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Maternal Exposure to Synthetic Chemicals and Obesity in the Offspring: Recent Findings

Yun Liu[1] · Karen E. Peterson[1,2,3]

Abstract Experimental studies suggest perinatal exposures to synthetic chemicals may be associated with early onset obesity, although this hypothesis has not been extensively examined in humans. This article summarizes the evidence relating maternal perinatal exposure to common persistent organic compounds (polychlorinated biphenyl, dichlorodiphenyldichloroethylene, dichlorodiphenyltrichloroethane, hexachlorobenzene, hexachlorocyclohexane), perfluoroalkyls, perfluorooctane sulfonate, polybrominated diphenyl ethers and tributyltin, and nonpersistent compounds (phthalates, bisphenol A) on child obesity during sensitive developmental periods. Twenty-two epidemiologic studies published from 2011 to 2015 offer inconsistent support for the obesogenic effects of most substances and are limited by relatively small sample sizes and indirect measures of adiposity. The clearest findings suggest an influence of maternal dichlorodiphenyldichloroethylene exposure on offspring overweight and obesity. Recommendations for future epidemiological research include longer follow-up of effects of pre- and postnatal exposures in large samples; utilization of direct measures of adiposity; and consideration of effect modification by sex, birth weight, dietary fat, and maternal weight status.

Keywords Environmental obesogen · Maternal exposure · Infant growth · Weight gain · Overweight · Obesity · Child

This article is part of the Topical Collection on *Synthetic Chemicals and Health*

✉ Karen E. Peterson
  karenep@umich.edu

  Yun Liu
  yunliu@umich.edu

1   Department of Nutritional Sciences, University of Michigan School of Public Health, 1415 Washington Heights, 1-1867, Ann Arbor, MI 48109-2029, USA

2   Center for Human Growth and Development, University of Michigan, Ann Arbor, MI, USA

3   Departments of Nutrition and of Health and Social Behavior, Harvard W.T. Chan School of Public Health, Boston, MA, USA

Introduction

In recent decades, childhood obesity has emerged as a global public health crisis. The number of infants and preschool children who were overweight and obese worldwide rose from 32 million in 1990 to 42 million in 2013, and this total is estimated to increase to 70 million by 2025 [1]. In the USA, the prevalence of obesity in children increased from 7 % in 1980 to 18 % in 2012 and the proportion of obese adolescents increased from 5 to 21 % over the same period [2, 3]. Early-onset obesity can lead to a number of major health conditions. In the short term, obese children are more likely to have a higher number of risk factors for cardiovascular disease [4] and to manifest prediabetes [5], fatty liver disease, musculoskeletal disease, breathing problems as well as social and psychological disorders [6–8]. Childhood obesity increases the likelihood of being obese as an adult [9] and is associated with greater morbidity and mortality in early adulthood [10–12] as well as risk of heart disease, type 2 diabetes, stroke, osteoarthritis and several types of cancer during later adulthood [13]. Obesity has surpassed cigarette smoking as the first preventable cause of death in the USA, imposing an enormous economic burden [14, 15]. Dramatic obesity trends coupled with challenges of short- and long-term management of this chronic condition [16] and highlight the importance of disentangling the origins of pediatric obesity as a basis for mounting effective prevention strategies.

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Obesity trends are widely attributed to changes in diet, a sedentary lifestyle and genetic predisposition, but these risk factors do not fully account for the genesis and pattern of the obesity epidemic [17, 18]. Since the late nineteenth century, the environment to which humans are exposed has changed due to the exponential growth in the production and use of synthetic chemicals [19]. In 2002, researchers proposed that endocrine disrupting chemicals (EDCs) may contribute to increases in obesity, offering ecologic evidence that elevated production of synthetic substances that coincided with US obesity trends [17]. Associations between high doses of EDCs and weight loss as well as low doses of the same chemicals and weight gain have been reported [17]. EDCs promoting weight gain and obesity collectively have been termed "obesogens" [20]. Scientific findings suggest these EDCs may cause obesity by interfering with lipid metabolism to stimulate adipogenesis and promote fat storage, shifting the metabolic set points to favor positive energy balance or altering hormonal control of appetite and satiety [20–22]. Compelling evidence suggests obesity is programmed as early in life as the intrauterine period [23, 24]. The environmental obesogen hypothesis [18] underlies the notion that fetal exposure to certain EDCs make affected persons susceptible to the induction of fat mass and excessive weight by modifying the epigenome of multipotent stromal stem cells, favoring them to the adipocyte lineage at the cost of bone. Thus, intrauterine exposure to obesogens may alter compartment of stem cells and predispose exposed individuals for adipogenic endpoints [24, 25]. Nevertheless, compared with relatively extensive animal studies, epidemiological research investigating the association of maternal toxicants with children's postnatal obesity is limited.

