Effects of early exposure to phthalates and bisphenols on cardiometabolic outcomes in pregnancy and childhood

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Abstract

Pregnant women are exposed to various chemicals, including endocrine-disrupting chemicals (EDCs) such as phthalates and bisphenols. Increasing evidence suggests that early life exposures to phthalates and bisphenols may contribute to cardiometabolic risks. The aim of this narrative review was to summarize current knowledge of the effects of fetal and childhood exposure to phthalates and bisphenols on child growth and child cardiometabolic outcomes and the effects on maternal outcomes. In total, 54 studies were identified and included. The majority of studies found effects of phthalates and bisphenols on maternal, child growth, and cardiometabolic outcomes. Currently results suggest that early life exposure to phthalates and bisphenols may have a substantial influence on perinatal and postnatal cardiometabolic programming. In a large part of the investigated outcomes studies show contradictory results. However, the majority of the existing evidence is based on non-cohort studies with single samples neglecting time-variant effects and complicating conclusions regarding causal inference. More studies are needed investigating the mechanisms and its potential interactions.

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Introduction

Pregnant women are exposed to a variety of chemicals,[1, 2] including endocrine-disrupting chemicals (EDCs) such as phthalates and bisphenols.[3-6] Increasing evidence suggests that early life exposures to phthalates and bisphenols may contribute to the burden of cardiovascular and metabolic disease in western countries. Recent work suggests that these exposures may be costly. Health care costs of obesity and diabetes attributable to adult phthalate and bisphenol exposure in Europe is in the order of €17 billion annually.[7] Insofar as prenatal and childhood exposures may even be more impactful, the costs of cardiometabolic conditions due to these exposures may be higher.

In this narrative review, we summarize current knowledge of the effects of fetal and childhood exposure to phthalates and bisphenols on child growth and child cardiometabolic outcomes. Additionally, we summarize the effects of phthalate and bisphenol exposure on maternal outcomes.

Phthalates and Bisphenols

Phthalates are synthetic chemical esters of phthalic acid that are widely used in a variety of consumer products to impart flexibility, pliability and elasticity to plastics and therefore known as "plasticizers".[8] Phthalates can be classified in two groups. Low molecular weight (LMW) phthalates (e.g. di-methyl phthalate (DMP), di-ethyl phthalate (DEP), di-n-butyl phthalate (DBP)) are frequently added to personal care products as aerosol delivery agents, emollients, to impart flexibility in nail polishes, and to retain scent.[9] High molecular weight (HMW) phthalates (e.g. di-2-ethylhexylphthalate (DEHP), di-isononylphthalate (DiNP), di-isodecylphthalate (DiDP), di-n-octylphthalate (DnOP), butylbenzyl phthalate (BBzP)) are used as plasticizers to impart flexibility in vinyl plastics (e.g. polyvinyl chloride plastics (PVC)) for diverse applications including flooring, medical devices and food packaging.[10] In the category of HMW phthalates, di-2-ethylhexylphthalate (DEHP) is of particular interest, considering many food packaging methods include the use of plastics containing DEHP.[11] However, the last few years DiNP and DiDP have replaced DEHP to a great extent, mainly due to governmental embargoes. [12]

Bisphenol A (BPA) is used to produce polycarbonate plastics and epoxy resins used in various consumer products, including the lining of metal cans, toys and water pipes.[13] The last few years, bisphenol A has been substituted by synthetic bisphenol analogues like bisphenol F (BPF) and bisphenol S (BPS), which has been determined in various food items[14]. BPS has been found as well in paper and paper products, including currency bills. [15]

Routes of Exposure and Metabolism

Phthalates are non-covalently bound to many plastics, creating a large risk for release into the environment over time.[9] Phthalates are generally lipophilic[16] and have short biological half-lives (less than 24h), undergoing hydrolysis and sometimes oxidation before

glucuronidation or sulfation before excretion into urine of feces, but it can be measured as well in blood and breast milk.[9] A portion of the unconjugated (free) monoester and/or its secondary metabolites may also be directly excreted in urine.[17] The primary routes of exposure to phthalates are ingestion, salivary absorption, inhalation, intravenous, and transdermal. Depending on the route of exposure, the chemical is distributed into various body parts based on vascular blood supply and affinity, which in turn may lead to a difference in bioavailability. Ingested chemicals often undergo a first-pass effect, entering the liver through the hepatic portal system for metabolization, which reduces bioavailability. Following inhalation, salivary absorption, intravenous, and transdermal exposure this first-pass effect is initially bypassed, provoking a higher bioavailability.[18]

Population based studies often use urine as a measurement for exposure to phthalates because it is noninvasive and notwithstanding the short biological half-life it may reasonably reflect the exposure in the last several weeks or even months.[18, 19] The majority of the population based studies using urinary phthalate concentrations measured the concentration of the free plus glucuronidated species of phthalate metabolites, together being the total concentration. However, the free metabolite concentrations are less stable over time than the total metabolite concentration, suggesting free metabolite concentrations are not a useful indicator of metabolic susceptibility. Time of collection is an important factor that must be taken into account, since concentrations of metabolites vary during the day as a result of timing of exposure.[17]

Various products containing polycarbonate plastics and epoxy resins have been studied to obtain more knowledge on bisphenol leaching. Regarding polycarbonate plastics, different results have been obtained on the effects of washing and heating on BPA leaching, although all studies found leaching. Several studies have been performed that found that heating temperature had a significant effect on BPA leaching from metallic coated food cans.[13]

Studies investigating the metabolism of BPS and BPF are lacking. Concerning BPA it is known that after ingestion BPA undergoes a first-pass metabolism in the gastrointestinal tract and liver consisting of glucuronidation and, to a lesser extent, sulfation metabolizing BPA to bisphenol A monoglucuronide (BPAG) and bisphenol A sulphate (BPAS) for approximately 98%. In plasma, more than 90% of BPA is bound, depending on the route of exposure. Exposure through inhalation and skin absorption have been reported as important routes of exposure, as unconjugated bisphenols might circulate longer in the plasma, while ingested bisphenols undergo the first-pass metabolism.[20, 21] However, it has been reported that UDP-glucuronosyltransferase (UGT) enzymes found in the airways exhibit a high activity towards bisphenols.[21] Both BPAG and BPAS are excreted in urine within 5-7 hours after oral administration.[20, 22] BPA penetrates and accumulates in the human placenta, with higher levels of BPA in the placenta compared to maternal and fetal plasma. [23] In a rat-study, BPF residues have been detected in the uterus, placenta, amniotic fluid, and fetuses, with comparable higher levels of BPF in the (intra)uterine compartment compared to maternal blood.[24]

