenones, parabens, and carbamate and pyrethroid insecticides were scarce or were not significant (appendix pp 46–47, 50).

Among the few papers published on EDCs and other female reproductive cancers (eg, endometrial and ovarian cancer), studies examined organophosphate pesticides, diazinon, and atrazine. However, there was not enough evidence to draw conclusions (appendix pp 48, 50).

Discussion

This Series paper suggests new adverse health effects of frequently used EDCs with a probability of causation and strengthens the evidence for many other EDCs that have been previously identified by an expert panel commissioned by WHO and UNEP.[11] The expanding evidence for these environmental contributors to non-communicable diseases suggests that synthetic chemicals are ignored or at least underappreciated as a focus of the 2030 Sustainable Development Goals (SDGs). Decreasing exposure to synthetic chemicals with endocrine-disrupting or other adverse properties is not identified as one of the SDGs, although the SDGs rightly emphasise air pollution and climate change as global priorities.[210]

The new exposure–outcome pairings proposed here have not been subject to systematic review methods[211] or application of GRADE Working Group[212] and other methods to evaluate the strength of evidence and probability of causation.[213] Full evaluation of the probability of causation and estimates of disease burden and costs for all of the identified exposure–outcome pairs represent a natural and logical extension of this work.

In reviewing hundreds of published studies, we have emphasised the many challenges in unravelling the complex relations of exposure to EDCs with disease and disability across the lifespan. These challenges include confounding, the complex mixtures of exposures and their inter-relationships, the variability in exposure distributions and timing across studies that could explain differences in results, the cross-sectional designs of many studies, and the imprecision of exposure assessment methods, especially for chemicals with short half-lives. Some of these challenges can be addressed through technological advances and novel study designs. In particular, given the high variability in concentrations of BPA and other non-persistent chemicals in individuals, prenatal studies relying on a spot biospecimen during pregnancy or a given pregnancy period (eg, in assessing associations with trimester-specific exposure) are likely to have strong attenuation bias and low power.[214] Studies should endeavour to collect frequent, repeated biospecimens across the duration of pregnancy to reduce measurement error. Another issue in human studies is

Search strategy and selection criteria

Using a combination of exposure and outcome keywords, we searched PubMed for articles on empirical research in humans published in English from January, 1990, to September, 2019. We used standardised searches that combined exposures (eg, organophosphorus and brominated flame retardants, phenols, phthalates, pesticides, pyrethroids, parabens, perfluoroalkyl substances, and benzophenones) and outcomes (eg, intelligence quotient, neurodevelopment, neurobehaviour, autism, attention deficit, fetal growth, birthweight, preterm birth, prematurity, obesity, diabetes, anogenital distance, cryptorchidism, hypospadias, testicular cancer, prostate cancer, testosterone, semen quality, polycystic ovarian syndrome, endometriosis, fibroids, breast cancer, uterine cancer, and ovarian cancer). As an example of our strategy, for the outcome of preterm birth, we used the search terms "((((PBDE OR brominated OR organophosphate OR chlorpyrifos OR POP OR phthalate OR DEHP OR BBP OR DBP OR DiBP OR phenol OR bisphenol OR BPA OR BPS OR BPF OR triclosan OR triclocarban OR benzophenone OR PFAS OR PFOA OR perfluoroalkyl OR perfluor* OR perfluorinated OR pyrethroid OR parabens OR paraben* OR phytoestrogen OR nonylphenol OR "endocrine disruptor*") AND ENGLISH[Language]) AND ("1990"[Date - Publication] : "2019/09"[Date - Publication])) AND (preterm OR "premature birth" OR "gestational duration"))". For neurodevelopmental, birth, and congenital outcomes, studies only with prenatal or perinatal exposure assessment are included in this Series paper.

the inability to readily measure chemicals in target tissues (eg, ovary) and the ongoing gaps in knowledge about the distribution and mobilisation of chemicals during physiological events, such as pregnancy and menopause.

Many of the papers described in this Series paper limit their examination to a single class of chemical exposures or their metabolites. Biostatistical developments have not yet yielded a superior method to manage the related exposures that might exist in the human body.[215] The composition of mixtures also varies across individuals, and the high cost of analytical technologies has generally restricted the needed and simultaneous study of the thousands of natural and synthetic compounds with endocrine effects.[216] Larger sample sizes are also needed to sufficiently power interaction testing across chemical mixtures. Cohorts such as the European LifeCycle or ATHLETE consortia, the Japan Environment and Children's Study, and the National Institutes of Health Environmental Influences on Child Health Outcomes programme are well poised to overcome the sample size challenge, as each cohort can contribute archived samples from tens of thousands of mother–infant pairs. Metabolomic technologies hold promise in the identification of a broad array of emerging and novel exposures, and other exposomic methods offer mechanistic insights and opportunities to develop intermediate markers that could reliably predict disease endpoints and aggregate effects of multiple interacting exposures. Additionally, genomics and related tools can carefully examine interactions between genes (or gene expression) and exposures (eg, paroxonase polymorphisms and their influence on the health outcomes of exposure to organophosphate pesticides[217]).

Intervention studies have produced rapid decreases in exposure to organophosphate pesticides, bisphenols, phthalates, parabens, and triclosans,[218] but these studies have not examined changes in disease or intermediate markers. Randomised designs of interventions to increase or decrease exposure generally have little applicability because of ethical and logistical considerations. That said, we identified crossover studies in which intentional administration of EDCs showed intermediate markers of disease risk.[135] These designs, under some circumstances, can offer promising opportunities to identify effects of EDCs more quickly, especially for conditions with long latency periods.

A theme throughout the studies reviewed is the emergence of effects on human health due to replacements of EDCs by compounds that have had little testing. These health effects include the neurodevelopmental effects of pyrethroids, which are replacing organophosphate pesticides, and of OPFRs used as substitutes for their brominated counterparts; metabolic effects of BPS and other BPA analogues as well as short-chain PFAS now being used as concern has grown regarding longer-chain versions; and reproductive effects of substituting diisononyl phthalate for DEHP. The few studies of the associations of these emerging exposures with human health, many of which have identified adverse effects, support the conclusion in the second paper in this Series[219] that regulators should treat chemicals as classes rather than individual compounds and strengthen premarketing toxicological testing.

Further research will always be needed to elaborate on the effects of EDCs and other synthetic chemicals on human health with greater precision. As Bradford Hill described in his landmark lecture on causality, actions—in this case, to reduce exposure to EDCs—require consideration of the evidence and the stakes involved in the decision.[220] In many cases, alternative manufacturing practices can be applied to mitigate exposure to EDCs. Additional costs to society will need to be weighed against the economic benefits of decreased disease and disability as well as other societal effects (eg, ecosystem effects).

