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

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Abstract

Exposures to synthetic chemicals are among the environmental influences implicated in the development of obesity, given that changes in the genetic background cannot explain dramatic trends in recent decades. Experimental studies suggest perinatal exposures to so-called obesogens may be associated with increased risk of early onset obesity, although this hypothesis has not been extensively examined in humans. This article reviews the latest evidence supporting or refuting effects of maternal exposure to 11 common synthetic chemicals on child obesity during sensitive developmental periods. Twenty-two epidemiologic studies conducted since 2011 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 DDE exposure on offspring overweight or obesity. We conclude with recommendations for future epidemiological research on the role of exposures in development of obesity in childhood.

Keywords

Environmental obesogen; maternal exposure; infant growth; weight gain; overweight; obesity; child

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 United States (U.S.), the prevalence of obesity in children increased from 7% in 1980 to 18% in 2012 and the proportion of obese adolescents

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increased from 5% to 21% over the same period (2, 3). Rising rates of pediatric obesity are of particular interest for many reasons. 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, 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 1st preventable cause of death in the U.S., imposing an enormous economic burden (14, 15). Dramatic obesity trends coupled with challenges of short and long term management of this chronic condition (16) highlight the importance of disentangling the origins of pediatric obesity as a basis for mounting effective prevention strategies.

Obesity trends are widely attributed to changes in diet, a sedentary life style, and genetic predisposition, but these traditional risk factors do not fully account for the genesis and pattern of the obesity epidemic (17, 18). Since late 19th century, the environment to which humans are exposed has changed, due to the exponential growth in producing and using 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 U.S. 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”. Scientific findings suggest these EDCs may cause obesity by interfering 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 affect persons susceptible to 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 prearranged exposed individuals for adipogenic endpoints (24, 25). Nevertheless, compared with relatively extensive animal studies, epidemiological research investigating associations of maternal toxicants with postnatal obesity is limited.

This review considers the recent evidence examining impacts of maternal exposure to synthetic compounds on obesity in human offspring. We focus on epidemiologic studies published over a five-year period from 2011 to 2015, given the availability of three extensive reviews of earlier studies (27, 28, 31).

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 PCBs may promote adipocyte differentiation, peroxisome proliferator activated receptor (PPAR) γ expression and weight gain in offspring (26), but most prospective studies published before 2011 found no

association to support this mechanism in humans (27). Several organochlorine pesticides (OCPs) 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 (27). The few cohort studies that examined the obesogenic effects of other OCPs such as hexachlorobenzene (HCB) and hexachlorocyclohexane (HCH) provided inconsistent conclusions, whereas animal studies did not support such a hypothesis (27). Far fewer researchers have examined the obesogenicity of other persistent organic pollutants (POPs), including perfluorinated compounds (PFCs), polybrominated diphenyl ethers (PBDE) or oganotins. Non-persistent compounds, in particular, phthalates and bisphenol A (BPA) have been related to offspring obesity in experimental studies, but human data are insufficient to support such a relationship (28). Although organophosphates potentially affect lipid metabolism (29, 30, 31), no available evidence supports their obesogenicity.

After searching PubMed, we identified 22 human reports published between 2011 and 2015 that examined perinatal exposure to: 1) **Persistent Organic Pollutants (POPs)** including PCBs, DDE, DDT, HCB, HCH, perfluroalkyls (PFOA), perfluorooctane sulfonate (PFOS), PBDE and Tributyltin (TBT) or 2) **Non-persistent Compounds** such as phthalates and BPA and obesity-related outcomes in offspring. No studies were found that investigated the obesogenic role of other synthetic chemicals. Most studies 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 anthropometric outcome measures including weight gain, body mass index (BMI), and waist circumference, while only two studies utilized direct measures of adiposity (Table 1).

Persistent Organic Pollutants (POPs)

POPs are known EDCs and a group of synthetic chemicals that can be intentionally or non-intentionally produced or released. Many POPs 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 Stockholm Convention treaty, these toxicants can bioaccumulate within the food chain and are still detectable in human tissues around the world (28). 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 PPARs expression (40) and by disturbing initiation of estrogen receptors to encourage the progress 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 (28) suggest that DDT and p,p′-DDE can exert toxicity through anti-androgenic, estrogenic and anti-estrogenic effects. HCB may lead to disrupted gluconeogenic reactions. PFOAs and TBT can affect fat storage, adipocyte differentiation and insulin sensitivity via interfering with PPARs expression (28).

