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Environmental contaminants and preeclampsia: A systematic literature review

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Abstract

Preeclampsia is a medical condition specific to pregnancy characterized by high blood pressure and protein in the woman's urine, indicating kidney damage. It is one of the most serious reproductive conditions, posing substantial risks to the baby and potentially fatal for the mother. The causes of preeclampsia are largely unknown and environmental contaminants merit further investigation. The aim of this review was to determine the association between environmental chemical exposures and preeclampsia.PubMed was searched for articles examining *a priori* chemical exposures and preeclampsia through April 2018. Studies were included in our review if they included at least 10 cases, evaluated preeclampsia independent of gestational hypertension, and used either measured or modeled exposure assessments.Our review contained 28 investigations examining persistent organic pollutants (POP) (6 studies), drinking water contaminants (1 study), atmospheric pollutants (11 studies), metals and metalloids (6 studies), and other environmental contaminants (4 studies). There were an insufficient number of investigations on most chemicals to draw definitive conclusions, but strong evidence existed for an association between preeclampsia and cadmium (Cd). There is suggestive evidence for associations between nitrogen dioxide (NO_2), particulate matter $(PM)_{2.5}$, and traffic exposure with preeclampsia.There is evidence for an association between preeclampsia and Cd but insufficient literature to evaluate many other environmental chemicals. Additional studies using repeated measures, appropriate biological matrices, and mixtures methods are needed to expand this area of research and address the limitations of previous studies.

Keywords

preeclampsia; environmental exposures; maternal health

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Conflicts of interest: none

Introduction

Preeclampsia is one of the leading causes of maternal mortality globally with an estimated prevalence of approximately 2–8% (Khan et al 2006; Duley 2009). Nearly 99% of maternal deaths resulting from pregnancy or childbirth complications occur in low- and middle-income countries, and an estimated 10–15% of those deaths are associated with preeclampsia and eclampsia (Lerberghe et al 2005; Duley 1992; Khan et al 2006). Although maternal mortality is lower in high-income countries such as the United States, preeclampsia and eclampsia are still associated with approximately 10–15% of maternal deaths (Ananth et al 1995). Even after the resolution of pre-eclamptic pregnancy, women face increased risk of cardiovascular events later in life (Irgens et al 2001; Mongraw-Chaffin et al 2010; Ahmed et al 2014; Kestenbaum et al 2003). A meta-analysis involving 43 studies identified elevated risk for cerebrovascular disease (OR: 2.28 [95% confidence interval (CI): 1.87, 2.78]), stroke (OR: 1.76 [95% CI: 1.43, 2.21]), and hypertension (RR: 3.13 [95% CI: 2.51, 3.89]) for women with a history of pre-eclampsia or eclampsia (Brown et al 2013). Further, Williams (2011) suggested that women may also be at an increased long-term risk of diabetes mellitus, kidney disease, thromboembolism, hypothyroidism, and impaired memory. In addition, a preeclamptic pregnancy poses risks for the fetus including preterm birth and all corresponding conditions, neonatal thrombocytopenia, and restricted fetal angiogenesis (Backes et al 2011).

The clinical definition and diagnosis of preeclampsia has changed relatively little in the last 60 years and is primarily characterized by new onset or worsening hypertension (blood pressure greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic). Prior to 2013, new-onset significant proteinuria at or after 20 weeks' gestation (excretion of ≥300 mg of protein in urine during a 24-hr urine collection, or protein/creatinine ratio ≥0.3) was required for diagnosis. However, the definition has expanded so that in combination with hypertension, any of the following (at or after 20 weeks' gestation) are sufficient for diagnosis: new-onset thrombocytopenia (platelet count <100,000/microliter), impaired liver function (abnormally elevated blood concentrations of liver enzymes and/or severe persistent right upper quadrant or epigastric pain), renal insufficiency (serum creatinine ≥1.1 mg/dl or a doubling of the serum creatinine concentration), pulmonary edema, or visual or cerebral disturbances (ACOG 2013).

However, our understanding of the complex etiology for this heterogeneous syndrome has grown in the last several decades. It is now widely accepted that preeclampsia may be explained in a two-model system. The first stage is associated with poor placentation and an incomplete remodeling of the uteroplacental spiral arteries that occurs in the first half of pregnancy (Pijnenborg et al 2006). The second stage is manifestation of maternal signs of the condition that arises from factors released by the placenta as it is placed under increasing amounts of oxidative stress (Redman and Sargent 2005). While this is the case for many preeclamptic episodes, not all preeclampsia originates from a compromised placenta and Redman and Sargent (2005) hypothesized that in some women the issue is an abnormal maternal response to an otherwise normal pregnancy termed "maternal preeclampsia". Evidence for this heterogeneity exists throughout the literature (Roberts and Von Versen-Hoeynck 2007; Eskenazi et al 1993; Roberts and Hubel 2009; Powers et al 2012), but

Redman and Staff (2015) proposed an alternative placental-derived explanation for the "maternal preeclampsia" subtype, which is defined by a rise in syncytiotrophoblast stress.

What is also becoming increasingly apparent is that there are many routes to developing clinical definitions of preeclampsia and most likely the final disorder arises from different interactions between environmental and genetic factors both from the mother and placenta (Valenzuela et al 2012; Williams and Broughton Pipkin 2011). Further, there are most likely different sub-types of preeclampsia that need to be identified and analyzed separately (Phipps et al 2016). Interestingly, the role common environmental contaminants may play has been extensively overlooked as both potential contributors and as modifiable targets.

Environmental contaminants may interfere with trophoblasts, cells that invade the mother in order to help establish the placenta (Goldman-Wohl and Yagel 2002). Inhibition or interference of the trophoblast migration may contribute to poor placentation, the postulated first stage of preeclampsia development (Goldman-Wohl and Yagel 2002). Both animal studies and *in vitro* evidence suggests that exposure to certain environmental contaminants may adversely affect trophoblasts, thus contributing to preeclampsia etiology (Bechi et al 2013; Fowler et al 2012).

This systematic literature review identified and summarized epidemiological studies that assess the relationship between environmental chemicals and preeclampsia. Tables are provided to summarize key study components, illustrate strengths and limitations of these studies, draw conclusions from the available data, and present recommendations for future work. To our knowledge, this constitutes one of the first comprehensive reviews of environmental exposures during pregnancy in relation to preeclampsia. Previous reviews on environmental toxicants, ambient air pollution, cadmium (Cd), and lead (Pb) in association with preeclampsia have been recently published (Kahn and Trasande 2018; Pedersen et al 2014; Poropat et al 2018; Pollack et al 2014).

However, the previous review of environmental contaminants was not comprehensive. The present review expands on the findings by 1) addressing additional exposures including air pollutants and drinking water contaminants; 2) providing more extensive descriptions of possible mechanisms of action; and 3) evaluating the strengths and limitations of the included studies. Lead was not included in this review due to the recent systematic review by Poropat et al (2018) and lack of new investigations since publication. Results from the review suggest strong evidence for an association between lead and preeclampsia. This review evaluates persistent organic pollutants (POP), drinking water contaminants, air pollutants, metals including arsenic (As), Cd, chromium (Cr) and mercury (Hg), and non-persistent environmental pollutants.

Methods

Selection Criteria

To organize the comprehensive summary, environmental contaminants were divided into 5 broad categories based upon a previously published systematic literature review of environmental contaminants and preterm birth (Ferguson et al 2013). The list included POP,

drinking water contaminants, atmospheric pollutants, metals and metalloids, and other environmental contaminants. Chemical classes in the previous review were selected to capture a comprehensive list of environmental contaminants. The specific chemicals included in our scope are listed in Supplemental Table 1. Literature was searched using the 12 POP initially identified by the Stockholm Convention (United Nations Environment Programme 2008a). Our atmospheric pollutant search was based around EPA's 6 criteria pollutants. Additional search terms were included based upon classes identified in the Ferguson et al (2013) review. Search terms for drinking water contaminants and other environmental pollutants were also based upon the Ferguson et al (2013) paper. Based upon previous literature on environmental metal exposures, an additional *a priori* list of toxic metals was selected (Jaishankar et al 2014; Tchounwou et al 2012). Dietary metals were not included as papers tended to focus on effects of supplementation rather than deleterious environmental exposures.