This review considers the recent evidence examining impacts of maternal exposure to synthetic compounds on obesity and related measures of fat mass and distribution in human offspring. We focus on epidemiologic studies published over a 5-year period from 2011 to 2015, given the availability of three extensive reviews of earlier studies [26–28], summarized below.

Prior to 2011, numerous experimental reports and a limited number of epidemiological studies linked developmental exposure to certain classes of synthetic chemicals to postnatal obesity. Animal studies suggested that low levels of polychlorinated biphenyl (PCBs) may promote adipocyte differentiation, peroxisome proliferator-activated receptor (PPAR)γ expression, and weight gain in offspring [29], but most prospective studies published before 2011 found no association to support this mechanism in humans [26]. Several organochlorine pesticides have been demonstrated to play a role in obesity. Earlier prospective human studies document an association between elevated levels of dichlorodiphenyltrichloroethane (DDT) or its main metabolite dichlorodiphenyldichloroethylene (DDE) during pregnancy

and postnatal obesity in offspring [26]. The few cohort studies that examined the obesogenic effects of other organochlorine pesticides such as hexachlorobenzene (HCB) and hexachlorocyclohexane (HCH) provided inconsistent conclusions, whereas animal studies did not support such a hypothesis [26]. Far fewer researchers have examined the obesogenicity of other persistent organic pollutants, including perfluorinated compounds (PFCs), polybrominated diphenyl ethers (PBDE), or oganotins. Nonpersistent compounds such as phthalates and bisphenol A (BPA) have been related to offspring obesity in experimental studies, but human data are insufficient to support such a relationship [27]. Although organophosphates potentially affect lipid metabolism [28, 30, 31], no available evidence supports their obesogenicity.

We identified 22 human reports published between 2011 and 2015 that examined the relationship of perinatal exposure to (1) *persistent organic pollutants* including PCBs, DDE, DDT, HCB, HCH, perfluroalkyls (PFOA), perfluorooctane sulfonate (PFOS), polybrominated diphenyl ethers (PBDE), and tributyltin (TBT) or (2) *nonpersistent compounds* such as phthalates and BPA with obesity-related outcomes in offspring. After consultation with a research librarian, we searched PubMed using keywords including "Environmental obesogen," "PCBs, DDE, DDT, HCB, HCH, PFOA, PFOS, PBDE and TBT," "maternal exposure," "infant growth," "weight gain, overweight, obesity." We restricted our review to human, nonexperimental studies with a prospective longitudinal design that examined the associations of maternal perinatal exposures to obesity-related outcomes in their offspring. Most reports considered the influence of POPs, particularly DDE and PCBs, while fewer investigated the impact of other compounds. Studies involved different lengths of follow-up that provide insights on toxicant effects during subsequent sensitive periods for obesity development [7], although few followed children into adolescence or early adulthood. Across the 22 studies, researchers primarily relied on measured anthropometry for obesity-related outcomes including weight gain, body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR), while only two studies utilized direct measures of adiposity (Table 1).