The past 5 years of research on EDCs have brought into sharp focus the substantial stakes involved for human health. Although there are actions that individuals can take to reduce their exposure, the definitive way to make a difference on a population level is through regulation. Regulation can eliminate environmental injustices when individuals are left to implement sometimes costly

For more on the **European LifeCycle project** see https://lifecycle-project.eu

For more on the **ATHLETE consortia** see https://www.humanexposome.eu./portfolios/athlete

For more on the **Japan Environment and Children's Study** see https://www.env.go.jp/chemi/ceh/en

For more on the **National Institutes of Health Environmental Influences on Child Health Outcomes programme** see https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program

changes to their daily lives (eg, buying organic food). The second paper in this Series[219] describes how policies can reduce exposure, prevent disease, and produce economic benefits that might even outweigh the costs of safer alternatives.

Contributors

LT conceptualised the Series paper, and equally contributed with RS, CP, and LGK. LGK compiled the narrative and oversaw construction of the tables. SFN reviewed multiple draft manuscripts, providing editorial support. LT had final editorial oversight.

Declaration of interests

LT reports personal fees from Houghton Mifflin Harcourt and Company, and Audible. LT and LGK acknowledge support from the National Institute of Environmental Health Sciences (R01ES022972, R01ES029779, and P30ES000260 [LT]; K99ES030403 [LGK]). The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. All other authors declare no competing interests.

Acknowledgments

This manuscript is dedicated to the memory of Jean-Pierre Bourguignon. We thank Paulina Jedynak, Ariane Guilbert, Vladislav Obsekov, and Fanny Trecourt, who assisted with the sections on birthweight, neurodevelopment, semen quality, and testosterone.

References

1 Carson R. Silent spring. Boston: Houghton Mifflin Company, 1962.
2 Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 1971; **284:** 878–81.
3 Vandenberg LN, Colborn T, Hayes TB, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev* 2012; **33:** 378–455.
4 Ding D, Xu L, Fang H, et al. The EDKB: an established knowledge base for endocrine disrupting chemicals. *BMC Bioinformatics* 2010; **11** (suppl 6)**:** 5.
5 European Commission. Endocrine Disruptors. 2015. https://ec.europa.eu/environment/chemicals/endocrine/documents/index_en.htm#SubThemes5 (accessed Nov 24, 2015).
6 Gore AC, Chappell VA, Fenton SE, et al. EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocr Rev* 2015; **36:** e1–150.
7 Di Renzo GC, Conry JA, Blake J, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int J Gynaecol Obstet* 2015; **131:** 219–25.
8 International Programme on Chemical Safety. Global assessment of state-of-the-science for endocrine disruptors. Geneva: World Health Organization, 2012. https://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en (accessed Oct 6, 2014).
9 Trasande L, Shaffer RM, Sathyanarayana S. Food additives and child health. *Pediatrics* 2018; **142:** e20181408.
10 Cohn BA, Cirillo PM, Terry MB. DDT and breast cancer: prospective study of induction time and susceptibility windows. *J Natl Cancer Inst* 2019; **111:** 803–10.
11 Trasande L, Zoeller RT, Hass U, et al. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. *J Clin Endocrinol Metab* 2015; **100:** 1245–55.
12 Trasande L, Zoeller RT, Hass U, et al. Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis. *Andrology* 2016; **4:** 565–72.
13 Vos LE, Oren A, Bots ML, Gorissen WH, Grobbee DE, Uiterwaal CS. Birth size and coronary heart disease risk score in young adulthood. The Atherosclerosis Risk in Young Adults (ARYA) study. *Eur J Epidemiol* 2006; **21:** 33–38.
14 Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med* 2005; **353:** 1802–09.
15 Philips EM, Jaddoe VWV, Trasande L. Effects of early exposure to phthalates and bisphenols on cardiometabolic outcomes in pregnancy and childhood. *Reprod Toxicol* 2017; **68:** 105–18.
16 Jain VG, Goyal V, Chowdhary V, et al. Anogenital distance is determined during early gestation in humans. *Hum Reprod* 2018; **33:** 1619–27.
17 Mendiola J, Stahlhut RW, Jørgensen N, Liu F, Swan SH. Shorter anogenital distance predicts poorer semen quality in young men in Rochester, New York. *Environ Health Perspect* 2011; **119:** 958–63.
18 Starling AP, Adgate JL, Hamman RF, et al. Perfluoroalkyl substances during pregnancy and offspring weight and adiposity at birth: examining mediation by maternal fasting glucose in the Healthy Start study. *Environ Health Perspect* 2017; **125:** 067016.
19 Yeung EH, Bell EM, Sundaram R, et al. Examining endocrine disruptors measured in newborn dried blood spots and early childhood growth in a prospective cohort. *Obesity (Silver Spring)* 2019; **27:** 145–51.
20 Steenland K, Barry V, Savitz D. Serum perfluorooctanoic acid and birthweight: an updated meta-analysis with bias analysis. *Epidemiology* 2018; **29:** 765–76.
21 Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008; **371:** 261–69.
22 Slama R, Ballester F, Casas M, et al. Epidemiologic tools to study the influence of environmental factors on fecundity and pregnancy-related outcomes. *Epidemiol Rev* 2014; **36:** 148–64.
23 Gao H, Wang YF, Huang K, et al. Prenatal phthalate exposure in relation to gestational age and preterm birth in a prospective cohort study. *Environ Res* 2019; **176:** 108530.
24 Ferguson KK, McElrath TF, Meeker JD. Environmental phthalate exposure and preterm birth. *JAMA Pediatr* 2014; **168:** 61–67.
25 Latini G, De Felice C, Presta G, et al. In utero exposure to di-(2-ethylhexyl)phthalate and duration of human pregnancy. *Environ Health Perspect* 2003; **111:** 1783–85.
26 Ferguson KK, Chen YH, VanderWeele TJ, McElrath TF, Meeker JD, Mukherjee B. Mediation of the relationship between maternal phthalate exposure and preterm birth by oxidative stress with repeated measurements across pregnancy. *Environ Health Perspect* 2017; **125:** 488–94.
27 Ferguson KK, Rosen EM, Rosario Z, et al. Environmental phthalate exposure and preterm birth in the PROTECT birth cohort. *Environ Int* 2019; **132:** 105099.
28 Diav-Citrin O, Park YH, Veerasuntharam G, et al. The safety of mesalamine in human pregnancy: a prospective controlled cohort study. *Gastroenterology* 1998; **114:** 23–28.
29 Bornehag CG, Carlstedt F, Jönsson BA, et al. Prenatal phthalate exposures and anogenital distance in Swedish boys. *Environ Health Perspect* 2015; **123:** 101–07.
30 Martino-Andrade AJ, Liu F, Sathyanarayana S, et al. Timing of prenatal phthalate exposure in relation to genital endpoints in male newborns. *Andrology* 2016; **4:** 585–93.
31 Sunman B, Yurdakök K, Kocer-Gumusel B, et al. Prenatal bisphenol A and phthalate exposure are risk factors for male reproductive system development and cord blood sex hormone levels. *Reprod Toxicol* 2019; **87:** 146–55.
32 Swan SH, Main KM, Liu F, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect* 2005; **113:** 1056–61.
33 Swan SH, Sathyanarayana S, Barrett ES, et al. First trimester phthalate exposure and anogenital distance in newborns. *Hum Reprod* 2015; **30:** 963–72.
34 Arbuckle TE, Agarwal A, MacPherson SH, et al. Prenatal exposure to phthalates and phenols and infant endocrine-sensitive outcomes: the MIREC study. *Environ Int* 2018; **120:** 572–83.
35 Wenzel AG, Bloom MS, Butts CD, et al. Influence of race on prenatal phthalate exposure and anogenital measurements among boys and girls. *Environ Int* 2018; **110:** 61–70.
36 Jensen TK, Frederiksen H, Kyhl HB, et al. Prenatal exposure to phthalates and anogenital distance in male infants from a low-exposed Danish cohort (2010–12). *Environ Health Perspect* 2016; **124:** 1107–13.
37 Ghassabian A, Trasande L. Disruption in thyroid signaling pathway: a mechanism for the effect of endocrine-disrupting chemicals on child neurodevelopment. *Front Endocrinol (Lausanne)* 2018; **9:** 204.
38 Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab* 2015; **100:** 1256–66.