It is uncertain whether preeclampsia and gestational hypertension are on a spectrum of the same disease or are diseases with different etiologies (Steegers et al 2010; Shen et al 2017). However, it was felt that the science pointed to the latter. For that reason, there was a focus on studies where authors considered preeclampsia as a distinct outcome, not in combination with gestational hypertension. Studies that examined gestational hypertension in combination with preeclampsia were not included in this review, resulting in the exclusion of three studies. Other inclusion criteria included at least 10 identified cases and directly measured or modeled exposure values. Studies were excluded if exposure was self-reported.

Search Strategy

PubMed was searched through April 19, 2018 using both the MeSH terms in combination with "preeclampsia" and the free terms listed in Supplemental Table 1. During preliminary searches, systematic literature reviews and meta-analyses on various individual environmental exposures and preeclampsia were identified. Investigations that were included in these reviews were not evaluated individually in this review. Results from the meta-analyses and systematic reviews were discussed in the text but not included in the tables.

Data Screening and Extraction

Titles and abstracts to be considered for review were screened. After the initial screening, the full text was read of those that met the inclusion criteria. Data extraction spreadsheets were created to extract the following relevant information: study design, location, and sample size; exposure measurement approach and timing; exposure levels; and modeled associations and reported measures of associations.

Results and Discussion

Among the 1,267 articles identified by PubMed, 28 satisfied our inclusion criteria. The characteristics of the included studies are summarized in Tables 1–5. Relevant systematic reviews on preeclampsia and air pollution (Pedersen et al 2014), and cadmium (Cd) (Pollack et al 2014) were identified and included in this review.

Chemicals were considered water contaminants if water is the main and typical exposure route. Two studies were found in which chemicals leached into the water following an industrial contamination incident, but ingestion of contaminated water is not the main exposure pathway for most individuals (Stein et al 2009; Savitz et al 2012). Those studies were discussed in the section corresponding to their compound class, rather than treating them as water contaminants.

Briefly, the 28 investigations were published between 2006–2018 with sample sizes ranging from 58 to 1.21 million women. There were 6 studies on POP (Eslami et al 2016; Murray et al 2018; Savitz et al 2012; 2014; Stein et al 2009; Starling et al 2014), one study on water contaminants (Carwile et al 2014), 11 investigations on air pollutants (Dadvand et al 2014; Lee et al 2013; Madsen et al 2017; Mendola et al 2016; Nahidi et al 2014; Pedersen et al 2017; Savitz et al 2015; Wang et al 2018b; Wesselink et al 2017; Wu et al 2016; Yorifuji et al 2015), 6 examining metals (Elongi Moyene et al 2016; Maduray et al 2017; Sandoval-Carrillo et al 2016; Laine et al 2015; Wang et al 2018a; Vigeh et al 2006), and 4 investigations evaluating non-persistent organic pollutants (Cantonwine et al 2016; Leclerc et al 2014; Ye et al 2017; Shaw et al 2018).

Out of the included studies, 12 were case-control or nested case-control, 12 were either prospective or retrospective cohort investigations, three were cross-sectional, and one was case-cohort. For studies using biomarkers, chemicals were analyzed from matrices of serum, plasma, urine, pubic hair, placenta, maternal blood, and cord blood. Five out of the 28 investigations, primarily studies of metals, compared chemical levels or crude measures among groups, while the other 23 modeled associations as odds ratios (OR), hazard ratios (HR), or risk ratios (RR). The timing of the exposure assessment ranged from modeled exposures during the conception period to delivery. The investigations were conducted in various locations including Africa, North America, Europe, and the Middle East. The majority of studies adjusted for covariates, primarily maternal age, pre-pregnancy body mass index (BMI), gestational age, and a socioeconomic indicator. Some investigations adjusted for smoking status while other excluded smokers from their sample. Most but not all studies excluded women with a history of hypertension or chronic high blood pressure. Some additional investigations excluded women if they had other chronic health conditions or a family history of preeclampsia.

The majority of studies defined preeclampsia using American College of Obstetricians and Gynecologists' (ACOG) 2013 guidelines, although some investigations employed ICD9 or ICD10 codes from medical records and a few others used self-report. ACOG defines proteinuria as excretion of ≥300 mg during a 24-hr period or a protein/creatinine ratio ≥0.3, but some investigators utilized a single urine dipstick measure, a protein/creatinine ratio ≥0.2, or 300 mg/dl urine. Unless other measures are not available, a dipstick reading is discouraged due to its variability (ACOG 2013).

Persistent Organic Pollutants (POP)

Persistent organic pollutants are organic chemical substances that remain in the environment for years, are widely distributed, bioaccumulate, and produce adverse effects to the environment and human health (United Nations Environment Programme 2008c). These

chemicals may be intentionally produced or released as byproducts, and are used for pest control, agriculture, and industrial processes (Environmental Protection Agency 2009). POP include organochlorine pesticides such as dichlorodiphenyltrychloroethande (DDT) and hexachlorocyclohexane (HCH); flame retardants like polybrominated diphenyl ethers (PBDEs); polychlorinated biphenyls (PCB) which are used in transformers, capacitors and electrical equipment; and perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), used in everyday materials like carpets, cookware, and food packaging.

Due to their known human health and environmental risks, over 150 countries signed on to the Stockholm Convention, a 2001 treaty aimed at eliminating or restricting the use of some of the most toxic POP (United Nations Environment Programme 2013). The chemicals of interest may be placed into three categories: pesticides (aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, toxaphene); industrial chemicals (hexachlorobenzene, PCB); and byproducts (hexachlorobenzene, dioxins, furans, and PCB). Although these compounds remain in the environment, it is important to note that the measures taken at the Stockholm Convention have resulted in declining environmental levels (Hung et al 2010; Schuster et al 2011; Venier and Hites 2010). Subsequently, levels of many POP measured in humans have been decreasing in recent years (Bjerregaard-Olesen et al 2017; Mannetje et al 2013; Fang et al 2015).

Although there are limitations in determining biologic plausibility from animal or *in vitro* studies, there is a dearth of experiments investigating mechanisms in humans. An investigation demonstrated that PFOA reduced the expression of hormones associated with trophoblasts and reduced trophoblast cell frequency in mice, but this study did not provide any information about how the dosage given to the mice compares with human exposures (Suh et al 2011). Similarly, PCB may induce abnormal growth within *in vitro* placental vasculature (Dubey et al 2000) and PBDE-47 increases reactive oxidative species generation in the human trophoblast cell line (Park et al 2014).

PCB & PBDE—Polychlorinated biphenyls (PCB) are a family of chlorinated hydrocarbons that were historically used in industrial and commercial products (Hu et al 2016; Agency for Toxic Substances and Disease Registry 2000). Due to evidence of dangers to the environment and human health, the U.S. ceased production of PCB in 1977 (Agency for Toxic Substances and Disease Registry 2000). However, because PCB are difficult to break down and persist in the environment, humans are still exposed.

Polybrominated diphenyl ether (PBDE) are structurally similar to PCB and were employed as flame retardants in commercial products (Siddiqi et al 2003). Similarly to PCB, these compounds were released into the environment at industrial manufacturing sites and regularly leached from household products (Siddiqi et al 2003).

Only one study to date examined the association between PBDE exposure and preeclampsia. In a case-control study by Eslami et al (2016), Iranian women diagnosed with preeclampsia displayed higher serum concentrations of total PCB and total PBDE compared to controls (Table 1). Preeclampsia cases were ascertained by two specialist physicians who considered women preeclamptic if they met ACOG's criterion for hypertension and exhibited any

degree of proteinuria. In models controlling for gestational age, pre-pregnancy BMI, and weight gain, Eslami et al (2016) measured OR of 1.77 (95% CI: 1.34, 2.32) for total PCB and OR of 2.19 (95% CI: 1.39, 3.45) for total PBDE, but the investigators did not account for the contrast associated with these results. In this population, the median level of total PCB for cases was 2.86 ng/g and 1.50 ng/g for controls; the median level for total PBDE was 1.51 ng/g among cases and 0.95 ng/g among controls (Eslami et al 2016).

Conversely, a study by Savitz et al (2014) found no marked association between total PCB exposure and preeclampsia. The effects of PBDE were not investigated. Using a large cohort of American women from the 1960s, Savitz et al (2014) noted that total PCB exposure appeared slightly protective against the development of preeclampsia, although these measures did not reach statistical significance. The median level of total PCB in this population was 2.69 μg/L (Savitz et al 2014). Cases were determined using ACOG's guidelines, with information presumably derived from medical record abstraction. Although necessitated by study design, it should be noted that the limitations of medical record documentation and abstraction may affect the accuracy of diagnoses.