Persistent Organic Pollutants

Persistent organic pollutants (POPs) are known EDCs and a group of synthetic chemicals that have been widely used as pesticides, solvents, pharmaceuticals, or industrial chemicals [32]. These chemicals have raised global concern due to their potential for long-range transport, capacity to persist in the environment, ability to bioaccumulate in ecosystems, as well as their marked negative effects on human health [33]. Humans are exposed to these persistent substances primarily through dietary ingestion, inhalation, or dermal exposure [34]. Although POPs are presently banned or restricted through the

Table 1 Prospective Studies of associations between maternal perinatal exposure to synthetic chemicals and child obesity and related outcomes, 2011–2015

First author, year	Population	Exposure	Child age at follow-up	Outcome	Main results[a]
Persistent chemicals					
Mendez 2011	518 Spanish mother-child pairs, Infancia y Medio-Ambiente (INMA) Study	First trimester serum (ng/g lipid): PCBs, DDE, HCB, and HCH	6, 14 months	Rapid growth (change in WAZ birth to 6 months), BMIz at 14 months	PCBs, HCB, HCH: NS; DDE: ↑WAZ birth to 6 months RR=2.42 (95 % CI 1.25, 4.67); ↑BMIz at 14 months RR=1.22 (95 % CI 0.96, 1.55)
Garced 2012	253 Mexican mother-child pairs residing in Morelos	Each trimester serum (ng/mL): DDE	Birth to 12 months	WAZ, BMIz	NS
Maisonet 2012	320 mother-child pairs, Avon Longitudinal Study of Parents and Children (ALSPAC)	Pregnancy serum (10–28 weeks) (ng/mL): PFOS and PFOA	20 months	Weight (g)	PFOS: [T3 (> 23.0 ng/mL) vs T1 (< 16.6 ng/mL)]↑ weight β=579.82 (95% CI: 301.40, 858.25); PFOA: NS
Valvi 2012	344 Spanish mother-child pairs, INMA Study	Cord blood (ng/mL): PCBs, DDE and DDT	6.5 years	Overweight	PCBs: [T3 (>0.9 ng/mL) vs T1 (<0.6 ng/mL)] ↑overweight RR=1.70 (95 % CI 1.09, 2.64); DDE: [T2 (0.7–1.5 ng/mL) vs T1 (<0.7 ng/mL)] ↑overweight RR=1.67 (95 % CI 1.10, 2.55); DDT in boys: [T2 (0.06–0.18 ng/mL) vs T1 (<0.06 ng/mL)] ↑overweight RR=1.96 (95 % CI 1.06, 3.62)
Halldorsson 2012	665 Danish mother-child pairs	Third trimester serum (µg/L): PFOA	20 years	BMI, WC, overweight, serum insulin (mmol/L), adiponectin (µg/L), leptin (ng/L)	PFOA in girls: [Q4 (4.8–19.8 µg/L) vs Q1 (0.1–2.8 µg/L)] ↑BMI β=1.6 (95 % CI 0.6, 2.6); ↑WC β=4.3 (95 % CI 1.4, 7.3); ↑overweight RR=3.1 (95 % CI 1.4, 6.9); ↑insulin β=4.5 (95 % CI 1.8, 7.2); ↑leptin β=4.8 (95 % CI 0.5, 9.4); ↓adiponectin β=−2.3 (95 % CI −4.5, −0.2); NS in boys
Andersen 2013	811 mother-child pairs, Danish National Birth Cohort	First and second trimester (ng/mL): PFOS and PFOA	7 years	BMI, WC, overweight	NS
Warner 2013	270 Mexican-American mother-child pairs, Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study	Second trimester serum (ng/g lipid): DDE and DDT	7 years	Obesity	DDE, DDT: ↑obesity trend with age (2, 3.5, 5, 7 years) NS at 7 years
Cupul-Uicab 2013	1915 mother-child pairs, US Collaborative Perinatal Project (CPP)	Third trimester serum (µg/L): DDE, DDT, PCBs, and HCH	7 years	Overweight and obesity	NS
Valvi 2014	1285 Spanish mother-child pairs. INMA study	First trimester serum (ng/g lipid): PCBs, DDE, and HCB	6, 14 months	Rapid growth (change in WAZ 6 to 14 months), overweight	PCBs: NS; DDE: ↑ WAZ RR=1.13 (95 % CI 1.01, 1.26); ↑overweight RR=1.15 (95 % CI 1.03, 1.28); HCB: ↑WAZ RR=1.13 (95 % CI 1.00, 1.29); ↑overweight RR=1.19 (95 % CI 1.05, 1.34)
Rantakokko 2014	110 mother-child pairs, Finnish cohort study	Placenta (ng/g fresh weight): TBT	Birth, 3, and 18 months	Weight gain (kg/week)	TBT: ↑weight gain at 3 months in boys β=0.024 (95 % CI 0.003, 0.044) NS at other time points
de Cock 2014	61 mother-child pairs, Dutch cohort study	Cord plasma (ng/L or ng/mL): DDE, PCB-153, PFOS, and PFOA	12 months	BMI	NS
Tang-Péronard 2014	561 mother-child pairs, Faroe Islands	Maternal serum and breast milk (µg/g): PCBs and DDE	5 and 7 years	BMI, WC at 7 years, BMI change 5 to 7 years	PCBs: ↑BMI β=1.13 (95 % CI 0.33, 1.93); WC β=0.60 (95 % CI 0.05, 1.16) at 7 years; ↑BMI change from 5 to 7 years in girls β=0.70 (95 % CI 0.26, 1.14) with overweight mothers; DDE: ↑WC β=0.93 (95 % CI 0.36, 1.51) at 7 years