39 Donauer S, Altaye M, Xu Y, et al. An observational study to evaluate associations between low-level gestational exposure to organophosphate pesticides and cognition during early childhood. *Am J Epidemiol* 2016; **184:** 410–18.

40 Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect* 2011; **119:** 1189–95.

41 Jusko TA, van den Dries MA, Pronk A, et al. Organophosphate pesticide metabolite concentrations in urine during pregnancy and offspring nonverbal IQ at age 6 years. *Environ Health Perspect* 2019; **127:** 17007.

42 Rauh VA, Garfinkel R, Perera FP, et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics* 2006; **118:** e1845–59.

43 Tanner EM, Hallerbäck MU, Wikström S, et al. Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. *Environ Int* 2020; **134:** 105185.

44 Engel SM, Wetmur J, Chen J, et al. Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. *Environ Health Perspect* 2011; **119:** 1182–88.

45 González-Alzaga B, Hernández AF, Rodríguez-Barranco M, et al. Pre- and postnatal exposures to pesticides and neurodevelopmental effects in children living in agricultural communities from south-eastern Spain. *Environ Int* 2015; **85:** 229–37.

46 Rauh VA, Perera FP, Horton MK, et al. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc Natl Acad Sci U S A* 2012; **109:** 7871–76.

47 Viel JF, Warembourg C, Le Maner-Idrissi G, et al. Pyrethroid insecticide exposure and cognitive developmental disabilities in children: the PELAGIE mother-child cohort. *Environ Int* 2015; **82:** 69–75.

48 Berghuis SA, Van Braeckel KNJA, Sauer PJJ, Bos AF. Prenatal exposure to persistent organic pollutants and cognition and motor performance in adolescence. *Environ Int* 2018; **121:** 13–22.

49 Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. *Environ Health Perspect* 2009; **117:** 1953–58.

50 Chen A, Yolton K, Rauch SA, et al. Prenatal polybrominated diphenyl ether exposures and neurodevelopment in U.S. children through 5 years of age: the HOME study. *Environ Health Perspect* 2014; **122:** 856–62.

51 Drobná B, Fabišiková A, Čonka K, et al. PBDE serum concentration and preschool maturity of children from Slovakia. *Chemosphere* 2019; **233:** 387–95.

52 Eskenazi B, Chevrier J, Rauch SA, et al. In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. *Environ Health Perspect* 2013; **121:** 257–62.

53 Herbstman JB, Sjödin A, Kurzon M, et al. Prenatal exposure to PBDEs and neurodevelopment. *Environ Health Perspect* 2010; **118:** 712–19.

54 Zhang H, Yolton K, Webster GM, et al. Prenatal PBDE and PCB exposures and reading, cognition, and externalizing behavior in children. *Environ Health Perspect* 2017; **125:** 746–52.

55 Castorina R, Bradman A, Stapleton HM, et al. Current-use flame retardants: maternal exposure and neurodevelopment in children of the CHAMACOS cohort. *Chemosphere* 2017; **189:** 574–80.

56 Roberts EM, English PB, Grether JK, Windham GC, Somberg L, Wolff C. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. *Environ Health Perspect* 2007; **115:** 1482–89.

57 Sagiv SK, Harris MH, Gunier RB, et al. Prenatal organophosphate pesticide exposure and traits related to autism spectrum disorders in a population living in proximity to agriculture. *Environ Health Perspect* 2018; **126:** 047012.

58 Shelton JF, Geraghty EM, Tancredi DJ, et al. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. *Environ Health Perspect* 2014; **122:** 1103–09.

59 von Ehrenstein OS, Ling C, Cui X, et al. Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population based case-control study. *BMJ* 2019; **364:** l962.

60 Furlong MA, Barr DB, Wolff MS, Engel SM. Prenatal exposure to pyrethroid pesticides and childhood behavior and executive functioning. *Neurotoxicology* 2017; **62:** 231–38.

61 Millenson ME, Braun JM, Calafat AM, et al. Urinary organophosphate insecticide metabolite concentrations during pregnancy and children's interpersonal, communication, repetitive, and stereotypic behaviors at 8 years of age: the home study. *Environ Res* 2017; **157:** 9–16.

62 Braun JM, Yolton K, Stacy SL, et al. Prenatal environmental chemical exposures and longitudinal patterns of child neurobehavior. *Neurotoxicology* 2017; **62:** 192–99.

63 Cowell WJ, Lederman SA, Sjodin A, et al. Prenatal exposure to polybrominated diphenyl ethers and child attention problems at 3–7 years. *Neurotoxicol Teratol* 2015; **52:** 143–50.