Eslami et al (2016) suggested that these results may disagree due to differences in the sample size, analytic approach, continuous vs. categorical measures of exposure, and exclusion criteria. Further, the two studies combined different congeners of PCB to estimate cumulative exposure to PCB. While summing may be useful, this limits comparison across studies. Eslami et al (2016) generated the total PCB measured by summing 9 congeners, whereas Savitz et al (2014) summed 11 congeners. Eslami et al (2016) combined the following congeners to create the total PCB measure: 28, 52, 99, 101, 118, 138, 153, 180, and 187. The combined measure in Savitz et al (2014) consisted of PCB 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, and 203.

It is possible that single congeners or subtypes of congeners such as dioxin-like vs. non-dioxin-like may be driving the association and combining multiple congeners into a "total PCBs" measure may obfuscate the relationship. Consistency of congeners measured and sufficient power to investigate the influence of specific congeners are needed to clarify the discrepancies surrounding this research question. In addition, total PCB and dioxins are fairly correlated within populations (Gladen et al 1999). Without measuring levels of both compounds, it is difficult to discern true associations. Further, samples in Eslami et al (2016) were lipid-adjusted while Savitz et al (2014) included triglycerides and cholesterol as covariates. For this reason, it is not possible to directly compare exposure distributions in these populations. There is no decisive evidence of a correlation between preeclampsia and PCB and PBDE and further research is warranted.

DDT & HCH—In the 1970s, the United States Environmental Protection Agency (US EPA) banned DDT, a powerful insecticide, due to evidence suggesting adverse effects on humans and the environment (Hanssen et al 2013). However, DDT continues to be used to combat malaria in South America, Africa, and Asia (van den Berg 2009). DDE is a metabolite of DDT that persists and might also exert harmful health effects (van den Berg 2009).

Similar to DDT, HCH is an insecticide. HCH exists as 8 isomers, one of which lindane, an insecticidal form that has not been produced in the United States since 1976 but is still available as an imported product (Agency for Toxic Substances and Disease Registry 2005). β-HCH is an isomer that was employed in technical-grade HCH, a product that has not been produced or used in the U.S. for over 20 years (Agency for Toxic Substances and Disease Registry 2005). However, detectable levels persist in soil and surface water at some locations throughout the U.S. (Agency for Toxic Substances and Disease Registry 2005). Humans are exposed to HCH through ingestion of contaminated food, water, and inhalation of contaminated air, or through some medications utilized to control scabies and head lice (Agency for Toxic Substances and Disease Registry 2005).

In the previously discussed study by Savitz et al, (2014) the association between ß–HCH, p,p'-DDE, p,p'-DDT and preeclampsia was also determined. The median level of DDE in the population was 24.5 μg/L; DDT exposure 9.25 μg/L; and median ß–HCH 1.39 μg/L. In a quintile analysis, the OR for DDE and DDT were null, although DDT presented some suggestions of an inverse relationship. Savitz et al (2014) did not provide the exposure levels used to create these quintiles. Associations between ß–HCH and preeclampsia were null. Savitz et al (2014) indicated that rather than a true underlying protective effect, their results may be more likely attributed to random error, unrecognized biases, or reverse causation.

A study of South African women examined the correlation between p,p'-DDT, p,p'-DDE, o,p'-DDT, and physician-diagnosed preeclampsia based upon medical records (Murray et al 2018). Case count was relatively low but null associations were seen for all 3 compounds. The median level of DDE in this population was 239 ng/g lipid and the median level of p,p-DDT was 52.5 ng/g lipid. Based upon very limited data, there does not appear to be a correlation between DDE, DDT, or HCH and preeclampsia.

PFAS—Per- and polyfluoroalkyl substances (PFAS) are a class of non-naturally occurring chemicals that are widely utilized in textiles and leather products, metal plating, semi-conductors, paper and packaging, coating additives, cleaning products, pesticides, among others (Environmental Protection Agency 2017). PFOA and PFOS are two types of PFAS that have historically been produced in the largest quantities in the U.S. (Environmental Protection Agency 2017) and although production has declined, exposure is still widespread due to their persistence (Environmental Protection Agency 2017; National Institute of Environmental Health Sciences 2016). Levels of other PFAS were detected in humans, but exposure is lower and less research is available on their health effects (Berg et al 2014; Agency for Toxic Substances and Disease Registry 2018; Mueller and Yingling 2017).

Two studies were conducted using highly-exposed participants in the Mid-Ohio Valley as part of the C8 Science Panel (Stein et al 2009; Savitz et al 2012). Both investigations were limited to self-reported measures of preeclampsia. While Stein et al (2009) measured serum PFOA and PFOS levels, Savitz et al (2012) generated historical estimates of PFOA exposure based upon the amount of PFOA released from the DuPont plant, wind patterns, river flow, groundwater flow, and participants' residential histories. Savitz et al (2012) did not consider PFOS in their study. Stein et al (2009) found modest associations between PFOA and preeclampsia (OR: 1.3 [95% CI: 0.9, 1.9]) and PFOS and preeclampsia (OR: 1.3 [95% CI:

1.1, 1.7]) when comparing women above the median of exposure vs. women below. The median PFOA exposure was 21.2 ng/ml while the median PFOS level was 13.6 ng/ml. In a quartile analysis, the relationship with PFOA was primarily driven by women in the 50–75th percentage (2nd quartile) of exposure (OR: 1.5 [95% CI: 1.0, 2.3]) rather than those in the highest group. The women in the 2nd quartile of exposure contained levels of 21.3 – 50 ng/ml while women in the 4th quartile levels ranging from 120.6 ng/ml – 894.4 ng/ml (Stein et al 2009). The association between PFOS and preeclampsia was strongest for women exposed >90th percentile (4th quartile; 23.2 – 83.4 ng/ml) and those exposed in the 50th-75th percentile (2nd quartile; 12.7– 17.7 ng/ml), but not significantly attenuated among women in the 75th-90th percentile (3rd quartile; 17.7 – 23.2 ng/ml). Savitz et al (2012) observed modest associations with PFOA estimates. Median PFOA levels varied by exposure year, but the highest median levels were noted for those who were exposed from 2000 – 2005 and were measured at 15.9 ng/ml. No significant dose-response trend was identified using a continuous exposure indicator. When Savitz et al (2012) used the measured levels from 2005–2006 to inform their modeled exposures, the observed relationship was strengthened.

A case-cohort study utilizing the Norwegian Mother and Child Cohort (MoBa) noted null HRs for preeclampsia in association with PFOA and PFOS (Starling et al 2014). The median level of PFOA was 2.78 ng/ml while the median level of PFOS was 12.87 ng/ml. Preeclampsia was determined by birth attendants at delivery and an antenatal review of medical records. Proteinuria was not defined employing ACOG's 24-hr urine collection, but rather as a urine dipstick measurement of at least 1+. It is of interest that Starling et al (2014) found inverse effects in which higher concentrations of perfluoroundecanoic acid (PFUnDA) were correlated with a lower hazard of preeclampsia. Starling et al (2014) were not able to explain these unexpected findings. The discrepant results between the C8 investigations and the MoBa study may be attributed to significantly higher levels in the C8 population, or the fact that the C8 investigation relied upon modeled exposure data and self-reported preeclampsia, whereas Starling et al (2014) determined levels in women and used validated preeclampsia diagnoses.

Drinking Water Contaminants

Although many contaminants enter the drinking water supply and may pose a health risk, certain chemicals are more likely to end up there either due to their chemical properties or their uses. Chlorinated disinfection byproducts are produced during the process of utilizing chlorine to treat drinking water, but exposure to hazardous byproducts has been linked to adverse reproductive outcomes (Gopal et al 2007; Nieuwenhuijsen et al 2000). No apparent studies on chlorinated disinfection byproducts and preeclampsia were identified. Chlorinated solvents are another class of common water contaminants, used in many commercial and industrial applications and thus among the most common pollutants at industrial sites (Matteucci et al 2015). Tetrachloroethylene (PCE) and trichloroethylene (TCE) are frequently used as metal degreasers and PCE is also employed in dry-cleaning facilities (Agency for Toxic Substances and Disease Registry 2014). PCE and TCE are some of the most frequently detected organic chemicals in groundwater and their ability to penetrate deep into aquifers creates risks of widespread groundwater contamination (Moran et al 2007).