Biomonitoring studies have observed high plasma concentrations not consistent with the observation of an extensive first-pass metabolism of oral BPA. However, concentrations of

urinary BPA tend to be much higher than serum concentrations. It has been hypothesized that these relatively high concentrations both in plasma and urine could be explained by sublingual absorption, bypassing the first-pass metabolism.[25] While another study has suggested that this hypothesis does not hold, the contradictory study is beset by critical differences in site of blood collection and volume of urinary output that actually support sublingual absorption as a substantial contributor to exposure.[22, 25]

A potentially important role in metabolism with a large effect on bioavailability is reserved for the human microbiome. The microbiome comprises the residential microbes humans are colonized by and there is a broad interindividual variation. Several bacterial species possess β-glucuronidases and β-glucuronides, enzymes involved in deconjugation and conjugation. Depending on the composition of the microbiome, phthalates and bisphenols could be conjugated or deconjugated after enterohepatic circulation, resulting in a smaller or larger exposure to unconjugated chemicals, respectively.[26, 27]

Potential Mechanisms of Effect

Hydrolysed phthalate metabolites have been shown to penetrate the human placenta.[28] In vitro studies demonstrated that several commercially used phthalates may bind to estrogen receptor alpha (ERα), having a weak estrogenic activity,[29, 30] and to androgen receptors (ARs), having a strong anti-androgen activity.[31, 32]

Another potential mechanism is by activation of nuclear transcription factor peroxisome proliferator-activated receptors (PPARs). PPAR-gamma (PPARγ), expressed predominantly in adipose tissue and to a lesser extent the macrophage and liver, acts as regulator for adipocyte differentiation, lipid metabolism and reduces inflammation resulting in improved insulin sensitization.[33, 34] However, despite potential benefits, PPARγ agonists have been shown to cause adverse effects regarding increased lipid accumulation and release of adipocyte-related hormones leading to an increased susceptibility for the development of obesity.[35] Several phthalates have been shown to be PPARγ activators, causing obesogenic effects.[34-37] PPARs form heterodimers with the retinoid X receptors (RXRs), binding together on the target DNA and thereby activating the expression of downstream genes. Therefore, RXRs have the same targets as PPARs. Many common phthalates have been shown to bind to RXRs.[37] Likewise, oxidative stress is a potential mechanism for phthalate effects. In a prospective cohort study of pregnant women all urinary phthalates were associated with increased oxidative stress markers.[38]

The potential mechanisms of action from bisphenols resemble those from phthalates to a great extent. Studies regarding the mechanism of action from BPF and BPS are scarce. Bisphenols are weak xenoestrogens binding to estrogen receptors (ER) and the G-protein-coupled receptor 30 (GPR30) in its unconjugated form, with greater binding affinity to ERβ compared to ERα, considering a 100 to 10.000-fold lower relative binding affinity of bisphenols to ERs compared to estradiol (E2).[20, 39, 40] However, findings suggest that BPA is equally potent as E2 and it is suggested that this results from actions through non-genomic pathways and disruption of steroidogenesis.[13, 20, 41] BPF and BPA have been reported to increase the level of 17β-estradiol. BPF appears to be even more potent than

BPA, given the higher concentrations of 17β-estradiol after exposure of H295R human adrenocortical carcinoma cell line to BPF.

Like phthalates, bisphenols have anti-androgen capacities, binding to ARs.[31, 39] A decrease in free testosterone level is reported when exposed to bisphenols, in the order BPF > BPS > BPA. Since the binding affinity of BPS to the AR is low, the testosterone effect of BPS seems to be androgen receptor independent.[39, 42] Both BPS and BPF increased progesterone levels, BPA and BPS decreased cortisol levels, and BPF increased cortisol levels. [42]

Similar to phthalates, BPA appears to induce an activation of PPARα and possibly to a smaller extent a weak activation of PPARγ, causing obesogenic effects.[34, 35, 37] Besides the binding to PPARs, also BPA binds to RXRs with more affinity to RXRs.[37] Likewise, oxidative stress is a potential mechanism for BPA effects. The same Puerto Rican prospective cohort study describing the association between phthalates during pregnancy and oxidative stress markers found a significant association between urinary BPA and oxidative stress markers in pregnant women.[43] An in vitro study showed oxidative stress effects from BPS and BPF.[42] Furthermore, BPA has been reported to have nitrosative stressor effects and effects on free fatty acids (FFAs). Oxidative stress and imbalances in FFAs are known mediators of tissue specific insulin resistance and inflammation.[44]

Adverse metabolic outcomes could also be hypothesized by interaction of phthalates and bisphenols with the adipocytokines leptin and adiponectin. Adiponectin and leptin are adipocyte-produced hormones having a role in metabolic regulation and function. In adults, leptin inhibits appetite, stimulates thermogenesis, enhances fatty acid oxidation, decreases glucose, and reduces body weight and fat. Paradoxically, leptin levels increase in obesity. [45] Meanwhile, in adults low adiponectin levels have been associated with insulin resistance, dyslipidemia, atherosclerosis, and metabolic syndrome.[45, 46] An overview of the potential mechanisms of effect is shown in Figure 1.