64 Gascon M, Vrijheid M, Martínez D, et al. Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. *Environ Int* 2011; **37:** 605–11.

65 Kim S, Eom S, Kim HJ, et al. Association between maternal exposure to major phthalates, heavy metals, and persistent organic pollutants, and the neurodevelopmental performances of their children at 1 to 2 years of age- CHECK cohort study. *Sci Total Environ* 2018; **624:** 377–84.

66 Lenters V, Iszatt N, Forns J, et al. Early-life exposure to persistent organic pollutants (OCPs, PBDEs, PCBs, PFASs) and attention-deficit/hyperactivity disorder: a multi-pollutant analysis of a Norwegian birth cohort. *Environ Int* 2019; **125:** 33–42.

67 Marks AR, Harley K, Bradman A, et al. Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS study. *Environ Health Perspect* 2010; **118:** 1768–74.

68 Fortenberry GZ, Meeker JD, Sánchez BN, et al. Urinary 3,5,6-trichloro-2-pyridinol (TCPY) in pregnant women from Mexico City: distribution, temporal variability, and relationship with child attention and hyperactivity. *Int J Hyg Environ Health* 2014; **217:** 405–12.

69 Dalsager L, Fage-Larsen B, Bilenberg N, et al. Maternal urinary concentrations of pyrethroid and chlorpyrifos metabolites and attention deficit hyperactivity disorder (ADHD) symptoms in 2–4-year-old children from the Odense Child Cohort. *Environ Res* 2019; **176:** 108533.

70 Viel JF, Rouget F, Warembourg C, et al. Behavioural disorders in 6-year-old children and pyrethroid insecticide exposure: the PELAGIE mother-child cohort. *Occup Environ Med* 2017; **74:** 275–81.

71 Braun JM, Yolton K, Dietrich KN, et al. Prenatal bisphenol A exposure and early childhood behavior. *Environ Health Perspect* 2009; **117:** 1945–52.

72 Braun JM, Kalkbrenner AE, Calafat AM, et al. Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics* 2011; **128:** 873–82.

73 Stacy SL, Papandonatos GD, Calafat AM, et al. Early life bisphenol A exposure and neurobehavior at 8 years of age: Identifying windows of heightened vulnerability. *Environ Int* 2017; **107:** 258–65.

74 Perera F, Vishnevetsky J, Herbstman JB, et al. Prenatal bisphenol A exposure and child behavior in an inner-city cohort. *Environ Health Perspect* 2012; **120:** 1190–94.

75 Roen EL, Wang Y, Calafat AM, et al. Bisphenol A exposure and behavioral problems among inner city children at 7–9 years of age. *Environ Res* 2015; **142:** 739–45.

76 Perera F, Nolte ELR, Wang Y, et al. Bisphenol A exposure and symptoms of anxiety and depression among inner city children at 10–12 years of age. *Environ Res* 2016; **151:** 195–202.

77 Harley KG, Gunier RB, Kogut K, et al. Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. *Environ Res* 2013; **126:** 43–50.

78 Evans SF, Kobrosly RW, Barrett ES, et al. Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. *Neurotoxicology* 2014; **45:** 91–99.

79 Casas M, Forns J, Martínez D, et al. Exposure to bisphenol A during pregnancy and child neuropsychological development in the INMA-Sabadell cohort. *Environ Res* 2015; **142:** 671–79.

80 Minatoya M, Araki A, Nakajima S, et al. Cord blood BPA level and child neurodevelopment and behavioral problems: the Hokkaido Study on Environment and Children's Health. *Sci Total Environ* 2017; **607–608:** 351–56.

81 Minatoya M, Itoh S, Yamazaki K, et al. Prenatal exposure to bisphenol A and phthalates and behavioral problems in children at preschool age: the Hokkaido Study on Environment and Children's Health. *Environ Health Prev Med* 2018; **23:** 43.

82 Philippat C, Nakiwala D, Calafat AM, et al. Prenatal exposure to nonpersistent endocrine disruptors and behavior in boys at 3 and 5 years. *Environ Health Perspect* 2017; **125:** 097014.

83 Maserejian NN, Trachtenberg FL, Hauser R, et al. Dental composite restorations and psychosocial function in children. *Pediatrics* 2012; **130:** e328–38.

84 Starling AP, Adgate JL, Hamman RF, Kechris K, Calafat AM, Dabelea D. Prenatal exposure to per- and polyfluoroalkyl substances and infant growth and adiposity: the Healthy Start Study. *Environ Int* 2019; **131:** 104983.

85 Halldorsson TI, Rytter D, Haug LS, et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. *Environ Health Perspect* 2012; **120:** 668–73.

86 Braun JM, Chen A, Romano ME, et al. Prenatal perfluoroalkyl substance exposure and child adiposity at 8 years of age: the HOME study. *Obesity (Silver Spring)* 2016; **24:** 231–37.

87 Hartman TJ, Calafat AM, Holmes AK, et al. Prenatal exposure to perfluoroalkyl substances and body fatness in girls. *Child Obes* 2017; **13:** 222–30.

88 Karlsen M, Grandjean P, Weihe P, Steuerwald U, Oulhote Y, Valvi D. Early-life exposures to persistent organic pollutants in relation to overweight in preschool children. *Reprod Toxicol* 2017; **68:** 145–53.

89 Mora AM, Oken E, Rifas-Shiman SL, et al. Prenatal exposure to perfluoroalkyl substances and adiposity in early and mid-childhood. *Environ Health Perspect* 2017; **125:** 467–73.

90 Chen Q, Zhang X, Zhao Y, et al. Prenatal exposure to perfluorobutanesulfonic acid and childhood adiposity: a prospective birth cohort study in Shanghai, China. *Chemosphere* 2019; **226:** 17–23.

91 Liu P, Yang F, Wang Y, Yuan Z. Perfluorooctanoic acid (PFOA) exposure in early life increases risk of childhood adiposity: a meta-analysis of prospective cohort studies. *Int J Environ Res Public Health* 2018; **15:** 1510.

92 Bowman A, Peterson KE, Dolinoy DC, et al. Phthalate exposures, DNA methylation and adiposity in Mexican children through adolescence. *Front Public Health* 2019; **7:** 162.

93 Yang TC, Peterson KE, Meeker JD, et al. Bisphenol A and phthalates in utero and in childhood: association with child BMI z-score and adiposity. *Environ Res* 2017; **156:** 326–33.

94 Valvi D, Casas M, Romaguera D, et al. Prenatal phthalate exposure and childhood growth and blood pressure: evidence from the Spanish INMA-Sabadell Birth Cohort Study. *Environ Health Perspect* 2015; **123:** 1022–29.