Table 1 (continued)

First author, year	Population	Child age at follow-up	Exposure	Outcome	Main results[a]
Hoyer 2014	1109 mother–child pairs from Greenland, Warsaw (Poland), and Kharkiv (Ukraine)	5 to 9 years	Second and third trimester serum and estimated postnatal (ng/g lipid): PCBs and DDE	BMI	↑BMI change 5–7 years in girls $\beta=0.46$ (95 % CI 0.12, 0.80) with overweight mothers; NS in boys
Delvaux 2014	114 Flemish mother–child pairs, Flemish Environment and Health Study 1 (FLEHS 1)	7 to 9 years	Cord blood (ng/g fat): PCBs, DDE, and HCB	BMI, WC, WHR, skinfolds	NS DDE in girls: ↑WC $\beta=0.013$ ($p=0.021$) ↑WHR $\beta=0.015$ ($p=0.004$) NS in boys; PCBs in girls: ↑WC $\beta=0.014$ ($p=0.033$); NS in boys; HCB: NS
Warner 2014	261 Mexican-American mother-child pairs from CHAMACOS Study	9 years	Second trimester serum (ng/g lipid): DDE and DDT	Overweight and obesity, WC	DDT in boys: ↑Overweight and obesity OR=2.51 (95 % CI 1.00, 6.28) ↑WC OR=2.05 (95 % CI 1.10, 3.82) NS in girls DDE: NS
Iszatt 2015	1864 mother-child pairs from 7 European birth cohorts	Birth and 24 months	Cord blood and postnatal exposure estimated with a validated pharmacokinetic model: PCBs and DDE	Weight change (change in WAZ birth to 24 months)	Prenatal DDE: ↑WAZ $\beta=0.12$ (95 % CI 0.03, 0.22) Postnatal PCBs: ↓WAZ $\beta=-0.10$ (95 % CI −0.19, −0.01)
Erkin-Cakmak 2015	224 Mexican-American mother-child pairs, CHAMACOS Study	7 years	Second and third trimester serum (ng/g lipid): PBDEs	BMIz, WC, and obesity	Maternal PBDEs: ↓ BMIz $\beta=-0.41$ (95% CI: −0.87, −0.05) in girls, NS in boys
Hoyer 2015	1022 mother-child pairs from Greenland and Ukraine	5 to 9 years	Second trimester serum (ng/mL): PFOA and PFOS	Overweight	NS
Nonpersistent chemicals					
Valvi 2013	402 Spanish mother-child pairs, INMA-Sabadell Birth Cohort Study	6, 14 months, and 4 years	First and third trimester urine (µg/g creatinine): BPA	Weight gain (change in WAZ), WC, overweight	BPA: ↑WC 4 years $\beta=0.28$ (95 % CI 0.01, 0.57) NS: change in WAZ, overweight
Harley 2013	311 Mexican-American mother-child pairs, CHAMACOS	9 years	First and second trimester urine (µg/L): BPA	Change in BMIz, WC, percent body fat, overweight, and obesity	BPA in girls: ↓ BMIz $\beta=-0.47$ (95 % CI −0.87, −0.07) ↓ body fat $\beta=-4.36$ (95 % CI −8.37, −0.34) ↓ overweight and obesity OR=0.38 (95 % CI 0.16, 0.91) NS in boys
Volberg 2013	188 Mexican-American mother-child pairs, CHAMACOS	9 years	First, second, and third trimester urine (µg/g creatinine): BPA	Plasma adiponectin (µg/mL) and leptin (ng/mL)	BPA during late pregnancy (first and second): ↑leptin in boys $\beta=0.06$ (95 % CI 0.01, 0.11) BPA during early pregnancy (second and third): ↑adiponectin in girls $\beta=3.71$ (95 % CI 0.38, 7.04)
de Cock 2014	61 mother-child pairs, Dutch cohort study	12 months	Cord plasma (ng/L or ng/mL): MEOHP	BMI	High MEOHP: ↓BMI in boys
Valvi 2015	391 Spanish mother-child pairs, INMA-Sabadell Birth Cohort Study	Birth and 6 months; 1, 4, and 7 years	First and third trimester urine (µg/g creatinine): phthalate metabolites	Weight gain at 6 months (change in WAZ) and BMI at 1, 4, 7 years	High molecular weight metabolites in boys: ↓WAZ 0–6 months $\beta=-0.41$ (95 % CI −0.75, −0.06) BMI at 4 years $\beta=-0.38$ (95 % CI −0.76, −0.01) BMI at 7 years $\beta=-0.40$ (95 % CI −0.78, −0.02) NS in girls