Maternal Pregnancy Outcomes

Two studies investigated the effect of phthalates and BPA on the time to pregnancy. A Canadian pregnancy cohort found no association between first trimester phthalates or BPA and recalled time to pregnancy.[47] Meanwhile, a preconceptional cohort study exploring the effects of phthalates and BPA on fertility in the both men and women in the United States found several phthalates to be associated with longer time to pregnancy in males, while other phthalates were associated with shorter time to pregnancy in females. Neither male nor female BPA concentration was associated with time to pregnancy.[48] Two human studies have pointed out that a higher level of BPA was associated with (recurrent) aneuploidy and euploid miscarriages.[49, 50]

During pregnancy maternal glucose levels increase to provide adequate nutrition for fetal growth and development. Two studies investigated the effect of phthalates and BPA on maternal glucose levels and gestational diabetes mellitus (GMD).[51, 52] Neither phthalates nor BPA was associated with increased maternal glucose levels or GMD. However, a small

cohort study of pregnant women found that women in the highest tertile of urinary MiBP and MBzP had lower blood glucose levels at time of the routine GMD screening compared to women in the lowest concentration tertile.[52] A Japanese study investigated the effect of DEHP on maternal triglycerides and fatty acid levels, detecting an inverse association between maternal serum MEHP concentrations and triglyceride and fatty acid levels during pregnancy. These findings could have implications for fetal health. The growth and development of the fetus and its organs depend on a sufficient supply of nutrients including fatty acids and lipids crossing the placenta, determining birth outcomes. However, in this particular study no effect on fetal growth was observed.[53]

Only one study explored the association with preeclampsia, investigating differences in the distribution of BPA between maternal, placental and fetal compartments. This small case-control study reported that preeclamptic women have significantly higher concentrations of BPA in placental tissue compared to normotensive pregnant women, while concentrations of BPA in maternal serum and cord blood did not differ significantly. Accordingly, BPA was equally distributed between maternal, placental and fetal compartments in the normotensive group, while preeclamptic women showed an unequal distribution with a high level of BPA in the placental compartment.[54]

Overall, the amount of studies for the separate outcome measures is limited. However, the presented outcomes suggest potential adverse effects of phthalates and bisphenols on fecundity, miscarriages, and preeclampsia. There are no studies reporting on pregnancy induced hypertension or HELLP syndrome. An overview of the included studies including outcomes, strengths and weaknesses is given in Table 1. Study characteristics and results of all included studies separately are shown in Supplementary Table 1.

Fetal Outcomes

In addition, the same mechanisms that affect maternal outcomes may also affect fetal outcomes. Phthalates have been investigated more thoroughly for their effects on prematurity compared to bisphenols. Nine studies explored the relationship between prenatal phthalate exposure and prematurity. In contrast to our hypothesis, two of these studies found a positive association between phthalate exposure and gestational age at delivery, reporting an increase of only one or two days to the gestational age at birth due to higher levels of phthalates. Both studies measured phthalates in urinary samples in the beginning of the third trimester.[55, 56] A French small prospective cohort study found no association of dibutylphthalate and its main metabolite monobutylphthalate in cord blood and breast milk with length of gestation.[57] The remaining six studies found a significant association between a higher exposure to phthalates and reduced gestational age at time of birth.[58-63] Two of these studies performed the measurements of exposure in cord blood samples.[58, 61] Of the remaining four studies with phthalate measurements performed in urinary samples, one found a significant reduction in gestational age which only remained in male infants after analysis was stratified for gender. Unfortunately, the timing of urinary sample collection was not specified.[63] Two included studies consist of the same birth cohort with up to four urinary samples during pregnancy investigating the overall relationship with prematurity and windows of vulnerability for spontaneous and placental preterm birth,

respectively. Both studies report that the odds of preterm birth compared to term birth are 1.3-1.5 times higher for children prenatally exposed to high levels of phthalates compared to children exposed to lower levels of phthalates.[59, 60] One of these studies revealed that spontaneous and placental preterm birth, defined as delivery with presentation of preeclampsia or intrauterine growth restriction, had different sensitivity windows of exposure to phthalates during pregnancy. Spontaneous preterm birth, defined as delivery with presentation of spontaneous labor of preterm premature rupture of membranes, showed to be significantly associated with higher phthalate metabolite concentrations measured at the beginning of the third trimester, while placental preterm birth was associated with higher phthalate metabolite concentrations measured during the first trimester.[60]

Regarding bisphenols, all four studies presented in this review examined only BPA and its relationship with prematurity.[56, 63-65] Three of these studies associated higher urinary BPA levels, mainly measured during third trimester, with a significant reduction in gestational age at time of birth of one to four days.[63-65] As for phthalates the gestational age reduction remained only significant in male infants in one of these pregnancy cohorts. [63] The remaining study on bisphenols found no relationship between BPA with gestational age at time of birth.[56]

The association of phthalates and bisphenols with fetal growth is explored with 7 studies reporting on phthalates and 7 studies on bisphenols, including the already presented results from the Japanese study investigating also fetal nutrients during pregnancy displaying no association between DEHP and fetal growth.[53] With respect to phthalates, of the remaining 6 studies, 4 all Chinese studies found that a higher exposure to phthalates was significantly related with reduced body size measures at birth.[58, 66-68] A cohort study among 207 women reported a reduction in birth weight of 15-139 grams per natural log increase in phthalate concentrations.[58] One of these studies also displayed a negative association between phthalates and DNA methylation in the human placenta, suggesting placental methylation as a possible mediator of the relationship between phthalates and birth measurements.[67] Contrasting with our hypothesis, two studies found positive associations between phthalates and fetal head circumference at time of birth.[56, 57]

Of the studies on BPA, 4 studies found no association between BPA and body size measures at birth.[56, 64, 69, 70] Two studies found higher BPA levels to be associated with decreased body size measures at birth.[71, 72] In a subset of the Dutch Generation R study fetal weight and head circumference were significantly decreased per unit increase in creatinine corrected BPA among women with three urinary BPA measurements during pregnancy. Children born to women in second highest exposure group had an average decrease of 683 grams birth weight. This relationship progressively attenuated among women with fewer BPA measurements.[72] On the contrary, a Korean multi-center birth cohort study found a higher creatinine corrected urinary BPA levels during third trimester to be associated with and increased birth weight in male neonates and increased ponderal index in female neonates.[73]

Hence, the majority of studies show mostly negative effects of phthalates and negative or no effects of BPA on gestational age and body size measures at birth. No studies have explored

the other bisphenols besides BPA. An overview of the included studies is given in Table 1. Details of all described studies are represented in Supplementary Table 1.