95 Deierlein AL, Wolff MS, Pajak A, et al. Longitudinal associations of phthalate exposures during childhood and body size measurements in young girls. *Epidemiology* 2016; **27:** 492–99.

96 Buckley JP, Engel SM, Braun JM, et al. Prenatal phthalate exposures and body mass index among 4- to 7-year-old children: a pooled analysis. *Epidemiology* 2016; **27:** 449–58.

97 Harley KG, Berger K, Rauch S, et al. Association of prenatal urinary phthalate metabolite concentrations and childhood BMI and obesity. *Pediatr Res* 2017; **82:** 405–15.

98 Kaya T, Mohr SC, Waxman DJ, Vajda S. Computational screening of phthalate monoesters for binding to PPARgamma. *Chem Res Toxicol* 2006; **19:** 999–1009.

99 Hoepner LA, Whyatt RM, Widen EM, et al. Bisphenol A and adiposity in an inner-city birth cohort. *Environ Health Perspect* 2016; **124:** 1644–50.

100 Valvi D, Casas M, Mendez MA, et al. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. *Epidemiology* 2013; **24:** 791–99.

101 Braun JM, Li N, Arbuckle TE, et al. Association between gestational urinary bisphenol A concentrations and adiposity in young children: the MIREC study. *Environ Res* 2019; **172:** 454–61.

102 Deierlein AL, Wolff MS, Pajak A, et al. Phenol concentrations during childhood and subsequent measures of adiposity among young girls. *Am J Epidemiol* 2017; **186:** 581–92.

103 Maserejian NN, Hauser R, Tavares M, Trachtenberg FL, Shrader P, McKinlay S. Dental composites and amalgam and physical development in children. *J Dent Res* 2012; **91:** 1019–25.

104 Liu X, Zhang L, Chen L, et al. Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women. *Environ Int* 2019; **127:** 85–93.

105 Wang H, Yang J, Du H, et al. Perfluoroalkyl substances, glucose homeostasis, and gestational diabetes mellitus in Chinese pregnant women: a repeat measurement-based prospective study. *Environ Int* 2018; **114:** 12–20.

106 Wang Y, Zhang L, Teng Y, et al. Association of serum levels of perfluoroalkyl substances with gestational diabetes mellitus and postpartum blood glucose. *J Environ Sci (China)* 2018; **69:** 5–11.

107 Rahman ML, Zhang C, Smarr MM, et al. Persistent organic pollutants and gestational diabetes: a multi-center prospective cohort study of healthy US women. *Environ Int* 2019; **124:** 249–58.

108 Zhang C, Sundaram R, Maisog J, Calafat AM, Barr DB, Buck Louis GM. A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. *Fertil Steril* 2015; **103:** 184–89.

109 Shapiro GD, Dodds L, Arbuckle TE, et al. Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: the MIREC Study. *Environ Res* 2016; **147:** 71–81.

110 Jensen RC, Glintborg D, Timmermann CAG, et al. Perfluoroalkyl substances and glycemic status in pregnant Danish women: the Odense Child Cohort. *Environ Int* 2018; **116:** 101–07.

111 Matilla-Santander N, Valvi D, Lopez-Espinosa MJ, et al. Exposure to perfluoroalkyl substances and metabolic outcomes in pregnant women: evidence from the Spanish INMA Birth Cohorts. *Environ Health Perspect* 2017; **125:** 117004.

112 James-Todd TM, Chiu YH, Messerlian C, et al. Trimester-specific phthalate concentrations and glucose levels among women from a fertility clinic. *Environ Health* 2018; **17:** 55.

113 James-Todd TM, Meeker JD, Huang T, et al. Pregnancy urinary phthalate metabolite concentrations and gestational diabetes risk factors. *Environ Int* 2016; **96:** 118–26.

114 Shaffer RM, Ferguson KK, Sheppard L, et al. Maternal urinary phthalate metabolites in relation to gestational diabetes and glucose intolerance during pregnancy. *Environ Int* 2019; **123:** 588–96.

115 Fisher BG, Frederiksen H, Andersson AM, et al. Serum phthalate and triclosan levels have opposing associations with risk factors for gestational diabetes mellitus. *Front Endocrinol (Lausanne)* 2018; **9:** 99.

116 Shapiro GD, Dodds L, Arbuckle TE, et al. Exposure to phthalates, bisphenol A and metals in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: the MIREC study. *Environ Int* 2015; **83:** 63–71.

117 Díaz Santana MV, Hankinson SE, Bigelow C, et al. Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: a prospective cohort study. *Environ Health* 2019; **18:** 20.

118 Song Y, Hauser R, Hu FB, Franke AA, Liu S, Sun Q. Urinary concentrations of bisphenol A and phthalate metabolites and weight change: a prospective investigation in US women. *Int J Obes* 2014; **38:** 1532–37.

119 Lind PM, Roos V, Ronn M, et al. Serum concentrations of phthalate metabolites are related to abdominal fat distribution two years later in elderly women. *Environ Health* 2012; **11:** 21.

120 Rodríguez-Carmona Y, Cantoral A, Trejo-Valdivia B, et al. Phthalate exposure during pregnancy and long-term weight gain in women. *Environ Res* 2019; **169:** 26–32.

121 Cardenas A, Hauser R, Gold DR, et al. Association of perfluoroalkyl and polyfluoroalkyl substances with adiposity. *JAMA Netw Open* 2018; **1:** e181493.

122 Liu G, Dhana K, Furtado JD, et al. Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: a prospective study. *PLoS Med* 2018; **15:** e1002502.

123 Barry V, Darrow LA, Klein M, Winquist A, Steenland K. Early life perfluorooctanoic acid (PFOA) exposure and overweight and obesity risk in adulthood in a community with elevated exposure. *Environ Res* 2014; **132:** 62–69.

124 Lundin JI, Alexander BH, Olsen GW, Church TR. Ammonium perfluorooctanoate production and occupational mortality. *Epidemiology* 2009; **20:** 921–28.

125 Conway B, Innes KE, Long D. Perfluoroalkyl substances and beta cell deficient diabetes. *J Diabetes Complications* 2016; **30:** 993–98.

126 Karnes C, Winquist A, Steenland K. Incidence of type II diabetes in a cohort with substantial exposure to perfluorooctanoic acid. *Environ Res* 2014; **128:** 78–83.

127 Lind L, Zethelius B, Salihovic S, van Bavel B, Lind PM. Circulating levels of perfluoroalkyl substances and prevalent diabetes in the elderly. *Diabetologia* 2014; **57:** 473–79.