PCBs

A total of 18 epidemiological studies between 2011 and 2015 evaluated 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 1st trimester were not associated with rapid weight gain in the first 6 months of life or subsequent overweight at 14 months (Table 1), although this study was limited by small sample size (42). Valvi et al. (43) expanded the original cohort to a larger study population to provide more robust estimates, but nevertheless confirmed earlier findings that PCBs were unrelated to infant growth in this cohort. In 2014, de Cock, et.al, also reported that infant's growth in the first year was not significantly associated with PCB-153 measured in cord blood (45). Two studies considered effects in school-age children. A prospective cohort study (44) of maternal-child pairs from Greenland, Warsaw (Poland) and Kharkiv (Ukraine) found no clear associations between pregnancy PCB and the BMIs of their children at 5–9 years. This study was consistent with earlier findings (46) among the U.S. Collaborative Perinatal Project (CPP) participants showing that high levels of total-PCB exposures during 3rd trimester were not linked to overweight or obesity among 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 U.S.

Counter to studies reporting null associations, 1 meta-analysis and 3 prospective studies provide evidence that prenatal PCBs exposure may affect growth rate, BMI and measures of fat distribution, but also suggest effects vary in direction, and by age and sex (Table 1). A pooled analysis of 7 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. However, the significant heterogeneity of DDE analysis introduced by pooling these cohorts could lead to imprecise estimates. In a prospective Flemish cohort(47), exposure to PCBs in cord blood was positively associated with the waist circumference (WC), an indirect measure of central fat distribution only in girls at ages 7–9 years, but PCBs were unrelated to BMI in either boys nor girls. These conclusions are consistent with a greater susceptibility of the female children observed in a Faroese population in which maternal PCB levels were related to higher BMI and WC in girls 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 (48). In contrast to her previous studies using the same cohort with shorter follow-up time, Valvi et al. (38) reported that concentration of PCBs in cord blood positively predicted BMI and overweight in Spanish children aged 6.5 years, an association that appeared to be stronger in girls than in boys.

Organochlorine Pesticides

Some persistent organochlorine pesticides have been suspected to play an important role in the development of early onset obesity. Of the 12 prospective studies of maternal exposure to DDE or DDT, 8 found a positive association with obesity in offspring (Table 1). Two reports from the Spanish INMA cohort documented a rapid growth in the first 6 months of life and subsequent overweight at 14 months of age in infants with in utero DDE exposure (42, 43). However, no direct measurements of fat mass or body fat distribution were available. Likewise, in the same cohort, authors reported that DDE concentrations in cord blood were related to an increased risk of overweight at 6.5 years of age. Associations between overweight and DDE were strongest in girls and DDT was only associated with overweight in males (38). Across the 7 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 (49). In school-age children, 2 cohort studies (47, 48) reported significant positive associations between prenatal DDE and subsequent BMI change from 5 to 7 years of age and obesity in girls but not in boys. Two prospective studies of 261 mother-offspring pairs from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) however, found that prenatal DDT concentrations were related to increased BMI and WC at 9 years of age only in boys (50), but also documented significant trend of increased odds of obesity across ages 2, 3.5, 5, 7 years among in all children (51).

Despite a preponderance of evidence linking persistent OPs to offspring weight gain and status in U.S. and European settings, 4 recent studies found no association of developmental exposure to DDE with infant or child obesity (Table 1). A study of 253 women residing in State of Morelos, Mexico suggested that maternal exposure to DDE during pregnancy may not affect infant growth (52). Similarly, 3 prospective studies found no clear association between maternal exposure to DDE or DDT and growth in first year of age children in Netherlands with small sample size (45), or BMI in Greenlandic, Polish and Ukrainian children aged 5–9 (44) or 7-year old children in U.S. with relatively high DDE exposure in utero (46).

Fewer human studies have been found to examine early life exposures to HCB and HCH (Table 1). Out of 4 epidemiological studies, 3 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 7–9 years old respectively (47). No association was found with HCH. Only one study reported HCB was positively associated with rapid growth and overweight in infants (43).

Other POPs

Other new POPs on the Stockholm Convention list, including PFOA, PFOS, PBDEs and TBT, have attracted attention given to their potential to promote obesity has been suggested by several animal studies. We identified only 5 longitudinal studies since 2011 that evaluated the effects of PFOA and PFOS on development of obesity in humans (Table 1). Maisonet et al. (53) reported that girls at 20 months of age with prenatal PFOS exposure in the upper tertile were 580g heavier comparing with those in the lower tertile, but no differences in weight were found with PFOA. A Danish cohort study (54) of 665 pregnant women with their children being followed to early adulthood found that *in utero* exposure to PFOA was associated with increased overweight and WC among females only, as well as levels of insulin, adiponectin and leptin No association was observed for PFOS. (54). One prospective study observed a null association of prenatal PFOA/PFOS with infant BMI at 24 months (45) and two observed 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 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

BPA is used in a wide range of consumer products including can linings, 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 (28). 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. Valvi, et.al., found a weak association of prenatal BPA with increased WC and BMI in 4 year-old children in a Spanish population, but an obesogenic effect of BPA was not seen at earlier ages (59). One study reported an inverse relationship between maternal urinary BPA concentrations and BMI and obesity in 9-year-old girls in the CHAMACOS cohort, effects that were not yet evident in 5 years (60). In the same population, Volberg et.al., observed that 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 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 greatly in males and females (62).