Childhood Outcomes

Phthalates and bisphenols have been reported to have an influence on childhood growth. All three studies exploring the relationship between prenatal phthalates and childhood growth discovered different results in males and females, predominantly resulting in negative associations with growth in males.[74-76] An extensive Spanish birth cohort reported that the molar sum of first and third trimester urinary HMW phthalates was significantly associated with reduced weight gain z-score in the first 6 months in boys and nonsignificantly with lower BMI z-scores in boys at any age (measured until 7 years of age). Meanwhile, in girls the molar sum of first and third trimester HMW phthalates was nonsignificantly associated with higher BMI z-scores.[76]

Two out of 4 studies reported that a higher level of prenatal BPA exposure was associated with an increase in several childhood growth parameters in preschoolers, including BMI z-score, weight and waist circumference.[69, 77] The remaining two studies showed prenatal BPA exposure to be related to a lower postnatal BMI in preschool till mid-childhood aged girls, not boys.[6, 78] After subdivision in prepubertal and pubertal girls, only in prepubertal girls prenatal BPA exposure remained negatively associated with BMI z-score and waist circumference.[6]

In total, 18 studies investigated the influence of exposure to phthalates and bisphenols during childhood on childhood growth. Five out of nine studies found childhood exposure to phthalates to be associated with increased growth parameters in mid-childhood till adolescence, including obesity indices consisting of subscapular skinfold thickness, BMI, hip- and waist circumference.[79-83] Four of these studies reported different effects in males and females, suggesting sex to be an effect modifier.[79-82] Also ethnicity is a potential modifier of effects. A cross-sectional analysis of the 2003-2008 NHANES data showed an increase in overweight and obesity among non-Hispanic blacks related to childhood phthalate exposure, while among other ethnic groups no significant associations have been found.[83] Two studies found childhood phthalate exposure to be associated with reduced mid-childhood growth measures, including BMI, fat mass, waist circumference, BSA, weight and height.[75, 84] The two remaining studies found no relationship between childhood phthalate exposure and preschool till adolescent growth, defined as a BMI >85th and >95th percentile, respectively.[85, 86]

Eleven studies examined the relationship between levels of BPA in childhood and growth, of which 2 studies did not find any relationship between BPA and preschool till mid-childhood growth measures, including weight, height, waist circumference and BMI.[87, 88] The earlier mentioned HOME study found two-sided outcomes: exposure early in childhood to higher levels of BPA was associated with a lower BMI at the age of two. However, their BMI slopes increased more rapidly between 2 and 5 years of age.[78] Six studies showed that higher BPA levels in childhood were associated with increased growth parameters, including BMI, waist circumference, waist-to-height ratio, hip circumference and body fat.

[6, 89-93] Measurements are obtained over the whole age spectrum of childhood and adolescence. Three of these studies were based on subsamples from the National Health and Nutrition Examination Survey (NHANES) in the United States. Samples were not identical as a result of heterogeneous inclusion criteria and outcome measures differed to a certain extent. However, all examined the relationship with BMI.[90-92] Both sex and ethnicity were shown to be potential effect modifiers of the relation between childhood exposure to BPA and childhood growth parameters. In the NHANES data, childhood urinary BPA concentrations were significantly associated with increased risks for obesity and increased waist-to-height ratios among non-Hispanic white boys.[90-92] Contrastingly, a study of Chinese schoolchildren found a significant association between childhood BPA exposure and increased BMI and hip circumference in girls, but not in boys. However, it must be noted that BPA concentrations were not adjusted for urinary dilution.[93] Two earlier mentioned studies found childhood BPA exposure to be associated with reduced overweight and obesity, respectively.[85, 86] One of these studies is the only study included in this review investigating not only BPA but also BPS. However, no associations have been found with BPS regarding growth measures.[86]

The aforementioned Spanish study showed that in girls the molar sum of prenatal exposure to both HMW and LMW phthalates was significantly associated with lower systolic blood pressure z-scores at 4 and 7 years of age. For both sexes there was a negative association with diastolic blood pressure, but none of the associations reached the level of significance. [76]

Four studies have examined childhood exposure to phthalates and bisphenols with respect to cardiovascular outcomes. All studies, including 2 studies published on phthalates and 2 studies on BPA, confirmed the hypothesis that childhood exposure to phthalates and bisphenols is associated with adverse cardiovascular outcomes in terms of increased blood pressure and low-grade albuminuria in preschool till adolescent age.[87, 94-96] Details are shown in Supplementary Table 1.

The relationship between childhood exposure to phthalates and bisphenols and childhood metabolic outcomes has been explored in six studies. The majority of studies used the homeostatic model assessment of insulin resistance (HOMA-IR) to assess insulin resistance in which a HOMA-IR   4.39 was defined as insulin resistance.[87, 88, 91, 97, 98] The analysis of the 2003-2008 NHANES data showed HMW phthalate metabolites to be related to a higher HOMA-IR in adolescents, which was mainly DEHP dependent. Adding BPA to the model did not change the association.[97] A recent follow-up analysis of the 2009-2012 NHANES data confirmed this association and explored whether the newer DINP, a replacement for DEHP, was also associated with increased insulin resistance. Also DINP showed to be associated with an increased insulin resistance.[98] Further evidence on the association with phthalates is lacking.

Three studies of BPA failed to find an association with childhood metabolic outcomes in mid-childhood till adolescent age, including adipokines, insulin resistance, blood lipids, insulin and glucose.[88, 91, 99] The earlier mentioned case study of obese children found a significant mainly negative non-monotonic exposure-response relationship between BPA and

fasting insulin and HOMA-IR in a case study of obese or overweight children aged 3-8 years. Unfortunately, BPA was not adjusted for urinary dilution in this analysis, which made it difficult to estimate its adjusted effect.[87]

To conclude, the greater part of studies examined the association of phthalates and bisphenols with growth, giving contradictory results. Sex, stage of puberty and ethnicity are proposed as potential effect modifiers. An overview of the included studies is given in Table 1. Details of all described studies are represented in Supplementary Table 1.