128 Sun Q, Zong G, Valvi D, Nielsen F, Coull B, Grandjean P. Plasma concentrations of perfluoroalkyl substances and risk of type 2 diabetes: a prospective investigation among US women. *Environ Health Perspect* 2018; **126:** 037001.

129 Cardenas A, Hivert MF, Gold DR, et al. Associations of perfluoroalkyl and polyfluoroalkyl substances with incident diabetes and microvascular disease. *Diabetes Care* 2019; **42:** 1824–32.

130 Li AJ, Xue J, Lin S, et al. Urinary concentrations of environmental phenols and their association with type 2 diabetes in a population in Jeddah, Saudi Arabia. *Environ Res* 2018; **166:** 544–52.

131 Duan Y, Sun H, Han L, Chen L. Association between phthalate exposure and glycosylated hemoglobin, fasting glucose, and type 2 diabetes mellitus: a case-control study in China. *Sci Total Environ* 2019; **670:** 41–49.

132 Murphy L, Mérida-Ortega Á, Cebrián ME, et al. Exposure to bisphenol A and diabetes risk in Mexican women. *Environ Sci Pollut Res Int* 2019; **26:** 26332–38.

133 Sun Q, Cornelis MC, Townsend MK, et al. Association of urinary concentrations of bisphenol A and phthalate metabolites with risk of type 2 diabetes: a prospective investigation in the Nurses' Health Study (NHS) and NHSII cohorts. *Environ Health Perspect* 2014; **122:** 616–23.

134 Hagobian T, Smouse A, Streeter M, Wurst C, Schaffner A, Phelan S. Randomized intervention trial to decrease bisphenol A urine concentrations in women: pilot study. *J Womens Health (Larchmt)* 2017; **26:** 128–32.

135 Stahlhut RW, Myers JP, Taylor JA, Nadal A, Dyer JA, Vom Saal FS. Experimental BPA exposure and glucose-stimulated insulin response in adult men and women. *J Endocr Soc* 2018; **2:** 1173–87.

136 Song Y, Chou EL, Baecker A, et al. Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: a systematic review and meta-analysis. *J Diabetes* 2016; **8:** 516–32.

137 Rancière F, Botton J, Slama R, et al. Exposure to Bisphenol A and Bisphenol S and incident type 2 diabetes: a case-cohort study in the French cohort D.E.S.I.R. *Environ Health Perspect* 2019; **127:** 107013.

138 Svensson K, Hernández-Ramírez RU, Burguete-García A, et al. Phthalate exposure associated with self-reported diabetes among Mexican women. *Environ Res* 2011; **111:** 792–96.

139 Lind PM, Zethelius B, Lind L. Circulating levels of phthalate metabolites are associated with prevalent diabetes in the elderly. *Diabetes Care* 2012; **35:** 1519–24.

140 Sharpe RM, Skakkebaek NE. Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. *Fertil Steril* 2008; **89** (suppl): e33–38.

141 Goodyer CG, Poon S, Aleksa K, et al. A case-control study of maternal polybrominated diphenyl ether (PBDE) exposure and cryptorchidism in Canadian populations. *Environ Health Perspect* 2017; **125:** 057004.

142 Trabert B, Chen J, Devesa SS, Bray F, McGlynn KA. International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973–2007. *Andrology* 2015; **3:** 4–12.

143 Lerro CC, Koutros S, Andreotti G, et al. Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study. *Occup Environ Med* 2015; **72:** 736–44.

144 Meyer TE, Coker AL, Sanderson M, Symanski E. A case-control study of farming and prostate cancer in African-American and Caucasian men. *Occup Environ Med* 2007; **64:** 155–60.

145 Kachuri L, Harris MA, MacLeod JS, Tjepkema M, Peters PA, Demers PA. Cancer risks in a population-based study of 70 570 agricultural workers: results from the Canadian Census Health and Environment Cohort (CanCHEC). *BMC Cancer* 2017; **17:** 343.

146 Lemarchand C, Tual S, Levêque-Morlais N, et al. Cancer incidence in the AGRICAN cohort study (2005–11). *Cancer Epidemiol* 2017; **49:** 175–85.

147 Boers D, Zeegers MP, Swaen GM, Kant I, van den Brandt PA. The influence of occupational exposure to pesticides, polycyclic aromatic hydrocarbons, diesel exhaust, metal dust, metal fumes, and mineral oil on prostate cancer: a prospective cohort study. *Occup Environ Med* 2005; **62:** 531–37.

148 Fritschi L, Glass DC, Tabrizi JS, Leavy JE, Ambrosini GL. Occupational risk factors for prostate cancer and benign prostatic hyperplasia: a case-control study in Western Australia. *Occup Environ Med* 2007; **64:** 60–65.

149 Axelsson J, Rylander L, Rignell-Hydbom A, Jönsson BA, Lindh CH, Giwercman A. Phthalate exposure and reproductive parameters in young men from the general Swedish population. *Environ Int* 2015; **85:** 54–60.

150 Chang WH, Li SS, Wu MH, Pan HA, Lee CC. Phthalates might interfere with testicular function by reducing testosterone and insulin-like factor 3 levels. *Hum Reprod* 2015; **30:** 2658–70.

151 Chang WH, Wu MH, Pan HA, Guo PL, Lee CC. Semen quality and insulin-like factor 3: associations with urinary and seminal levels of phthalate metabolites in adult males. *Chemosphere* 2017; **173:** 594–602.

152 Chen SY, Hwang JS, Sung FC, et al. Mono-2-ethylhexyl phthalate associated with insulin resistance and lower testosterone levels in a young population. *Environ Pollut* 2017; **225:** 112–17.

153 Joensen UN, Frederiksen H, Blomberg Jensen M, et al. Phthalate excretion pattern and testicular function: a study of 881 healthy Danish men. *Environ Health Perspect* 2012; **120:** 1397–403.

154 Jurewicz J, Radwan M, Sobala W, et al. Human urinary phthalate metabolites level and main semen parameters, sperm chromatin structure, sperm aneuploidy and reproductive hormones. *Reprod Toxicol* 2013; **42:** 232–41.

155 Meeker JD, Calafat AM, Hauser R. Urinary metabolites of di(2-ethylhexyl) phthalate are associated with decreased steroid hormone levels in adult men. *J Androl* 2009; **30:** 287–97.

156 Meeker JD, Ferguson KK. Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011–2012. *J Clin Endocrinol Metab* 2014; **99:** 4346–52.

157 Pant N, Kumar G, Upadhyay AD, Patel DK, Gupta YK, Chaturvedi PK. Reproductive toxicity of lead, cadmium, and phthalate exposure in men. *Environ Sci Pollut Res Int* 2014; **21:** 11066–74.