Overweight defined as BMI≥85th and <95th percentile for age and sex; *obesity* defined as children BMI≥95th percentile for age and sex based on reference growth curves used by primary authors.

BMI body mass index, *BMIz* BMI Z-score for age and sex, *RR* relative risk, *T* tertile, *WAZ* weight-for-age Z-score for age and sex, *Q* quartile, *OR* odds ratio, *NS* nonsignificant statistical test of association, *WHR* waist/hip ratio, *PCBs* polychlorinated biphenyls, *DDE* dichlorodiphenyldichloroethylene, *DDT* dichlorodiphenyltrichloroethane, *HCB* hexachlorobenzene, *WC* waist circumference in centimeters, *HCH* hexachlorocyclohexane, *TBT* tributyltin, *PFOA* perfluorooctanoic acid, *PFOS* perfluorooctane sulfate, *PBDEs* polybrominated diphenyl ethers, *BPA* bisphenol A, *MEOHP* mono-2-ethyl-5-oxohexyl phthalate

[a] Change in outcome per 1 unit change in the exposure unless otherwise specified

Stockholm Convention treaty, these toxicants can bioaccumulate within the food chain and are still detectable in human tissues around the world [27]. For instance, certain persistent chemicals can be detected at measurable levels in pregnant women. Specifically, PCBs, organochlorine pesticides, PFCs, and PBDEs were found in 99–100 % of pregnant women [35]. Additionally, several POPs have been measured in cord blood, placental, and amniotic fluid as well as in human breast milk [36–38]. Therefore, it is possible that perinatal POPs exposure may start in utero by passing through the placenta and continue after delivery through breastfeeding. POPs are categorized into dioxins/dioxin-like substances or non-dioxin-like substances, as determined by their capacity to bind the aryl hydrocarbon receptor (AhR) [39]. Dioxins and dioxin-like compounds such as coplanar PCBs can promote adipogenesis by increasing PPAR expression [40] and by disturbing initiation of estrogen receptors to encourage the development of obesity [41]. In contrast, the underlying mechanism is not fully understood for non-dioxin-like compounds such as non-coplanar PCBs, organochlorine pesticides, HCB, HCH, PFCs, and PBDE. Previous studies [27] suggest that DDT and p,p′-DDE can exert toxicity through antiandrogenic, estrogenic, and antiestrogenic effects. HCB may lead to disrupted gluconeogenic reactions. PFOAs and TBT can affect fat storage, adipocyte differentiation, and insulin sensitivity via interfering with PPAR expression [27].