Discussion

We identified many studies investigating potential effects of prenatal and childhood phthalate and bisphenol exposure on growth and cardiometabolic risks. As presented throughout the paragraphs, exposure to phthalates and bisphenols is believed to induce pathways towards several adverse health effects. This conceptual model of mechanisms is shown in Figure 2. In vitro studies showed that exposure to phthalates and bisphenols causes hormonal disruption, epigenetic changes, oxidative and nitrosative stress. The effects could be affected by the time of exposure, both during fetal life and childhood. Exposure during fetal life may induce prematurity and low birth weight. Aside from the many disadvantageous outcomes from premature birth, both premature birth and low birth weight have been associated with cardiometabolic dysfunction, including overweight in adolescence and adulthood, dyslipidemia, insulin resistance, endothelial and glomerular dysfunction. [100-103] As shown before, exposure during childhood is associated with aberrant growth patterns inducing overweight and obesity and early signs of cardiovascular and metabolic dysfunction, including glomerular and endothelial dysfunction, increased blood pressure and increased insulin resistance. Together with the earlier mentioned cellular changes both fetal and childhood exposure to phthalates and bisphenols may give rise to an increased risk for cardiovascular and metabolic disease in adulthood. As shown in the earlier paragraphs, effects could be affected by the time of exposure, both during fetal life and childhood, as well as by the sex and race of the child.

Little is known about the epigenetic changes phthalates and bisphenols can cause and what mechanism lies behind it. The epigenetic effects of fetal BPA exposure were explored in mouse models. This study showed that BPA induces DNA hypomethylation, while maternal nutritional supplementation of methyl donors like folate negated the BPA-induced DNA hypomethylation in the offspring.[104] This could be a major point of engagement, yet has not been examined in humans. An in vitro study of human adipocytes from prepubertal non-obese children investigated the effect of BPA on gene expression in adipocytes, disclosing an increase in pro-inflammatory cytokines involved in the lipid metabolism and a decrease in a gene involved in insulin production.[105] As mentioned in the mechanisms paragraph phthalates and bisphenols are reported to interfere with PPARs and RXRs, potentially causing epigenetic changes. RXRs form heterodimers using its nuclear receptor with all members of the class 1 nuclear receptors, including PPARs, but also the vitamin D3 receptor and the thyroid hormone receptor. Several drugs and mechanisms are claimed to interfere with the nuclear receptor from RXRs.[106, 107] However, little is known about the interaction mechanisms. Overall, very few studies have been investigating the mechanisms

of phthalates and bisphenols combined with clinical outcomes in humans. More studies are needed investigating mechanisms and potential.

This review shows several limitations in the present literature, especially regarding time of exposure. One of the main limitations is the inconsistent exposure-response relationship in almost all studies performed so far, causing non-differential misclassification of exposure leading to underestimation of the effect. Only one study controlled for puberty, while the degree of puberty could be an important modifier of effects. Only one study described in this review investigated the effects of exposure to BPS, while all other studies only examined BPA. Exposure to BPF has not been studied at all. As shown in the paragraph on maternal pregnancy outcomes, studies on maternal pregnancy outcomes are scarce, in particular studies investigating the effect of phthalates. Studies investigating prenatal exposure to phthalates and bisphenols and metabolic outcomes are lacking, just as studies investigating prenatal exposure to bisphenols and childhood cardiovascular outcomes. The cardiovascular effects of prenatal phthalates have only been examined in one study; therefore it is difficult to draw conclusions. Adult studies on delayed effects of prenatal and childhood exposure to phthalates and bisphenols are lacking. Due to the long effect latency this might be harder to investigate.

In total, 54 studies are included in this review, of which the majority uses urinary samples to estimate phthalate or bisphenol exposure. Eight cohort studies collected more than one urine sample during pregnancy,[6, 59, 60, 72, 76-78, 99] of which 3 studies collected additionally childhood urine samples.[6, 78, 99] Only three of these multi-sample studies during pregnancy did not take the average of measured concentrations, but analyzed the samples separately, trying to find windows of vulnerability.[6, 60, 99] An overview of the included studies and their strengths and weaknesses is presented in Table 1.

Concluding, the human evidence for effects of these chemicals is suggested but limited by methodological difficulties that complicate interpretation. However, an underestimation of effect is most likely. Future studies should focus on also the newer phthalates and bisphenols investigated in a distinct range of time with preferably multiple urine samples to reveal windows of sensitivity for the various biomarkers of effect. When windows of sensitivity during pregnancy would be uncovered, future parents could be informed through preconceptional consults or in early pregnancy. Moreover, to gain a better understanding in the effects, more studies are needed investigating the mechanisms and its potential interactions preferably combined with clinical outcomes. Furthermore, to provide more evidence on prolonged health effects epigenetics should be included in future studies in order to guide evidence-based prevention of harmful exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AR	androgen receptor
BBzP	butylbenzyl phthalate
BMI	body mass index
BPA	bisphenol A
BPAG	bisphenol A monoglucuronide
BPAS	bisphenol A sulphate
BPF	bisphenol F
BPS	bisphenol S

DBP	di-n-butyl phthalate
DEHP	di-2-ethylhexylphthalate
DEP	di-ethyl phthalate
DiDP	di-isodecylphthalate
DiNP	di-isononylphthalate
DnOP	di-n-octylphthalate
DMP	di-methyl phthalate
DOHaD	Developmental Origins of Health and Disease
E2	estradiol
EDC	endocrine disrupting chemical
ER	estrogen receptor
FFA	free fatty acid
GMD	gestational diabetes mellitus
HDL	high-density lipoprotein
HMW	high molecular weight
HOMA-IR	homeostatic model assessment of insulin resistance
IGF-1	insulin-like growth factor 1
LMW	low molecular weight
MiBP	mono-isobutyl phthalate
MBzP	monobenzyl phthalate
MECPP	mono(2-ethyl-5-carboxypentyl) phthalate
MEHHP	mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate
NHANES	National Health and Nutrition Examination Survey
PPAR	peroxisome proliterator-activated receptor
PVC	polyvinyl chloride plastics
RXR	retinoid X receptor
UGT	UDP-glucuronosyltransferase

Highlights

- Early exposure to bisphenols and phthalates may have a great influence on health

- In a large part of the investigated outcomes studies show contradictory results