158 Specht IO, Toft G, Hougaard KS, et al. Associations between serum phthalates and biomarkers of reproductive function in 589 adult men. *Environ Int* 2014; **66:** 146–56.

159 Wang YX, Zeng Q, Sun Y, et al. Phthalate exposure in association with serum hormone levels, sperm DNA damage and spermatozoa apoptosis: a cross-sectional study in China. *Environ Res* 2016; **150:** 557–65.

160 Wen HJ, Sie L, Su PH, et al. Prenatal and childhood exposure to phthalate diesters and sex steroid hormones in 2-, 5-, 8-, and 11-year-old children: a pilot study of the Taiwan Maternal and Infant Cohort Study. *J Epidemiol* 2017; **27:** 516–23.

161 Sathyanarayana S, Grady R, Barrett ES, et al. First trimester phthalate exposure and male newborn genital anomalies. *Environ Res* 2016; **151:** 777–82.

162 Ferguson KK, Peterson KE, Lee JM, et al. Prenatal and peripubertal phthalates and bisphenol A in relation to sex hormones and puberty in boys. *Reprod Toxicol* 2014; **47:** 70–76.

163 Araki A, Mitsui T, Goudarzi H, et al. Prenatal di(2-ethylhexyl) phthalate exposure and disruption of adrenal androgens and glucocorticoids levels in cord blood: the Hokkaido Study. *Sci Total Environ* 2017; **581–582:** 297–304.

164 Axelsson J, Rylander L, Rignell-Hydbom A, Lindh CH, Jönsson BA, Giwercman A. Prenatal phthalate exposure and reproductive function in young men. *Environ Res* 2015; **138:** 264–70.

165 Watkins DJ, Sanchez BN, Tellez-Rojo MM, et al. Impact of phthalate and BPA exposure during in utero windows of susceptibility on reproductive hormones and sexual maturation in peripubertal males. *Environ Health* 2017; **16:** 69.

166 Hart RJ, Frederiksen H, Doherty DA, et al. The possible impact of antenatal exposure to ubiquitous phthalates upon male reproductive function at 20 years of age. *Front Endocrinol (Lausanne)* 2018; **9:** 288.

167 Li DK, Zhou Z, Miao M, et al. Urine bisphenol-A (BPA) level in relation to semen quality. *Fertil Steril* 2011; **95:** 625–30.

168 Lassen TH, Frederiksen H, Jensen TK, et al. Urinary bisphenol A levels in young men: association with reproductive hormones and semen quality. *Environ Health Perspect* 2014; **122:** 478–84.

169 Adoamnei E, Mendiola J, Vela-Soria F, et al. Urinary bisphenol A concentrations are associated with reproductive parameters in young men. *Environ Res* 2018; **161:** 122–28.

170 Knez J, Kranvogl R, Breznik BP, Vončina E, Vlaisavljević V. Are urinary bisphenol A levels in men related to semen quality and embryo development after medically assisted reproduction? *Fertil Steril* 2014; **101:** 215–221.e5.

171 Meeker JD, Ehrlich S, Toth TL, et al. Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic. *Reprod Toxicol* 2010; **30:** 532–39.

172 Mínguez-Alarcón L, Williams PL, Chiu YH, et al. Secular trends in semen parameters among men attending a fertility center between 2000 and 2017: Identifying potential predictors. *Environ Int* 2018; **121:** 1297–303.

173 Omran GA, Gaber HD, Mostafa NAM, Abdel-Gaber RM, Salah EA. Potential hazards of bisphenol A exposure to semen quality and sperm DNA integrity among infertile men. *Reprod Toxicol* 2018; **81:** 188–95.

174 Vitku J, Heracek J, Sosvorova L, et al. Associations of bisphenol A and polychlorinated biphenyls with spermatogenesis and steroidogenesis in two biological fluids from men attending an infertility clinic. *Environ Int* 2016; **89–90:** 166–73.

175 Ghayda RA, Williams PL, Chavarro JE, et al. Urinary bisphenol S concentrations: potential predictors of and associations with semen quality parameters among men attending a fertility center. *Environ Int* 2019; **131:** 105050.

176 Meeker JD, Ryan L, Barr DB, et al. The relationship of urinary metabolites of carbaryl/naphthalene and chlorpyrifos with human semen quality. *Environ Health Perspect* 2004; **112:** 1665–70.

177 Melgarejo M, Mendiola J, Koch HM, Moñino-García M, Noguera-Velasco JA, Torres-Cantero AM. Associations between urinary organophosphate pesticide metabolite levels and reproductive parameters in men from an infertility clinic. *Environ Res* 2015; **137:** 292–98.

178 Yucra S, Gasco M, Rubio J, Gonzales GF. Semen quality in Peruvian pesticide applicators: association between urinary organophosphate metabolites and semen parameters. *Environ Health* 2008; **7:** 59.

179 Louis GM, Chen Z, Schisterman EF, et al. Perfluorochemicals and human semen quality: the LIFE study. *Environ Health Perspect* 2015; **123:** 57–63.

180 Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jørgensen N. Do perfluoroalkyl compounds impair human semen quality? *Environ Health Perspect* 2009; **117:** 923–27.

181 Song X, Tang S, Zhu H, et al. Biomonitoring PFAAs in blood and semen samples: investigation of a potential link between PFAAs exposure and semen mobility in China. *Environ Int* 2018; **113:** 50–54.

182 Toft G, Jönsson BA, Lindh CH, et al. Exposure to perfluorinated compounds and human semen quality in Arctic and European populations. *Hum Reprod* 2012; **27:** 2532–40.

183 Buck Louis G, Cooney M, Peterson C. The ovarian dysgenesis syndrome. *J Dev Orig Health Dis* 2011; **2:** 25–35.

184 Wang W, Zhou W, Wu S, et al. Perfluoroalkyl substances exposure and risk of polycystic ovarian syndrome related infertility in Chinese women. *Environ Pollut* 2019; **247:** 824–31.

185 Vagi SJ, Azziz-Baumgartner E, Sjödin A, et al. Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol A in polycystic ovary syndrome: a case-control study. *BMC Endocr Disord* 2014; **14:** 86.

186 Heffernan AL, Cunningham TK, Drage DS, et al. Perfluorinated alkyl acids in the serum and follicular fluid of UK women with and without polycystic ovarian syndrome undergoing fertility treatment and associations with hormonal and metabolic parameters. *Int J Hyg Environ Health* 2018; **221:** 1068–75.