PCBs

Eighteen of the 22 prospective studies between 2011 and 2015 we reviewed evaluated the associations between maternal exposures to POPs and the development of obesity in offspring. Most of the prospective studies we reviewed failed to support the hypothesis that PCBs during pregnancy predict the risk of infant or child obesity prior to adolescence (Table 1). In the Spanish Infancia y Medio-Ambiente (INMA)-Sabadell birth cohort, serum PCB levels during the first trimester were not associated with rapid weight gain in the first 6 months of life or subsequent overweight at 14 months, although this study was limited by sample size [n=518] [42•]. An expansion of the original INMA-Sabadell cohort to a larger study population [n=1285] confirmed earlier findings that PCBs were unrelated to infant growth in this cohort [43]. A Dutch cohort study also found no association between PCB-153 measured in cord blood and infant growth [44•]. Two studies found no evidence for effects of PCBs on weight status in school-age children. A prospective cohort study [45] of maternal-child pairs from Greenland, Poland, and Ukraine found no clear associations between pregnancy PCB and the children's BMIs at 5 to 9 years. This study was consistent with earlier findings [46] from the US Collaborative Perinatal Project (CPP) showing that high levels of total PCB exposures during the third trimester were not linked to overweight or obesity in

children aged 7 years. Notably, PCB exposure levels were relatively high in this population since blood samples were collected before these toxic substances were phased out in the USA.

Counter to the studies above that failed to demonstrate a relationship of PCBs to obesity-related outcomes in infancy or at school entry, three reports provide evidence that prenatal PCB exposure may affect growth rate, BMI, and measures of fat distribution and suggest effects on different anthropometric outcomes may vary in direction, as well as by age and sex (Table 1). In a Flemish cohort [47], PCB levels in cord blood were positively associated with the WC, an indirect measure of central fat distribution in girls at ages 7–9 years, but cord blood PCB levels were unrelated to BMI in either boys nor girls. Maternal PCB levels in pregnancy of Faroese women were related to higher WC in female children at aged 7 years who had overweight mothers [48]. Additionally, these authors found a significant association between prenatal PCBs and a change of BMI in girls from 5 to 7 years of age as well as BMI at 7 years [48]. In the INMA Spanish cohort study, the concentration of PCBs in cord blood positively predicted BMI and overweight in Spanish children aged 6.5 years, in contrast to NS findings at earlier ages, an association that appeared to be stronger in girls than in boys [38]. A pooled analysis of seven European birth cohorts [49•], the largest study to date examining obesogenic effects of POPs, found a negative association between postnatal exposure to PCBs and weight gain from birth to 24 months. Nevertheless, the heterogeneity of levels of DDE exposure introduced by pooling cohorts potentially could lead to imprecise estimates of these associations.

Organochlorine Pesticides

Some persistent organochlorine pesticides have been suspected to play a prominent role in the development of early-onset obesity. Of the 12 prospective studies of maternal exposure to DDE or DDT, 8 found a significant positive association with obesity in offspring (Table 1). Among maternal-child dyads in the Spanish INMA cohort, in utero DDE exposure was related to rapid growth in the first 6 months of life and subsequent overweight at age 14 months [42•, 43]. In the same cohort, DDE concentrations in cord blood were also related to an increased risk of overweight at 6.5 years of age but DDT was associated with overweight in boys [38]. Across seven pooled European birth cohorts, DDE levels in cord blood were associated with greater weight change from birth to 24 months of age, but this effect was not seen in infants with postnatal exposure via breastfeeding [49•]. Studies [47, 48] conducted in Flemish and in Faroese children reported significant positive associations between prenatal DDE and BMI change from 5 to 7 years of age and obesity at 7 years in girls but not in boys, respectively. Two reports from the Center for the Health Assessment

of Mothers and Children of Salinas (CHAMACOS) study, however, found that prenatal DDT concentrations were related to increased BMI and WC at 9 years of age, but only in boys [50]. These authors also documented a significant trend of increased odds of obesity across ages 2, 3.5, 5, and 7 years in boys and girls combined [51].