Phthalates

Phthalates (monoethylhexyl phthalate (MEHP), diethylhexyl phthalate (DEHP), 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 PPARs (63). Previous studies of associations between prenatal phthalate and obesity among children are limited to a few cross-sectional reports. A recent prospective study in a Danish sample (n=61) reported 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 offspring (45). Similar results were seen in a prospective study of DEHP and postnatal growth using Spanish INMA-Sabadell Birth Cohort, in which prenatal exposure to DEHP was associated with reduced weight gain in the first 6 months of life and subsequent decreased BMI in 4–7 years old of boys. Alternatively, phthalate compounds were non-significantly related to elevated BMI in girls (64).

Conclusions

The recent longitudinal 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 the latest human studies on the effects of perinatal 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 22 recent 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 non-persistent 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 to categorical measures of exposure, typically quartiles, which may reduce statistical power. Given that quantiles were not created accordingly to clinical relevance, these studies also might not reveal biologically meaningful associations. Among strengths of the 22 studies reviewed here was a prospective design which enhances 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 patterns of associations observed, especially for those less studied chemicals, and to explore potential underlying mechanisms. Studies with longer follow-up time to ascertain the persistence of compounds' effects into later ages should be considered as a priority for future investigations. Research with complete information about both maternal prenatal and postnatal exposure assessed with direct measures of adiposity also is recommended. Considering that many studies have concluded with inconsistent results regarding differential effects on boys and girls, subsequent studies interaction by sex are warranted. Other factors that appear to serve as effect modifiers of chemical exposures such as intake of fat, maternal weight status and birth weight require confirmation by larger studies. Among these, birth weight deserves special attention as it shows divergent functions in different analysis. For instance, it has been treated as a confounder that may compound the effect on obesity in some studies. Nonetheless, birth weight has found to be in the causal pathway in other studies. Lastly, studies of mixture of chemicals should be taken into consideration in the future 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 are intriguing; although there are still many uncertainties that 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.

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Table 1

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

First Author, year	Design	Population	Exposure	Child age at follow-up	Outcome	Main findings
Mendez, 2011	Prospective cohort	518 Spanish mother-child pairsfrom the Infancia y Medio-Ambiente (INMA) study	1st trimester serum (ng/g lipid): PCBs, DDE, HCB and HCH	6, 14 months	Rapid growth and overweight	PCBs, HCB, HCH: no effect DDE: ↑ growth and overweight
Garced 2012	Prospective cohort	253 Mexican mother-child pairs residing in Morelos	Pregnancy serum (ng/mL): DDE	Birth to 1 year	Weight and BMI	DDE: No effect
Maisonet 2012	Prospective cohort	320 mother-child pairs from the AvonLongitudinal Study of Parents and Children (ALSPAC)	Pregnancy serum (ng/mL): PFOS and PFOA	20 months	Weight	PFOS: ↑ weight in girls PFOA: no effect
Valvi 2012	Prospective cohort	344 mother-child pairs from Spanish INMA-Sabadell Birth Cohort Study	Cord blood (ng/mL): PCBs, DDE and DDT	6.5 years	Overweight	PCBs, DDE: ↑overweight DDT: ↑overweight only in boys
Halldorsson 2012	Prospective cohort	665 Danish mother-child pairs	Pregnancy serum (μg/L): PFOA	20 years	BMI, waist circumference, overweight, serum insulin, adiponectin and leptin	PFOA: ↑ BMI, waist circumference, overweight, serum insulin, and leptin but ↓ adiponectin in girls
Valvi 2013	Prospective cohort	402 mother-child pairsfrom Spanish INMA-Sabadell Birth Cohort Study	Pregnancy urine (μg/g creatinine): BPA	6, 14 months and 4 years	Weight gain, waist circumference and BMI	BPA: weakly ↑waist circumference and BMI at4 years
Andersen 2013	Prospective cohort	811 mother-child pairsfrom the Danish National Birth Cohort	Maternal plasma (ng/mL): PFOS and PFOA	7 years	BMI, waist circumferenceand overweight	PFOS and PFOA: No effect
Warner 2013	Prospective cohort	270 Mexican-American mother-child pairs from CHAMACOS	Pregnancy serum (ng/g lipid): DDE and DDT	7 years	Obesity	DDE, DDT: No effect at 7 years but ↑ obesity trend with age (2, 3.5, 5, 7 years)
Cupul-Uicab, 2013	Prospective cohort	1,915 mother–child pairs from U.S. Collaborative Perinatal Project (CPP).	3rd trimester serum (μg/L): DDE, DDT, PCBs and HCH	7 years	BMI and obesity	PCBs, DDE, DDT, and HCH: No effect
Harley 2013	Prospective cohort	311 Mexican-American mother-child pairs from CHAMACOS	Pregnancy urine (μg/L): BPA	9 years	Change in BMI, waist circumference, percent body fat, and obesity	BPA: ↓ BMI, body fat, and obesity in girls
Volberg 2013	Prospective cohort	188 Mexican-American mother-child pairs from CHAMACOS	Pregnancy urine (μg/g creatinine): BPA	9 years	Plasma adiponectin and leptin	BPA during late pregnancy: ↑ leptin in boys BPA during early pregnancy: ↑adiponectin in girls
Valvi, 2014	Prospective cohort	1285 Spanish mother-child pairs from INMA study	1st trimester serum (ng/g lipid): PCBs, DDE and HCB	6, 14 months	Rapid growth and overweight	PCBs: no effect DDE, HCB: ↑ growth and overweight