Although few data are available on the effects of water contaminants and placental function, limited evidence from *in vitro* investigations suggests potential consequences. Results from one study by Hassan et al (2016) reported that a bioactive intermediate of TCE increased pro-inflammatory cytokines, leading to disruptions in trophoblast functions necessary for placental development. However, concentrations used in the study by Hassan et al (2016) were a magnitude higher than the US EPA's maximum contaminant level standard for drinking water for TCE. Chen et al (2004) examined bromodichloromethane, a trihalomethane, and found that exposure disrupted syncytiotrophoblast formation. The lowest concentrations noted to disrupt formation were 200 mM, while human concentrations have been documented at 0.0013 nM to 0.57 nM (Chen et al 2004; Miles et al 2002).

Only one epidemiological study on drinking water contaminants was identified. It examined the association between PCE and preeclampsia in a retrospective cohort of 1,766 women living in Cape Cod between 1969–1983 (Table 2) (Carwile et al 2014). Residents were exposed to PCE-containing water through contaminated distribution pipes. Exposure was assigned retrospectively, first using crude pipe distribution maps. Among those women identified as potentially exposed, exposure was assigned more finely with leaching transport models. These models calculated the woman's cumulative PCE exposure during the year of her last menstrual period. In 2002–2003, women self-reported any preeclamptic pregnancies occurring during 1969–1983. In multivariate models, higher levels of PCE were correlated with lower risk of self-reported preeclampsia. Compared to women with no exposure, women with levels above the median (0.57 g) exhibited a RR of 0.36 (95% CI: 0.12, 1.07) and females with any reported levels also displayed a lower risk than those with no exposure (RR: 0.37, [95% CI: 0.17, 0.83]). However, there were only 8 women with PCE exposure and preeclampsia, and thus it is difficult to draw conclusions from this limited sample. Further, all measures of outcome were self-reported.

Air Pollutants

Criteria pollutants are 6 common air pollutants with known adverse health effects that are monitored and regulated by the EPA. These include ground level ozone (O_3), particulate matter (PM_{10} and $PM_{2.5}$), carbon monoxide (CO), lead (Pb), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) (Environmental Protection Agency 2018).

Results from previous *in vitro* studies suggest biologic plausibility between air pollutant exposure and placental changes associated with or leading to preeclampsia. Polycyclic aromatic hydrocarbons (PAH), specifically benzo(a)pyrene (BaP), have been associated with inhibition of migration and invasion of human trophoblast cells (Liu et al 2016). Although the doses used in the study (1, 5, 10, 25, 50 or 100 μM) were higher than average female dietary dose (0.07 μg/day) (Marti-Cid et al 2008), it was argued that dietary levels may not explain the full body burden due to other exposure routes and the lipophilicity and long half-life of BaP. While *in vitro* studies are helpful in identifying biological mechanisms, these investigations are conducted in isolation and may not accurately represent processes in the overall organism.

In an epidemiologic study of Brazilian women, NO_2 was associated with a decreased vascular index (Hettfleisch et al 2017). Further, van den Hooven et al (2012) reported

correlations between maternal air pollution exposure and markers of placental growth and function.

Pedersen et al (2014) and Hu et al (2014) both independently published systematic literature reviews and meta-analyses examining the association between air pollutants and preeclampsia. Pedersen et al (2014) reviewed 16 studies and Hu et al (2014) reviewed 10 investigations; all but one of the studies reviewed by Hu et al (2014) was also included in the Pedersen et al (2014) paper. For that reason, the Pedersen et al (2014) paper will serve as the focus of this discussion. The one study not included in the Pedersen et al (2014) paper was evaluated in this present review. Of the 16 studies reviewed by Pedersen et al (2014), 10 examined exclusively preeclampsia rather than a combination of gestational hypertension and preeclampsia.

In the recent review, Pedersen et al (2014) compiled the following exposures: $PM_{2.5}$ and PM_{10}; NO_2; nitrogen oxides (NO_x); CO; O_3; proximity to major roads, and traffic density. Four studies examined $PM_{2.5}$ and NO_2 and three studies assessed NO_x, PM_{10}, CO, O_3, and traffic. Pedersen et al (2014) reported pooled OR using random effects models of the exposures. Significant associations were seen between preeclampsia and $PM_{2.5}$, NO_2, and traffic. Although point estimates tended to be elevated, no significant correlations associations were observed between NO_x, PM_{10}, CO, or O_3 and preeclampsia. However, heterogeneity was relatively high between studies for $PM_{2.5}$ and CO (82 and 83.4%, respectively).

As noted by Pedersen et al (2014), limitations of these meta-analyses include the small number of investigations, inclusion of studies that assessed exposure only in the first trimester, exclusion of data that did not distinguish between gestational hypertension and preeclampsia, and possible underreporting of cases. Since the publication of the reviews, 11 additional studies were found that met our inclusion criteria (Table 3).

A retrospective cohort study in New York City noted no marked association between $PM_{2.5}$ or NO_2 and preeclampsia (Savitz et al 2015). In fact, slight protective associations were observed for both compounds in relation to mild and severe preeclampsia. The median $PM_{2.5}$ level for the 2^{nd} trimester was 11.67 $\mu g/m^3$ while the 2^{nd} trimester median for NO_2 was 26.44 ppb. Preeclampsia was ascertained using ICD-9 discharge diagnoses. However, Savitz et al (2015) noted concerns regarding differential reporting and disease coding across multiple hospitals. Results were similar whether modeling exposure in the first trimester or second trimester.

Similarly, null results for NO_2 levels were reported in a retrospective investigation of the MoBa cohort where the mean level was 13.6 $\mu g/m^3$ (Madsen et al 2017). Cases of preeclampsia were identified through a standardized form completed during pregnancy, often by midwives or obstetricians. Diagnostic criteria for preeclampsia on this form matched the ACOG hypertension and proteinuria cutoffs. There was no significant association with NO_2 exposure and preeclampsia in selected urban and county areas across Norway. However, risk was increased for women living near (<15 m) highly trafficked roads. Three other studies also demonstrated no marked association with NO_2 (Mendola et

al 2016; Wang et al 2018b; Nahidi et al 2014). In these studies, NO_2 levels were higher: the median level in the study by Mendola et al (2016) was 29.1 ppb, while the mean level in the Wang et al (2018b) cohort was 45.9 μg/m^3. Population levels were not reported by Nahidi et al (2014).

Two studies, however, demonstrated significant associations between NO_2 and higher risk of developing preeclampsia (Pedersen et al 2017). A large investigation from the Danish National Cohort found the strongest effects for mild preeclampsia and early-onset preeclampsia with more limited results for severe preeclampsia (Pedersen et al 2017). In this study, the median level of exposure was 11 μg/m^3 and preeclampsia cases were ascertained from the Danish National Patient Registry using ICD-10 codes, a method shown to have acceptable validity (Klemmensen et al 2007). An investigation involving 1.21 million birth records in China reported a significant association between PM_{10}, SO_2, and NO_2 exposure and preeclampsia (Wang et al 2018b). In this study, preeclampsia was diagnosed based upon a blood pressure reading >140/90 mm Hg and 30 mg/dl protein in urine or 1+ on two or more urine dipsticks. It was not specified whether this information was provided by obstetricians directly or later abstracted from medical records. Levels of PM_{10} were approximately 2-fold higher than those noted by Mendola et al (2016). Interestingly, Wang et al (2018b) demonstrated strong interactive effects between humidity (measured by dew point) and the influence of PM_{10} on preeclampsia: preeclampsia risk enhanced by nearly 25% when dew point was between 5^{th} – 95^{th} percentile but by 30% when dew point was > 95^{th} percentile. Other studies identified suggestive associations between air pollution and hypertensive disorders of pregnancy, but lacked clinically-diagnosed outcomes or ascertainment of preeclampsia independent of general hypertensive disorders of pregnancy (Hu et al 2017; Agrawal and Yamamoto 2015).

There is mixed evidence for the effect of PM on preeclampsia, but PM_{10} appears to exert higher risks than $PM_{2.5}$. There was no significant association with PM_{10} or $PM_{2.5}$ and preeclampsia in a retrospective US cohort (Mendola et al 2016). Diagnosis of cases was performed through medical records and/or maternal discharge summary abstraction using ICD-9 codes. Dadvand et al (2014) did not observe an association with overall PM mass, but when PM mass originated from traffic-related exposure sources, there was a significant association with an interquartile range (IQR) rise in PM_{10}. No enhanced risk was noted with $PM_{2.5}$. Similarly, Dadvand et al (2014) found an increased risk with exposure to brake dust for PM_{10} but not $PM_{2.5}$. In this investigation preeclampsia cases were defined using a blood pressure reading ≥140/90 mm Hg and proteinuria ≥300 mg/dl. The means of ascertainment for these data were not discussed.