Despite a preponderance of evidence linking persistent organochlorine pesticides to offspring weight gain and status in US and European settings, four recent studies found no association of developmental exposure to DDE with infant or child obesity (Table 1). For instance, one study of 253 women residing in the state of Morelos, Mexico, suggested that maternal exposure to DDE during pregnancy may not affect infant growth [52]. Similarly, three prospective studies found no clear association between maternal exposure to DDE or DDT and growth in the first year of age of children in Netherlands [44•] or BMI in Greenlandic, Polish, and Ukrainian children aged 5 to 9 years [45] or 7-year-old children in USA with relatively high DDE exposure in utero [46], respectively.

Few human studies have examined early life exposures to HCB and HCH (Table 1). Of four epidemiological studies considering these perinatal exposures, three found no significant association between prenatal HCB and infant growth at 6 and 14 months [42•], obesity in children aged 7 years [46], or obesity in children aged 7 to 9 years old [47], respectively. No association with HCH was found in these three studies. Only one study reported HCB was positively associated with rapid growth and overweight in Spanish infants in the INMA cohort [43].

Other POPs

Other new POPs on the Stockholm Convention list, including PFOA, PFOS, PBDEs, and TBT, have attracted attention because their potential to promote obesity has been suggested by several animal studies. We identified only five longitudinal studies since 2011 that evaluated the effects of PFOA and PFOS on offspring obesity in humans (Table 1). British girls at 20 months of age with prenatal PFOS exposure in the upper tertile were 580 g heavier comparing with those in the lower tertile, but no differences in weight were found with PFOA [53]. In contrast, a Danish cohort study [54•] of 665 pregnant women found that in utero exposure to PFOA was associated with increased overweight and WC among female offspring followed to early adulthood, as well as levels of insulin, adiponectin, and leptin, but no association was observed for PFOS [54•]. One prospective study observed a null association of prenatal PFOA/PFOS with infant BMI at 24 months [44•], and two found no significant association with overweight in school-aged children [55, 56]. In the single human study of developmental exposure to PBDEs and risk of obesity in the Salinas Valley, California, maternal PBDE serum levels during pregnancy were significantly related to decreased BMI in 7-year-old girls [57]. Despite the relatively

extensive number of experimental studies of TBT, we identified only one study exploring the possible obesogenic effect of TBT in humans. A Finnish cohort study presents that TBT levels in placental tissue were associated with infant weight gain during the first 3 months of life, but no associations were observed at 3 or 18 months [58].

Short-lived Ubiquitous Pollutants

Bisphenol A

Bisphenol A (BPA) is used in a wide range of consumer products including can linings and packaging materials and in children's toys. BPA is considered an EDC that can regulate insulin and leptin production by exerting estrogenic activity, acting as agonist and antagonist of PPARγ [27]. Experimental data suggest that prenatal BPA promotes weight gain in offspring; but this association has not extensively been studied in humans in longitudinal studies. Three prospective studies that examined the effects of urinary BPA levels during pregnancy on postnatal growth and obesity report inconsistent results [59–61]. In the Spanish population participating in the INMA study, prenatal BPA was weakly associated with increased WC in 4-year-old children but not at earlier ages [59]. In the CHAMACOS cohort, maternal urinary BPA concentrations were inversely associated with BMI and obesity in 9-year-old Mexican-American girls, effects that were not yet evident at 5 years [60]. In the same population, BPA exposure during late pregnancy was related to increased leptin in boys whereas BPA in early pregnancy was associated with increased adiponectin in girls at 9 years of age [61]. Although the mechanistic pathways for sex-specific effects seen in these studies are not fully understood, one potential explanation is that BPA may affect estrogen activity by interrupting original binding at nuclear estrogen receptors. The synthesis and function of estrogen as well as the distribution of estrogen receptors vary in males and females [62].