187 Akgül S, Sur U, Duzceker Y, et al. Bisphenol A and phthalate levels in adolescents with polycystic ovary syndrome. *Gynecol Endocrinol* 2019; **35:** 1084–87.

188 Akin L, Kendirci M, Narin F, et al. The endocrine disruptor bisphenol A may play a role in the aetiopathogenesis of polycystic ovary syndrome in adolescent girls. *Acta Paediatr* 2015; **104:** e171–77.

189 Hossein Rashidi B, Amanlou M, Behrouzi Lak T, et al. The association between bisphenol A and polycystic ovarian syndrome: a case-control study. *Acta Med Iran* 2017; **55:** 759–64.

190 Konieczna A, Rachoń D, Owczarek K, et al. Serum bisphenol A concentrations correlate with serum testosterone levels in women with polycystic ovary syndrome. *Reprod Toxicol* 2018; **82:** 32–37.

191 Vahedi M, Saeedi A, Poorbaghi SL, Sepehrimanesh M, Fattahi M. Metabolic and endocrine effects of bisphenol A exposure in market seller women with polycystic ovary syndrome. *Environ Sci Pollut Res Int* 2016; **23:** 23546–50.

192 Takeuchi T, Tsutsumi O, Ikezuki Y, Takai Y, Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. *Endocr J* 2004; **51:** 165–69.

193 Gu J, Yuan T, Ni N, et al. Urinary concentration of personal care products and polycystic ovary syndrome: a case-control study. *Environ Res* 2019; **168:** 48–53.

194 Jedrzejuk D, Kuliczkowska-Plaksej J, Milewicz A, Wilczewska K, Namiesnik J, Rutkowska A. Bisphenol A levels are negatively correlated with serum vitamin D-binding protein and sex hormone-binding globulin levels in women with polycystic ovary syndrome: a pilot study. *Pol Arch Intern Med* 2019; **129:** 133–36.

195 Campbell S, Raza M, Pollack AZ. Perfluoroalkyl substances and endometriosis in US women in NHANES 2003–2006. *Reprod Toxicol* 2016; **65:** 230–35.

196 Louis GM, Peterson CM, Chen Z, et al. Perfluorochemicals and endometriosis: the ENDO study. *Epidemiology* 2012; **23:** 799–805.

197 Wang B, Zhang R, Jin F, et al. Perfluoroalkyl substances and endometriosis-related infertility in Chinese women. *Environ Int* 2017; **102:** 207–12.

198 Nazir S, Usman Z, Imran M, Lone KP, Ahmad G. Women diagnosed with endometriosis show high serum levels of diethyl hexyl phthalate. *J Hum Reprod Sci* 2018; **11:** 131–36.

199 Kim SH, Cho S, Ihm HJ, et al. Possible role of phthalate in the pathogenesis of endometriosis: in vitro, animal, and human data. *J Clin Endocrinol Metab* 2015; **100:** E1502–11.

200 Moreira Fernandez MA, Cardeal ZL, Carneiro MM, André LC. Study of possible association between endometriosis and phthalate and bisphenol A by biomarkers analysis. *J Pharm Biomed Anal* 2019; **172:** 238–42.

201 Cohn BA, La Merrill MA, Krigbaum NY, et al. In utero exposure to poly- and perfluoroalkyl substances (PFASs) and subsequent breast cancer. *Reprod Toxicol* 2020; **92:** 112–119.

202 Mancini FR, Cano-Sancho G, Gambaretti J, et al. Perfluorinated alkylated substances serum concentration and breast cancer risk: evidence from a nested case-control study in the French E3N cohort. *Int J Cancer* 2020; **146:** 917–28.

203 Bonefeld-Jørgensen EC, Long M, Fredslund SO, Bossi R, Olsen J. Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort. *Cancer Causes Control* 2014; **25:** 1439–48.

204 Wielsøe M, Kern P, Bonefeld-Jorgensen EC. Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. *Environ Health* 2017; **16:** 56.

205 Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P. Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. *Eur J Public Health* 2018; **28:** 180–85.

206 Hurley S, Goldberg D, Wang M, et al. Breast cancer risk and serum levels of per- and poly-fluoroalkyl substances: a case-control study nested in the California Teachers Study. *Environ Health* 2018; **17:** 83.

207 Engel LS, Werder E, Satagopan J, et al. Insecticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. *Environ Health Perspect* 2017; **125:** 097002.

208 Mills PK, Dodge JL, Bush J, Thompson Y, Shah P. Agricultural exposures and breast cancer among Latina in the San Joaquin Valley of California. *J Occup Environ Med* 2019; **61:** 552–58.

209 Tayour C, Ritz B, Langholz B, et al. A case-control study of breast cancer risk and ambient exposure to pesticides. *Environ Epidemiol* 2019; **3:** e070.

210 Figueres C, Landrigan PJ, Fuller R. Tackling air pollution, climate change, and NCDs: time to pull together. *Lancet* 2018; **392:** 1502–03.

211 Vandenberg LN, Ågerstrand M, Beronius A, et al. A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. *Environ Health* 2016; **15:** 74.

212 Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008; **336:** 1106–10.

213 Intergovernmental Panel on Climate Change. Guidance notes for lead authors of the IPCC fourth assessment report on addressing uncertainties. 2005. https://www.ipcc.ch/site/assets/uploads/2018/02/ar4-uncertaintyguidancenote-1.pdf (accessed June 26, 2020).

214 Vernet C, Philippat C, Calafat AM, et al. Within-day, between-day, and between-week variability of urinary concentrations of phenol biomarkers in pregnant women. *Environ Health Perspect* 2018; **126:** 037005.

215 Bellavia A, James-Todd T, Williams PL. Approaches for incorporating environmental mixtures as mediators in mediation analysis. *Environ Int* 2019; **123:** 368–74.

216 Agier L, Basagaña X, Maitre L, et al. Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. *Lancet Planet Health* 2019; **3:** e81–92.

217 Engel SM, Bradman A, Wolff MS, et al. Prenatal organophosphorus pesticide exposure and child neurodevelopment at 24 months: an analysis of four birth cohorts. *Environ Health Perspect* 2016; **124:** 822–30.

218 Rudel RA, Gray JM, Engel CL, et al. Food packaging and bisphenol A and bis(2-ethyhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Perspect* 2011; **119:** 914–20.

219 Kassotis CD, Vandenberg LN, Demeneix BA, et al. Endocrine-disrupting chemicals: economic, regulatory, and policy implications. *Lancet Diabetes Endocrinol* 2020; **8:** 719–30.

220 Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; **58:** 295–300.