Mendola et al (2016) examined additional criteria pollutants and found no marked association with preeclampsia and CO, NO_x, O_3, or SO_2. Although few studies looked at CO or O_3, the findings from those investigation coupled with data from the Pedersen et al (2014) review suggest that there is no significant association between either exposure and preeclampsia (Lee et al 2013; Nahidi et al 2014; Mendola et al 2016). Lee et al (2013) identified cases through a medical records database that collects detailed information on reproductive outcomes, while preeclampsia cases were self-reported in Nahidi et al (2014).

The null findings among the criteria pollutants are consistent with Savitz et al (2015) and Madsen et al (2017). Evidence for a relationship between SO_2 and preeclampsia was only seen among the Chinese population where exposure levels were much higher than elsewhere, and not in an USA or Iranian population (Mendola et al 2016; Nahidi et al 2014; Wang et al 2018b). The median level was 15.6 $\mu g/m^3$ in the Chinese population and 3.3 ppb in the US population.

Mendola et al (2016) reported no significant correlation between PAH and preeclampsia. However, multiple positive associations were observed between volatile organic compounds (VOC) and preeclampsia. Among the VOC, the strongest effects were seen with exposure to xylenes and toluene. Across the exposures, the effects were generally stronger among asthmatic women compared to non-asthmatic. No other apparent studies measured VOC or PAH.

Four studies examined traffic exposure and three of these used proximity to major roadways as their exposure metric (Yorifuji et al 2015; Wesselink et al 2017; Wu et al 2016; Madsen et al 2017). These investigations considered the overall effect of traffic exposure rather than attempting to separate individual pollutants. The findings differed across studies. With elevated traffic exposure, Wu et al (2016) noted an elevation in late-onset preeclampsia compared to early-onset, but also that controls were subject to increased traffic exposure compared to cases. Cases in this study were women who were being treated for preeclampsia, but no further information regarding diagnostic criteria was provided.

Yorifuji et al (2015) and Madsen et al (2017) noted elevated traffic exposure among cases, although the measures in Madsen et al (2017) did not reach statistical significance. In the study by Yorifuji et al (2015), preeclampsia was determined by trained obstetricians as hypertension with proteinuria after 20 weeks gestation. No marked effect was seen by Wesselink et al (2017) although case count was low and they relied on self-reported outcome. Approximately 26% of women in this investigation reported smoking during the first trimester.

The literature on the association between air pollution and preeclampsia is not definitive, with many discordant results noted. Differences may be due to varying baseline exposure levels in populations, and there may be a minimum exposure level necessary to induce effects. Further, different methods were employed to model pollutant exposure: studies used various methods including fitting spatiotemporal models based upon street-level measures (Savitz et al 2015), a combination of modelled air pollution exposures utilizing non-concurrent measurements of air pollution combined with concurrent temporal variability from monitoring stations (Madsen et al 2017), actual determinations from daily monitors (Wang et al 2018b), and space-time ordinary kriging interpolation (Lee et al 2013). These models have various strengths and limitations and the extent to which model specifics may have affected results remains unclear.

Metals and metalloids

Metals and metalloids, such as As, Cd, and Hg, are naturally occurring elements and often have industrial, domestic, and agricultural uses (Jaishankar et al 2014; Tchounwou et al

2012; Barbosa 2017; da Cunha Martins et al 2018). Most human exposure is from anthropogenic sources such as mining and smelting operations, industrial production, agricultural use of metals, and from consumption of water or food contaminated by such processes (Jaishankar et al 2014; Tchounwou et al 2012; Barbosa 2017; Branco et al 2017).

There is biologic plausibility for a relationship between metals and development of preeclampsia. Studies found that both Cd and Cr exerted deleterious effects on trophoblasts (Henson and Chedrese 2004; Stasenko et al 2010; Banu et al 2017), and that expression levels of an As transporter were elevated in placentae from preeclamptic mothers (Damiano et al 2006; Henson and Chedrese 2004). Seven epidemiologic studies were reviewed analyzing the association between our *a priori* metals and preeclampsia.

Arsenic (As)—Arsenic is a metalloid that naturally occurs in soil and until 2003, was used in wood preservatives (Agency for Toxic Substances and Disease Registry 2007). Humans are typically exposed through inhalation and ingestion; the primary food sources include seafood, rice/rice cereal, mushrooms, and poultry (Agency for Toxic Substances and Disease Registry 2007). Arsenic from industrial waste or agricultural fertilizers may contaminate ground water, leading to additional exposure through consumption of well water (Centers for Disease Control and Prevention 2015).

Three studies examined As exposure in relation to preeclampsia: two case-control studies and a cross-sectional study (Table 4a) (Elongi Moyene et al 2016; Sandoval-Carrillo et al 2016; Maduray et al 2017). Both case-control investigations measured As levels in urine, while one additionally determined metal concentrations in local drinking water (Elongi Moyene et al 2016; Sandoval-Carrillo et al 2016). Elongi Moyene et al (2016) measured a panel of 14 trace metals for 176 women in the Democratic Republic of Congo (DRC) and matched on age, gestational age, type of pregnancy (singleton vs. higher-order), and number of live-born children. Preeclampsia was defined as blood pressure >140/90 mm Hg and a positive dipstick test or >300 mg protein over 24 hr. It was not stated how this information was obtained.

Sandoval-Carrillo et al (2016) conducted their study among 306 Mexican women and adjusted for maternal age and gestational age. The characterization of hypertension matched that described by ACOG, but they had a less stringent criterion for urinary protein levels which was considered as 30 mg/dl protein sufficient for preeclampsia diagnosis while ACOG required 300 mg/dl. This difference may have resulted in an over-diagnosis of preeclampsia. Sandoval-Carrillo et al (2016) did not provide detail on the source of diagnostic information.

Exposure levels were different in two of the study populations; women in the DRC contained higher median As levels (46.9 μg/L among cases and 26.8 μg/L among controls) compared to the Mexican study (7.1 μg/L among cases and 6.78 μg/L among controls) (Sandoval-Carrillo et al 2016). The third study population determined concentrations in different matrices and thus levels are not directly comparable.

Elongi Moyene et al (2016) reported that As levels were higher in cases than controls, both overall and when stratified on season (dry vs. rainy). Sandoval-Carrillo et al (2016) in Mexico, however, observed no marked association with As, either in crude comparisons of mean levels or in adjusted logistic models. In the logistic models, authors compared women in the highest tertile of exposure (>11.49 μg/L) to women in the lowest tertile (≤7.50 μg/L). Sandoval-Carrillo et al (2016) postulated that their null findings were due to the low concentrations in their population; indeed, levels in this study were lower than those in other investigations where associations with other reproductive outcomes (fetal death, low birth weight) were identified.

The third study, a cross-sectional analysis performed in a homogenous cohort of black South Africans, noted no significant difference between As levels in cases and controls (Maduray et al 2017). This population was overweight, where cases exhibited an average BMI of 31 kg/m^2 and controls a mean BMI of 43 kg/m^2. No information was provided on the criteria or means of ascertainment for preeclampsia diagnoses. Maduray et al (2017) determined concentrations in blood and pubic hair and did not specify the timing of exposure measurements. Blood is not the preferred matrix for As detection, as it primarily detects recent high-dose exposures (Hughes 2006). Further, hair measurements are susceptible to exposure from other sources such as bathing in contaminated water; current methods are not able to distinguish between externally and internally derived arsenic in hair (Hughes 2006). These concentrations are not directly comparable to urinary measures and thus it is difficult to relate exposure levels among this population to the previous two studies. All three studies measured total As rather than speciated metal. Speciated As is preferred as it provides additional information regarding the As content, as total As may reflect benign organic As compounds commonly found in seafood (Kales et al 2006). Although research is limited, higher levels of As do not appear to be associated with preeclampsia.

Cadmium (Cd)—Similar to As, Cd is naturally occurring; however, this metal also enters the environment through anthropogenic means. Non-ferrous metal mining and refining, fossil fuel combustion, waste incineration, and manufacture and application of phosphate fertilizers are some of the main sources of environmental Cd (Agency for Toxic Substances and Disease Registry 2012). Smokers are primarily exposed through inhalation of Cd that accumulates in tobacco leaves, while non-smokers are predominantly exposed through consumption of contaminated foods, particularly leafy vegetables, potatoes and grains, peanuts, and soybeans (Agency for Toxic Substances and Disease Registry 2012).