Phthalates

Phthalates (monoethylhexyl phthalate (MEHP), diethylhexyl phthalate (DEHP), and oxidative DEHP metabolite mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)) are used in hundreds of consumer products including plastics, cosmetics, and personal care products. Growing experimental evidence has shown that phthalates are thyroid hormone and androgen antagonists and may affect adipogenesis, lipid accumulation, and insulin resistance by regulating activation of PPARγ [63]. Previous studies of associations between prenatal phthalate exposure and obesity among children are limited to a few cross-sectional reports. A recent prospective study in a small Danish sample ($n=61$) reported that higher MEOHP in cord blood was related to lower BMI in male offspring from birth to

11 months old, whereas a reverse association was revealed in female children [44•]. Similar results were seen in a prospective study of DEHP and postnatal growth in the Spanish INMA-Sabadell Birth Cohort; prenatal exposure to DEHP was associated with reduced weight gain in the first 6 months of life and lower BMI at 4 to 7 years in boys [64].

Conclusions

The 22 studies discussed here reveal inconsistent conclusions about obesogenic effects of maternal exposure to man-made compounds that may be attributable to differences in the study population, chemical congeners, levels of exposure, time windows for outcomes, and measured and unmeasured confounders. To date, the mechanistic pathways to explain such associations are not fully understood. Most of human studies on the effects of early-life exposure to synthetic chemicals on overweight or obesity in later life have focused on the prenatal period, whereas few have examined exposure via breastfeeding or combination of both. Rapid growth, overweight, and obesity among children were largely assessed using indirect measures of adiposity including weight gain, BMI and WC, and direct measures were less commonly employed, e.g., skin folds, bio-impedance, dual-energy X-ray absorptiometry, or adipokines. Most current epidemiological data consider the influence of these chemicals on overweight and obesity during infancy and early childhood, up to 9 years of age, but few studies examine the persistence of obesity in adolescence and adulthood due to challenges of long-term follow-up. Of the reports we reviewed, the majority focused on understanding the obesogenicity of DDE and PCBs, while investigations of other environmental toxicants were scarce, particularly for PBDEs, organotin compounds and nonpersistent chemicals. Overall, we found continued support for a predominantly positive effect for maternal DDE and child obesity and less consistent associations for other substances. Several studies were limited by relatively small to modest sample sizes, whereas those with large sample size were constrained by heterogeneity across pooled populations which could contribute to imprecision. Many authors modeled relationships with categorical measures of exposure, typically quartiles, which may reduce statistical power. Given that quantiles of exposure were not necessarily assigned according to clinical relevance, these studies also might not reveal biologically meaningful associations. Nevertheless, categorical measures could reveal nonlinear or non-monotonic relationships that could be explored in studies with larger sample sizes. A strength of the 22 studies reviewed here was that all utilized a prospective, longitudinal design that can enhance causal inference. A few studies used advanced modeling for estimating postnatal exposure and measured levels of adipokines and skinfolds to assess adiposity.

Further research in larger study populations and various settings worldwide is needed to confirm the observed associations, especially for less studied chemicals, and to evaluate potential underlying mechanisms. Studies with longer follow-up time to ascertain the persistence of compounds' effects into later ages and developmental periods, including the transition to young adulthood, should be considered as a priority for future investigations. Research with complete information about both maternal prenatal and postnatal exposure and that utilize direct measures of adiposity is recommended. Considering that many studies report inconsistent results regarding differential effects on boys and girls, the systematic evaluation of interaction by sex is needed. Other factors that appear to serve as effect modifiers of chemical exposures, such as intake of fat, maternal weight status, and birth weight, also require confirmation in larger studies. Among these, birth weight deserves special attention as it shows divergent functions in different analysis. For instance, birth weight has been considered a confounder that may compound the effect on obesity and alternatively has been treated as a variable in the causal pathway. Lastly, studies of mixtures of chemicals should be taken into consideration given that humans have detectable levels of various obesogenic compounds.

In conclusion, the studies of risk of obesity in relation to environmental obesogen exposures during early life provide suggestive evidence for some but not all chemicals, and many uncertainties require further exploration. With prospective study designs, large sample size, improved exposure assessment, direct measures of obesity, and advanced statistical analysis, data generated from these studies can contribute to a strong evidence base for recommendations and strategies to prevent pediatric obesity and its long-term sequelae.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

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