- Most evidence is based on single sampling studies neglecting time-variant effects
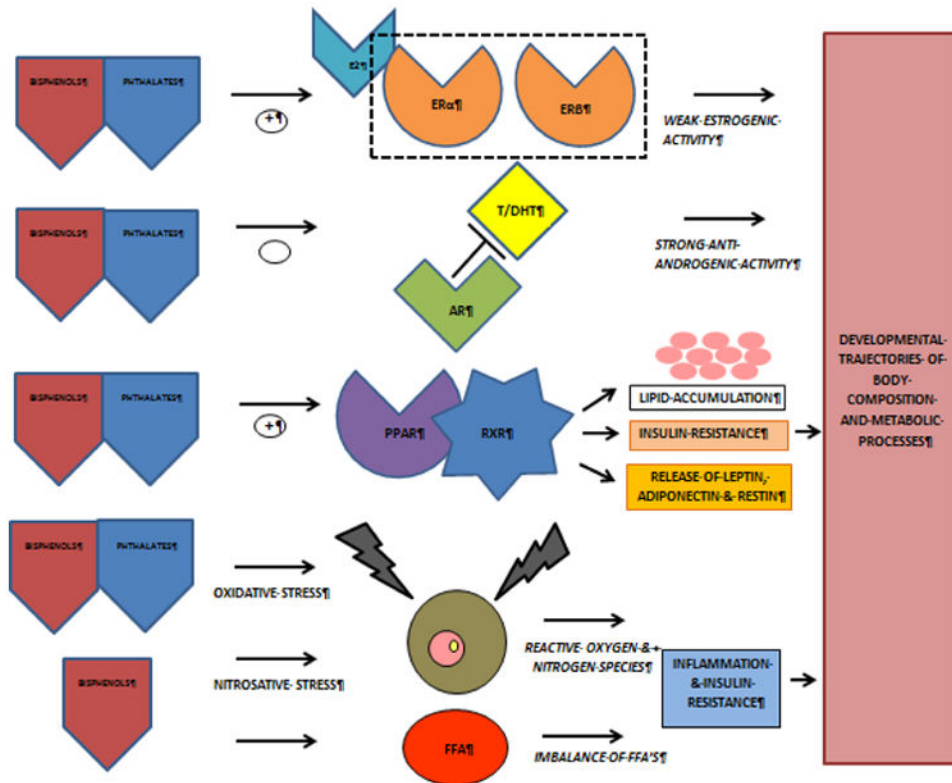
Figure 1. Potential mechanisms of effect
ERα: estrogen receptor alpha ; ERβ: estrogen receptor beta ; E2: estradiol ; AR : androgen receptor ; T/DHT: testosterone / dihydrotestosterone ; PPAR: peroxisome proliferator-activated receptors ; RXR: retinoid X receptors ; FFA: free fatty acids.
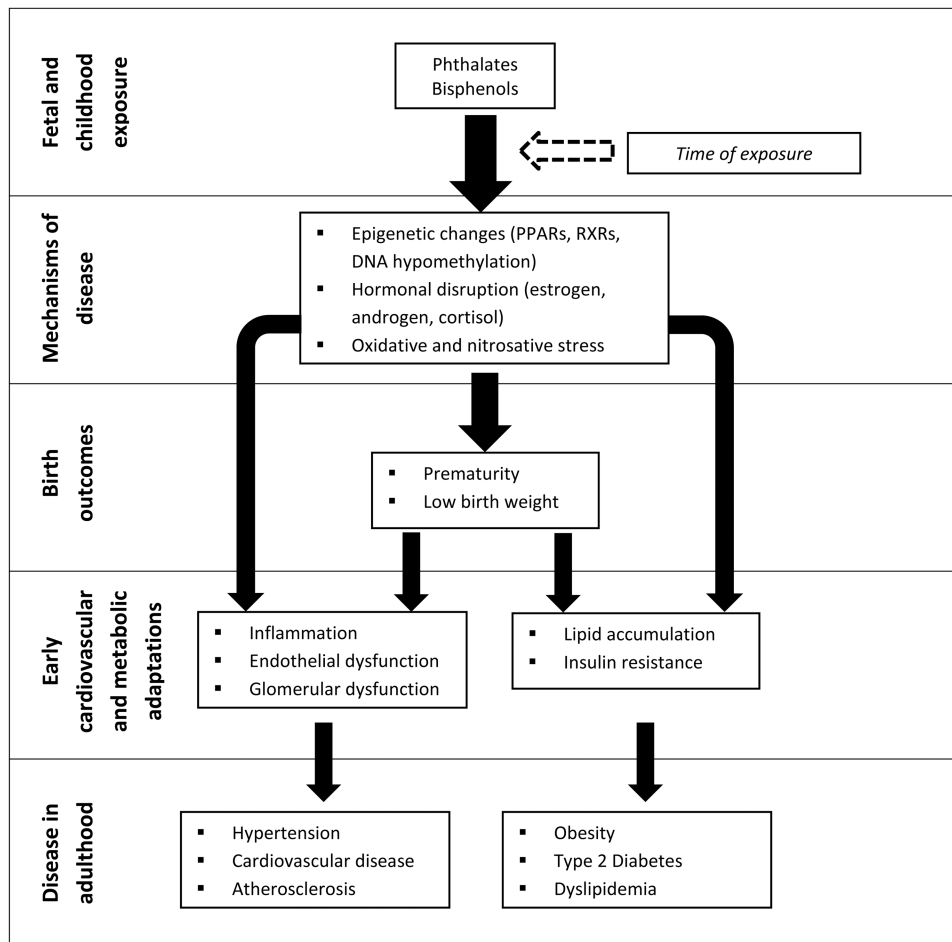
Figure 2.
Exposure to phthalates and bisphenols is believed to induce pathways towards several adverse health effects, including epigenetic changes, hormonal disruption, oxidative and nitrosative stress. Effects could be affected by the time of exposure, both during fetal life and childhood. Fetal exposure has been linked with prematurity and low birth weight. Childhood exposure has been associated with early signs of cardiovascular and metabolic dysfunction. Both prematurity and low birth weight have also been associated with cardiometabolic dysfunction. Therefore, both fetal and childhood exposure may give rise to an increased risk of cardiovascular and metabolic disease in adulthood.