A 2014 systematic review of the epidemiologic evidence for the relationship between cadmium levels and reproductive health outcomes identified three studies that met their inclusion criteria and investigated preeclampsia (Pollack et al 2014). Two of the investigations were cross-sectional, only one adjusted for potential confounders, and one examined preeclampsia at 37–40 weeks, likely missing the most severe cases. Although these studies had limitations, all three found an association between elevated maternal Cd levels and preeclampsia.

Four additional investigations were identified (Table 4b). Laine et al (2015) used a nested case-control design and assessed Cd amounts in the placenta. Preeclampsia was defined as

hypertension and proteinuria according to the ACOG guidelines, but Laine et al (2015) did not provide information on whether this data was abstracted from medical records or provided directly from physicians. After adjustment, Laine et al (2015) observed that higher placental Cd levels were associated with preeclampsia. Two additional studies, described above for their examination of As, also measured Cd (Maduray et al 2017; Elongi Moyene et al 2016). Maduray et al (2017) noted no marked difference between median blood Cd concentrations measured in preeclamptic and control women. Elongi Moyene et al (2016) detected higher levels in cases than controls when metal was measured in urine. Elongi Moyene et al (2016) examined correlations and found that Cd was significantly associated with many metals including As, Cr, cobalt (Co), nickel (Ni), and selenium (Se). However, none of the models attempted to account for these correlations.

A 2018 case-control study conducted in a Chinese medical center identified an elevated risk of preeclampsia with elevated maternal blood concentrations of Cd, when metal levels were measured between the 28^{th}-40^{th} week of pregnancy (Wang et al 2018a). In this study, Wang et al (2018a) defined preeclampsia using the hypertension guidelines of ACOG, and proteinuria defined in any of the following ways: urine protein greater than 300 mg/24 hr; one positive dipstick; or a protein/creatinine ratio >0.3. In addition, preeclampsia was diagnosed if women exhibited new-onset hypertension and any of the following conditions in place of proteinuria: thrombocytopenia; serum creatinine >97.3 μmol/L; liver transaminases at least 2-fold greater than the upper limit of normal; pulmonary edema; or persistent cerebral or visual symptoms. Mean Cd concentrations were higher in cases than controls and Wang et al (2018a) also detected an association in a logistic regression adjusting for BMI, maternal age, parity, gestational age at sample collection, and maternal calcium and magnesium levels. Women in the highest tertile of exposure (≥1.36 μg/L) were compared to women in the lowest tertile of exposure (<0.93 μg/L). Wang et al (2018a) also compared levels of placental Cd and reported higher levels among controls compared to cases (3.61 μg/kg wet weight vs. 4.28 μg/kg wet weight).

The above studies employed different matrices to determine Cd, including placenta (Laine et al 2015), hair (Maduray et al 2017), serum (Maduray et al 2017; Pollack et al 2014), blood (Wang et al 2018a; Pollack et al 2014), urine (Elongi Moyene et al 2016), and amniotic fluid (Pollack et al 2014). Cadmium measured in whole blood or serum reflects recent exposure rather than body burden, while urinary concentrations primarily reflect total body burden and are preferred (Agency for Toxic Substances and Disease Registry 2012). Concentrations in hair are useful for measuring relatively long-term Cd quantities, although samples are susceptible to external contamination (Agency for Toxic Substances and Disease Registry 2012). Some evidence shows that the placenta is a reliable indicator of Cd exposure (Piasek et al 2014), but a systematic review concluded that the use of placenta to assess heavy metal exposure is not yet properly developed (Esteban-Vasallo et al 2012).

Chromium—In 1997, nearly 31 million pounds of hexavalent chromium (Cr VI) were released from large processing facilities into soil in the U.S., accounting for approximately 94% of total environmental metal releases (Agency for Toxic Substances and Disease Registry 2011). Additional sources of Cr exposure include airborne emissions and effluents from chemical plants and incineration facilities, road dust from catalytic converter erosion,

and consumer products such as stainless steel cookware or wood treated with copper dichromate (Agency for Toxic Substances and Disease Registry 2011, 2012).

Only two studies examining the link between maternal Cr levels and preeclampsia were identified, both of which measured other metals that were described earlier in this review (Table 4c) (Maduray et al 2017; Elongi Moyene et al 2016). Elongi Moyene et al (2016) observed that urinary Cr concentrations in cases were approximately 5-fold higher than controls. Similarly, Maduray et al (2017) found higher concentrations of Cr in cases when this metal was measured in both pubic hair and serum, even though only measurements in hair reached statistical significance.

Urinary measures of Cr are limited by frequent contamination, inability to distinguish between benign Cr(III) and toxic Cr(VI), and the fact that these only reflect the prior 48 hr exposure (Environmental Protection Agency 2010). Similarly, concentrations determined in hair cannot distinguish between Cr bound within the hair during protein synthesis from external contamination (Environmental Protection Agency 2010). Chromium has been previously measured in hair of populations with no known environmental metallic exposure, indicating that measurements in hair may also reflect Cr bound within the hair during protein synthesis (Agency for Toxic Substances and Disease Registry 2013). Chromium determined in blood may be differentiated into Cr(III) and Cr(VI) utilizing specific analytic methods, but it is unclear if Maduray et al (2017) used these techniques (Agency for Toxic Substances and Disease Registry 2013). Despite the shortcomings of the measurements in these studies, the concordant results suggest that elevated Cr concentrations may be associated with preeclampsia.

Mercury (Hg)—Mercury might enter the environment through the natural breakdown of minerals in rocks and soils, but estimates put anthropogenic contributions at 1/3 to 2/3 of total Hg releases (Agency for Toxic Substances and Disease Registry 1999). Atmospheric levels of Hg are low and most human exposure occurs through consumption of fish containing methylmercury, the major source of organic Hg for humans. Less commonly, individuals are exposed to Hg through imported jewelry, dental fillings, or consumer products such as thermometers, barometers, and switches (Agency for Toxic Substances and Disease Registry 1999).

Only one study analyzing Hg and preeclampsia was identified (Table 4e) (Vigeh et al 2006). This study involved 396 Iranian women who had no occupational exposure to trace metals and Hg was determined in maternal whole blood. Preeclampsia was diagnosed according to ACOG guidelines, although Vigeh et al (2006) did not provide information on how diagnoses were conducted. Only mean levels of Hg were compared, but there was no marked difference in concentrations between cases and controls. Mercury measured in blood reflects recent exposure to both organic and inorganic metal, but does not provide information regarding past exposures (United Nations Environment Programme 2008b). Hair is often the preferred matrix as it provides an estimate of long-term average exposure (United Nations Environment Programme 2008b). Although this study does not seem to support an association, there is a large gap in the knowledge regarding Hg exposure and preeclampsia.

Other environmental contaminants

In contrast to POP, non-persistent pollutants possess a shorter lifespan in the environment. Non-persistent environmental contaminants such as non-persistent pesticides, bisphenol-A (BPA), and phthalates do not accumulate in humans. However, these compounds may still present health dangers due to the ubiquity of exposures (Centers for Disease Control and Prevention 2018; Environmental Protection Agency 2013). Phthalates are a group of plasticizers that are also used in products such as cosmetics, personal care items, medical tubing, and solvents. Individuals are primarily exposed through use of personal care products or consumption of food and drinks that have been in contact with phthalates (Hauser and Calafat 2005; Centers for Disease Control and Prevention 2017).

Similarly, BPA is non-persistent but widely produced (National Institute of Environmental Health Sciences 2018). BPA is primarily employed in the production of polycarbonate plastics, often used for food and drink packaging. As such, diet is the largest source of BPA exposure for most, although air, dust, and water exposures are also possible (National Institute of Environmental Health Sciences 2018). Most persistent pesticides were banned in the U.S. in the 1970s, and since that time, non-persistent pesticides have increased in usage (Centers for Disease Control and Prevention 2003). Non-persistent pesticides do not accumulate and thus need to be applied more frequently.

In both rodent models and human cell lines, BPA exposure was associated with adverse alterations to trophoblasts, suggesting a possible mechanism for preeclampsia development (Tachibana et al 2007; Benachour and Aris 2009). Further, some phthalate metabolites were associated with decreases in placental growth factor in human populations (Ferguson et al 2015).