First Author, year	Design	Population	Exposure	Child age at follow-up	Outcome	Main findings
Rantakokko 2014	Prospective cohort	110 mother-child pairs from a Finnish cohort study	Placenta (ng/g fresh weight):TBT	Birth, 3 and 18 months	Weight gain	TBT: ↑weight gain at 3 months in boys
de Cock, 2014	Prospective cohort	61 mother-child pairs from a Dutch cohort study	Cord plasma (ng/L or ng/mL): DDE, PCB-153, PFOS, PFOA and MEOHP	12 months	BMI	PCB-153, DDE, PFOS, and PFOA: no effect High MEOHP: ↓ BMI in boys
Tang-Péronard, 2014	Prospective cohort	561 mother-child pairs from the Faroe Islands	Maternal serum and breast milk (mg/g): PCBs and DDE	5 and 7 years	BMI and waist circumference	PCBs: ↑ BMI and waist circumference at 7 years and ↑ BMI change from 5–7 years in girls with overweight mothers DDE: ↑ waist circumference at 7 years and ↑ BMI change from 5–7 years in girls with overweight mothers
Hoyer, 2014	Prospective cohort	1109 mother–child pairs from Greenland, Warsaw (Poland), and Kharkiv (Ukraine)	Maternal pregnancy serum and estimated postnatal (ng/g lipid): PCBs and DDE	5–9 years	BMI	PCBs and DDE: No effect
Delvaux, 2014	Prospective cohort	114 Flemish mother-child pairs from first Flemish Environment and Health Study (FLEHS I)	Cord blood (ng/g fat): PCBs, DDE and HCB	7–9 years	BMI, waist circumference, waist/hip ratio and skinfolds	DDE: ↑ waist circumference and waist/hip ratio in girls PCBs: ↑ waist circumference in girls HCB: no effect
Warner 2014	Prospective cohort	261 Mexican-American mother-child pairs from Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study	2nd trimester serum (ng/g lipid): DDE and DDT	9 years	BMI, waist circumference and body fat	DDT: ↑ BMI, waist circumference in boys DDE: no effect
Iszatt 2015	Meta-analysis	1864 mother-child pairs from 7 European birth cohorts	Prenatal and postnatal using a validated pharmacokinetic model: PCBs and DDE	Birth and 24 months	Weight change	Prenatal DDE: ↑ growth postnatal PCBs↓ growth
Valvi 2015	Prospective cohort	391 mother-child pairsfrom Spanish INMA-Sabadell Birth Cohort Study	Pregnancy urine (μg/g creatinine): Phthalate metabolites	Birth and 6 months; 1, 4 and 7 years	Weight gain, BMI	High molecular weight phthalate metabolites: ↓ weight gain at 0–6 months and BMI at 4 and 7 years old in boys
Erkin-Cakmak 2015	Prospective cohort	224 Mexican-American mother-child pairs from CHAMACOS	Pregnancy serum (ng/g lipid): PBDEs	7 years	BMI, waist circumference and obesity	PBDEs: ↓ BMI in girls
Hoyer BB 2015	Prospective cohort	1022 mother-child pairs from Greenland and Ukraine	Pregnancy serum (ng/mL): PFOA and PFOS	5–9 years	Overweight	PFOA and PFOS: No effect