Table 1

Overview of the included studies per outcome

Outcome	Phthalates and/or bisphenols	Sample size	Time of exposure	Associations	Outcome	Strenghts (S)/Weaknesses (W)
MATERNAL PREGNANCY OUTCOMES						
Time to Pregnancy[47-48]	Phthalates	200I[47] 501[48]	First trimester[47] Preconceptional inclusion[48]	Positive / negative / null	One pregnancy cohort found no association between first trimester phthalates and recalled time to pregnancy.[47] A preconceptional cohort found several phthalates to be associated with longer time to pregnancy in males, while other phthalates were associated with shorter time to pregnancy in females.[48]	S: 1 preconceptional cohort study, couples with infertility/sterility excluded, urinary samples adjusted for urinary dilution, the preconceptional study explored both males and females W: 1 retrospective analysis in a cohort study based on recalled data.
	BPA	200I[47] 501[48]	First trimester[47] Preconceptional inclusion[48]	Null	One pregnancy cohort found no association between first trimester BPA and recalled time to pregnancy.[47] A preconceptional cohort found no associations between BPA and time to pregnancy. [48]	S: 1 preconceptional cohort study, couples with infertility/sterility excluded, urinary samples adjusted for urinary dilution, the preconceptional study explored both males and females W: 1 retrospective analysis in a cohort study based on recalled data
Miscarriage risk[49-50]	BPA	115[49] 50[50]	First trimester[49-50]	Positive	Both studies found a positive association between the level of BPA and (recurrent) aneuploidy and euploid miscarriages.[49,50]	S: 1 cohort study, only unknown etiology of miscarriages included W: 1 case-control study, blood samples instead of urinary samples
Maternal blood glucose, triglycerides and fatty acid levels[51-53]	Phthalates	72[52] 318[53]	First trimester[52] Second trimester[53]	Negative	Women in the highest tertile of urinary MiBP and MBzP had lower blood glucose levels at time of routine GMD screening	S: 2 cohort studies, quite accurate about the time of sampling W: Only one sample, 1 study with blood samples, regarding triglycerides and fatty acids only DEHP and MEHP measured

Outcome	Phthalates and/or bisphenols	Sample size	Time of exposure	Associations	Outcome	Strenghts (S)/Weaknesses (W)
					compared to women in the lowest tertile. [52] Maternal serum MEHP concentrations were associated with lower triglyceride and fatty acid levels during pregnancy.[53]	
	BPA	94[51]	Third trimester[51]	Null	No association between BPA and gestational diabetes mellitus was found. [51]	S: Accurate about time of sampling W: Case-control study, only one urinary sample
Preeclampsia [54]	BPA	58	Before delivery and umbilical cord blood	Positive	Preeclamptic women have significantly higher concentrations of BPA in placental tissue compared to normotensive pregnant women, while concentrations in serum and cord blood did not differ significantly.[54]	S: Placental biopsies W: Case-control study, blood samples instead of urinary samples, only BPA measured
FETAL OUTCOMES						
Gestational age at birth[55-65]	Phthalates	283[55] 404[56] 86[57] 207[58] 482[59] 482[60] 84[61] 60[62] 72[63]	First trimester[55] Third trimester[56,62] Shortly postpartum or cord blood[57,58,61] Four samples over pregnancy[59-60] Term not specified[63]	Mainly negative	Six studies found a significant association between phthalate exposure and gestational age reduction or preterm delivery.[58-63] One study found no association [58] and two studies found a positive correlation between phthalate exposure and gestational age at delivery.[55, 56]	S: All (subsets from) cohort studies, mainly urinary samples used all corrected for dilution, the majority of studies reported information on gestational age estimation W: Only 2 studies multiple sampling, sampling often taken over broad time, sampling time in one study not specified, various outcome measures used
	BPA	404[56] 72[63] 567[64] 60[65]	Third trimester[56,65] Term not specified[63] Before delivery[64]	Mainly negative	Three studies found a significant association between BPA and gestational age reduction [63-65] of which in one this association	S: All cohort studies or subsets from cohort studies, mainly urinary samples used all corrected for dilution, the majority of studies reported information on gestational age estimation

Outcome	Phthalates and/or bisphenols	Sample size	Time of exposure	Associations	Outcome	Strenghts (S)/Weaknesses (W)
					only remained in male infants after stratification for gender.[63] One study found no associations.[56]	W: No multiple sampling, sample often taken over a broad period of time, sampling time in one study not specified, various outcome measures used
Body size measures at birth[53,56–58,64,66–73]	Phthalates	318[53] 404[56] 86[57] 207[58] 126[66] 119[67] 201[68]	Second trimester[53] Third trimester[56,66,67] Shortly postpartum or cord blood[57,58,68]	Mainly negative	Four studies found a negative effect of phthalates on body size measures at birth.[58,66-68] One study found no associations.[53] Two studies found positive associations between LMW phthalates and head circumference at birth.[56,57]	S: The majority of studies were cohort studies or subsets from cohort studies, based on urinary samples corrected for dilution W: No multiple sampling, sample often taken over a broad period of time
	BPA	404[56] 567[64] 520[69] 550[70] 97[71] 219[72] 737[73]	Second trimester[69,70] Third trimester[56, 73] Before delivery[64, 71] Cord blood[71] Three samples over pregnancy[72]	Mainly null, study with repeated measurements negative	Four studies found no associations. [56,64,69,70] Two studies, including a study with up to 3 measurements during pregnancy, found a negative association between BPA exposure and body size measures at birth.[71,72] One study found a positive association between BPA and birth weight in male neonates and ponderal index in female neonates. [73]	S: The majority of studies were cohort studies or subsets from cohort studies, based on urinary samples corrected for dilution. One study collected up to three samples W: The majority of studies collected only one sample, which was often taken over a broad period of time.
CHILDHOOD OUTCOMES						
Childhood growth, prenatal exposure[6,69, 74–78]	Phthalates	89[74] 234[75] 391[76]	Cord blood[74] Third trimester[75] First & third trimester[76]	Boys: negative Girls: positive	All three studies found prenatal exposure to phthalates to be associated with reduced BMI in boys. Additionally, one of the studies found also a reduced fat mass and waist circumference in	S: All studies were cohort studies, 1 study with repeated sampling, one of the studies collected additionally multiple childhood samples, urinary samples corrected for dilution W: Study with multiple urinary samples did not analyse the measurements separately but averaged the results, 1 smaller study with cord blood