One study was identified looking at phthalate exposure and BPA exposure in relation to preeclampsia (Cantonwine et al 2016), while another two examined solely BPA exposure (Ye et al 2017; Leclerc et al 2014) (Table 4). Cantonwine et al (2016) conducted a nested case-control study assessing the correlation between 9 urinary phthalate metabolites and BPA in relation to preeclampsia. Cantonwine et al (2016) measured exposure levels at multiple visits and found significant associations between the averaged values of mono (2-ethylhexyl) phthalate (MEHP) as well as summed di(2-ethylhexyl) phthalate (∑DEHP) metabolites, both per IQR rise, and preeclampsia. No marked associations were detected for the other urinary phthalate metabolites and there was no correlation between BPA exposure and preeclampsia. However, upon stratifying by infant gender, there was an elevation in the HR for BPA levels at visit 1 among females compared to males. The geometric mean of BPA in this population at visit 1 was 1.34 ng/ml. Cantonwine et al (2016) reviewed women's deidentified medical records to identify cases of preeclampsia. Women were considered to display preeclampsia according to ACOG's hypertension guidelines, and proteinuria defined as >300 mg/24 hr or a protein/creatinine ratio >0.2.

Leclerc et al (2014) conducted a case-control study among nulliparous women to examine the relationship between BPA and preeclampsia and observed higher placental BPA levels in pre-eclamptic women compared to controls. However, no marked differences were noted in BPA levels in maternal serum or fetal serum between pre-eclamptic and normotensive

women. Leclerc et al (2014) did not provide information on the diagnostic criteria of pre-eclamptic women nor the means by which the diagnosis was performed.

Ye et al (2017) conducted a nested case-control study involving Chinese women in which determined free BPA in maternal serum. Data on preeclampsia was abstracted from medical records and women were considered cases if they met ACOG's diagnostic criteria. In contrast to Leclerc et al (2014), significantly higher maternal serum BPA concentrations were detected in cases compared to controls (median: 3.4 μg/L vs. 1.5 μg/L). The results remained significant in a logistic model after adjusting for maternal age, parity, and BMI. Further, women with mild preeclampsia possessed significantly higher BPA concentrations than women with severe preeclampsia (median: 5.2 μg/L vs. 1.8 μg/L).

One study investigating the association between non-persistent pesticide exposure and preeclampsia was identified. It was conducted in the San Joaquin Valley of California and did not detect any elevated risk among exposure to 543 pesticides and preeclampsia (Shaw et al 2018). Exposure was assigned using mother's residential address at the time of delivery, pesticide use reporting records, and land-use surveys. Shaw et al (2018) characterized pesticide use within 500 meters of the mother's residential address at each month of pregnancy and one month prior to conception. Preeclampsia cases were diagnosed using ICD-9 codes. When comparing any gestational pesticide exposure vs. none, no OR above 1 reached statistical significance when stratifying on preeclampsia phenotype (superimposed, severe, mild) and timing of preeclampsia (weeks 20–31 vs. weeks 32–36). Exposure was examined one month prior to conception and each subsequent month of pregnancy. Results were similarly null when Shaw et al (2018) stratified by chemical class. Given their large number of comparisons, Shaw et al (2018) indicated that they expected more elevated OR by chance than they actually observed.

Strengths, Limitations, and Recommendations

The strengths of the reviewed texts varied, but the majority of studies excluded women with preexisting hypertension or a history of high blood pressure. Many studies also excluded women with chronic metabolic or renal disease, and others excluded women with any chronic disease. Other strengths were specific to the class of chemical evaluated. For example, all POP studies accounted for lipophilicity of compounds when needed. In addition, because the investigations on air pollution modeled exposure rather than measuring it directly, investigators were able to select exposure windows that preceded outcome. Both the studies on air pollution and data resulting from the C8 contamination event had large sample sizes. The use of biomarkers, when used appropriately, allows for precise measurement of exposure levels.

There were a number of overarching limitations identified in the literature reviewed. Firstly, exposure and outcome assessment may have been subject to misclassification bias in several ways. In certain studies, outcome was ascertained through self-report (Stein et al 2009; Savitz et al 2012; Carwile et al 2014; Nahidi et al 2014; Wesselink et al 2017) instead of physician diagnosis, potentially affecting the validity of outcome measures. Over-reporting

of outcome after a high-profile environmental disaster such as the contamination incident in the Mid-Ohio is of particular concern.

Diagnostic strategies differed across studies, both in terms of the criteria for preeclampsia diagnoses and the way in which those criteria were evaluated and/or ascertained. Diagnosis by an obstetrician or midwife is preferred, as they are considered the gold standard for accuracy of preeclampsia diagnoses. Preeclampsia diagnoses ascertained from ICD codes might result in an overestimate of true cases. Similarly, information abstracted from medical records may be less accurate if abstractors are not trained in the nuances and specifics of preeclampsia. There were some minor differences in diagnostic criteria across studies; some utilized dipstick measurements for diagnosis of proteinuria. ACOG notes that when coupled with hypertension, a dipstick reading of 1+ suggests preeclampsia, but this method has both many false-positive and false-negative readings and should be used only in the absence of quantitative measures (ACOG 2013).

Studies with self-report of exposure were excluded from our review, but among the included investigations, exposure was measures in different ways with varying degrees of predicted accuracy. In one study, measures of PFOA exposure were reconstructed instead of measured directly (Savitz et al 2012). However, a similar but more sophisticated model yielded modeled exposure levels that were highly correlated with determined levels, mitigating concerns of significant exposure misclassification (Shin et al 2011).

As is the case with most large air pollution studies, exposure was measured through models. None of the studies measured air pollution using personal monitoring devices and exposure was instead assigned using geographic information such as residential address or hospital referral region. These methods do not capture information on where women spend their time, potential exposure to indoor pollutants, occupational exposures, or mobility during the study period. Although some studies were able to capture both spatial and temporal variation, others relied only on single monitoring sites. Moreover, others still did not possess women’s addresses and thus forced to assign exposures as city-wide averages or by referral region. Further, few studies assigned exposures in a way that accounted for meteorological factors and instead assumed that air pollution concentrations measured at each station reflected regional exposures. Finally, one investigation required use of temporal back-extrapolation of exposure because air pollution sampling was performed retrospectively (Madsen et al 2017), and another study provided little information regarding how exposure was assigned (Nahidi et al 2014). Three studies measured traffic pollution, a measure that comprises both air pollutants and noise. Some evidence suggests that noise may also be associated with preeclampsia risk, and therefore the findings do not solely represent the association between air pollutants and preeclampsia.

When levels were measured directly using biomarkers, the most appropriate matrix was not always utilized. For example, 4 investigations using 7 different matrices evaluated Cd levels in relation to preeclampsia, but urine, the preferred matrix, was only utilized once. Because studies by Elongi Moyene et al (2016) and Maduray et al (2017) tested many metals from the same samples, it was not possible to select the most relevant matrix and thus

concentrations for some metals are more reliable measures of long-term exposure than others.

Of the three studies on BPA, two of them determined exposure in serum (Ye et al 2017; Leclerc et al 2014), while Cantonwine et al (2016) assessed exposure in urine. Urine is the preferred biological matrix and a recent commentary noted that although BPA, phthalate diesters, and their metabolites can be measured in serum, these determinants are not valid measures of exposure (Calafat et al 2013). Conjugated BPA is a more valid exposure biomarker than free BPA, but conjugated BPA is only present to a significant degree in urine. Because two of the investigators collected serum samples, they were not able to measure conjugated BPA (Ye et al 2017; Leclerc et al 2014). Given the inaccuracies of measuring BPA in blood, data from these two studies may be of questionable validity. Cantonwine et al (2016) performed their measurements in urine, ensuring the most accurate concentrations of any biological matrix. Although preferred, urinary phthalate measurements are not without limitations: phthalates measured in urine do not provide information about exposure impacts at specific tissues and measures are subject to high levels of within-day variance (Johns et al 2015).

Exposure was often measured after the diagnosis of preeclampsia, limiting the ability to establish temporality. Lower levels of metals in preeclamptic women may reflect reduced vascularization and therefore decreased transport of metal, rather than a causal relationship. Similarly, glomerular filtration rate decreases with preeclampsia (Moran et al 2004). Thus, if a metal is excreted renally, levels might increase after the onset of disease.

It is unclear if the concentrations measured at or around delivery would approximate exposure during the duration of pregnancy. Because questions remain about the development of preeclampsia, the precise window of susceptibility and thus the ideal timing for measurement of exposure remains unknown. Prospective cohort studies and repeated samples across pregnancy would have enabled assessment of change in levels across pregnancy and whether one time point seems most relevant for determining outcome.

The potential for confounding was also noted in many studies. A number of investigations only compared crude levels of contaminants, with no control for any covariates. Other studies left out important covariates such as a measure for maternal socioeconomic status, known to affect both exposure to environmental contaminants and preeclampsia risk (Silva et al 2008; Evans and Kantrowitz 2002). Similarly, assessment of traffic exposure in association with preeclampsia may be confounded by socioeconomic status, a measure that is difficult to control fully.