Outcome	Phthalates and/or bisphenols	Sample size	Time of exposure	Associations	Outcome	Strenghts (S)/Weaknesses (W)
					boys, not girls.[75] In one of the studies prenatal exposure to phthalates was associated with a higher BMI in girls.[76]	
	BPA	402[6] 520[69] 402[77] 297[78]	First & second trimester[6] Second trimester[69,78] First & third trimester[77]	Positive / negative	Two studies showed that prenatal BPA exposure had a negative effect on BMI in girls, not boys.[6, 78] After stratification for puberty stage in one of these studies, only in prepubertal girls prenatal BPA exposure remained negatively associated with BMI and waist circumference.[6] Two studies, of which one consisted only of boys, reported a positive effect of prenatal BPA exposure on several growth parameters, including height adjusted weight (not significant), waist circumference and BMI.[69,77]	S: All studies were cohort studies with urinary samples, 3 studies collected two pregnancy samples, two of the studies collected additionally multiple childhood samples, all except for one study corrected for urinary dilution, one study performed sensitivity analyses for BPA measurements by trimester W: Studies with multiple urinary samples did not analyse the measurements separately but averaged the results
Childhood growth, childhood exposure [6,75,78-93]	Phthalates	234[75] Not specified [79] 493[80] 259[81] 387[82] 2884[83] 845[84] 90[85] 76[86]	Toddlers till adolescence[86] Preschoolers[75] Preschool till mid childhood[84] Mid Childhood[80,82,85] Mid childhood till adolescence[79,81,83]	Mainly positive, most for boys	Five studies found a positive effect of childhood exposure to phthalates on childhood growth parameters, including BMI, subscapular skinfold thickness, hip-and waist circumference, predominantly found in boys.[79-83] Two studies found no associations.[85,86] Two studies found a	S: All included studies collected urinary samples of which 1 study with multiple childhood samples, all samples were corrected for dilution

Outcome	Phthalates and/or bisphenols	Sample size	Time of exposure	Associations	Outcome	Strenghts (S)/Weaknesses (W)
					negative association between childhood exposure to phthalates and mid-childhood growth, including, BMI, BSA, weight and height.[75,84]	
	BPA BPS	402[6] 297[78] 90[85] 76[86] 39[87] 80[88] 259[89] 2838[90] 3370[91] 2200[92] 1326[93]	Toddlers till adolescence[86] Preschool till mid childhood[87,93] Mid childhood[85,88] Mid childhood till adolescence[89-92]	Mainly positive, not enough evidence to draw conclusions for BPS	Six studies found a positive effect of childhood exposure to BPA on childhood growth parameters measured from preschool till adolescence, including BMI, waist-to-height ratio and hip circumference. [6,89-93] One study found that early childhood exposure was associated with a lower BMI at the age of two, but BMI slopes increased more rapidly between 2 and 5 years of age.[78] No clear difference between the sexes. Two studies found no associations. [87,88] Two studies found a negative association between childhood exposure to BPA and BMI. [85,86] One of these studies also investigated BPS, but no associations were found.[86]	S: All included studies collected urinary samples of which 2 studies with multiple childhood samples, all samples were corrected for dilution, one study also included the newer bisphenol BPS
Cardiovascul ar risk, prenatal exposure, outcome measured during childhood[76]	Phthalates	391[76]	First & third trimester	Negative	In girls the molar sum of both HMW and LMW phthalates were significantly associated with lower systolic blood pressure z-score. No	S: Cohort study with two maternal urinary samples, reasonable follow-up, samples corrected for urinary dilution W: Urinary samples were averaged in the analysis, only phthalates measured, only blood pressure as a cardiovascular risk outcome

Outcome	Phthalates and/or bisphenols	Sample size	Time of exposure	Associations	Outcome	Strengths (S)/Weaknesses (W)
Cardiovascular risk, childhood exposure and outcome[87,94-96]					studies have been performed on bisphenols.	
	Phthalates	2838[94] 667[96]	Mid childhood till adolescence[94,96]	Positive	Both studies reported a positive link between phthalate exposure during childhood and adverse cardiovascular outcomes, including systolic blood pressure z-score and increased albuminuria.[94,96]	S: Childhood urinary samples corrected for urinary dilution, 1 study on blood pressure, 1 on albuminuria W: 2 cross-sectional studies, no studies with multiple sampling
	BPA	39[87] 770[95]	Preschool till mid childhood[87] Mid childhood till adolescence[95]	Positive	Both studies showed also a positive association between childhood BPA exposure and adverse cardiovascular outcomes, including increased albuminuria and in boys an increased diastolic blood pressure.[87,95]	S: Childhood urinary samples corrected for urinary dilution, 1 study on blood pressure, 1 on albuminuria. W: 1 cross-sectional and one small case study, no studies with multiple sampling, one study measured also lipid levels but did not report on that outcome.
Metabolic risk, childhood exposure and outcome[87-88,91,97-99]	Phthalates	766[97] 356[98]	Adolescence[97,98]	Positive	Both studies found a positive association between childhood HMW phthalate exposure, mainly DEHP, and the newer DINP and insulin resistance.[97,98]	S: Both studies based on urinary samples corrected for urinary dilution W: No multiple sampling, both cross-sectional studies
	BPA	39[87] 80[88] 3370[91] 188[99]	Preschool till mid childhood[87] Mid childhood[88,99] Mid childhood till adolescence[91]	Mainly null	One study showed a negative association between childhood BPA exposure and fasting insulin and insulin resistance, unfortunately not adjusted for urinary dilution.[87] Three studies did not find any associations between BPA and childhood metabolic outcomes.[88,91,99]	S: All studies collected urinary samples corrected for urinary dilution, except for one all studies used insulin resistance as an outcome measure W: No multiple sampling