Further, parity may act as a confounder in the association of POP and preeclampsia: nulliparity is a known risk factor for preeclampsia and breastfeeding can lower body burden of certain chemicals (Odegard et al 2000; Nickerson 2006). Although parity is a crude proxy for previous breastfeeding, inclusion of parity in the models may have reduced some confounding.

Smoking affects both Cd levels and preeclampsia, and thus either adjustment for smoking or exclusion of smokers is necessary to avoid confounding. Only three of the investigations

evaluated either excluded smokers or adjusted for smoking in statistical models (Wang et al 2018a; Laine et al 2015; Elongi Moyene et al 2016). As smoking is protective against preeclampsia (Wikstrom et al 2010) and is measured with error, estimates of the Cd-preeclampsia relationship might be biased towards the null even with adjustment for tobacco use. Future studies need to stratify by smoking status to minimize this concern of bias.

Concerns of selection bias in the reviewed studies were minimal. There was the possibility of selection bias into the MoBa cohort based on the low participation rate (41%), but it is not clear which factors affecting selection might also alter preeclampsia risk and exposure to PFAS (Starling et al 2014). In one of the investigations on organochlorines, Savitz et al (2014) excluded women from their original population due to missing data and noted that females who were excluded presented with higher BMI and were older, factors that may plausibly be associated with both organochlorine concentrations and preeclampsia.

Although not an issue of selection bias, a number of studies were limited by small sample sizes, and very small case counts. In these situations, observations are less robust and measures of association may be artificially inflated.

Women are often exposed to many of these chemicals simultaneously. Whether the mixtures are metabolites of phthalates, or structurally similar PFAS, or highly correlated metals, women rarely encounter these compounds individually. Performing mixtures analyses using specifically designed statistical methods enables investigators to identify specific “bad actors” among groups, account for co-pollutant confounding, and examine interactive effects. The methodology on mixtures continues to develop and disentangling mixtures in relation to preeclampsia is an under-researched field. None of the reviewed studies looked at multiple exposures simultaneously using a mixtures method. Including multiple components of a mixture in the same model without controlling for their correlations may result in unstable models. In the future, studies need to consider mixtures of these compounds and take measures to statistically separate them to identify true associations.

Studying preeclampsia in association with environmental exposures presents unique challenges that need to be considered in future studies. Preeclampsia is a disease of placental dysfunction, but biomarkers often measure circulating levels of contaminants rather than placental levels. Even measures collected in the placenta are complicated by the heterogeneity of the organ. As the accuracy of biomarkers continues to develop, future research needs to aim to measure exposure at the most biologically relevant location and time window. Because the mechanisms leading to development of preeclampsia are poorly understood, the precise time frame of susceptibility to environmental insults is unknown. If exposure to the environmental chemicals changes across pregnancy, which might occur if women altered their behaviors, a summary measure for total pregnancy exposure or concentrations measured at delivery may not be the appropriate time-frame of measurement.

Further, some studies stratified on subtype of preeclampsia (early onset vs. late; mild vs. severe), but many did not. It is unknown if different manifestations of preeclampsia share etiology and combining all subtypes into one heterogeneous group may conceal different relationships. Indeed, some of the investigations that did stratify noted different effects

across phenotypes. Addressing this issue requires a large sample size and additional information on diagnosis date and severity, two restrictions that not all studies are able to address.

Conclusions

Overall, the literature suggests that concentrations of certain environmental chemicals are elevated in pre-eclamptic women compared to normotensive women. However, for most exposures, studies are relatively sparse and results often inconsistent. Evaluation of the strength of evidence was determined after an assessment of the following: study methodology, sample size, statistical considerations, precision of estimates, magnitude of effects, and consistency between studies. Findings from systematic reviews were weighted more heavily to account for their accumulated body of evidence.

Including recent systematic reviews, only Cd and air pollutants were examined in more than 5 studies. There is strong evidence for a correlation between Cd and preeclampsia. Among air pollutants, there is a suggestive association between NO_2 and preeclampsia, $PM_{2.5}$ and preeclampsia, and traffic exposure and preeclampsia. Pedersen et al (2014) noted strong correlations between $PM_{2.5}$ and preeclampsia, but associations were limited in the newly reviewed studies. There does not appear to be an association between PM_{10}, CO, O_3, or SO_2 and preeclampsia. There is insufficient data to determine relationships between the other environmental contaminants addressed in this review and preeclampsia. These findings, in concert with the body of research on the effects of environmental contaminants, ought to be considered seriously for future policy recommendations on public health standards.

The pathophysiology of preeclampsia is hypothesized to be a multistep process (Burton et al 2009; Redman and Sargent 2005). In pregnancy, maternal uterine spiral arteries undergo remodeling from a complex interaction between maternal decidual immune cells in the uterine wall and invasive trophoblasts (Meekins et al 1994; Lyall 2002; Burton et al 2009). During remodeling in normal pregnancies, it has been shown that the arterial diameter increases 5 to 10-fold, thus enabling proper blood flow to the placenta and continued maintenance of the pregnancy. In many preeclampsia cases, the spiral arteries are incompletely remodeled from a deficient trophoblast invasion (Gerretsen et al 1981; Brosens et al 1972; Lain and Roberts 2002). The resulting abnormal uteroplacental flow is associated with hypoperfusion-reperfusion injury and a rise in placental oxidative stress (Burton et al 2009). Excess placental oxidative stress in turn stimulates release of soluble angiogenic proteins into maternal circulations, which play a crucial role in the presence of extensive endothelial dysfunction and enhanced systemic inflammatory stress in preeclampsia (Gerretsen et al 1981; Brosens et al 1972; Kanter et al 2010; Roberts and Cooper 2001; Brosens et al 1967). While not all preeclampsia cases exhibit signs of abnormal uteroplacental flow, the presence of excessive systemic oxidative and inflammatory stress, above the levels seen in normal pregnancies, is ubiquitous. Environmental exposures may theoretically either disrupt normal placentation leading to this cascade of endothelial dysfunction or disrupt other physiological systems further enhancing the maternal inflammatory burden. However, the determination of temporality between physiological stress and preeclampsia remains difficult to resolve and an area warranting further study.

The chemicals searched and reviewed in this investigation represent some of the most significant and ubiquitous exposures faced today, but their association with preeclampsia remains unclear. Future studies with improved exposure assessment methods and which are designed specifically to answer these questions are required to help reduce the incidence of preeclampsia and improve maternal and child health globally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

ACOG. 2013 Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 122:1122–1131. doi: 10.1097/01.aog.0000437382.03963.88. [PubMed: 24150027]

Agency for Toxic Substances and Disease Registry. 1999 Toxicological Profile for Mercury 1600 Clifton Road NE, Atlanta GA 30333: U.S. Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. 2000 Toxicological Profile for Polychlorinated Biphenyls (PCBs) 1600 Clifton Road NE, Atlanta GA 30333: U.S. Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. 2005 Toxicological Profile for Alpha-, Beta-, Gamma-, and Delta-Hexachlorocyclohexane 1600 Clifton Road NE, Atlanta GA 30333: U.S. Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. 2007 Toxicological Profile for Arsenic 1600 Clifton Road NE, Atlanta GA 30333: U.S. Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. 2011 Chromium Toxicity U.S. Department of Health and Human Services [cited July 8, 2018]. Available from https://www.atsdr.cdc.gov/csem/csem.asp?csem=10&po=5.

Agency for Toxic Substances and Disease Registry. 2012 Toxicological Profile for Cadmium 1600 Clifton Road NE, Atlanta GA 30333: U.S. Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. 2013 Chromium Toxicity - Clinical Assessment, Laboratory Tests. In Environmental Health and Medicine Education: Agency for Toxic Substances and Disease Registry.

Agency for Toxic Substances and Disease Registry. 2014 Draft for Toxicological Profile of Tetrachloroethylene 1600 Clifton Road NE, Atlanta GA 30333: U.S. Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. 2018 Per- and Polyfluoroalkyl Substances and Your Health U.S. Department of Health & Human Services [cited August 1, 2018]. Available from https://www.atsdr.cdc.gov/pfas/index.html.

Agrawal S, and Yamamoto S. 2015 Effect of indoor air pollution from biomass and solid fuel combustion on symptoms of preeclampsia/eclampsia in Indian women. Indoor Air 25:341–352. doi: 10.1111/ina.12144. [PubMed: 25039812]

Ahmed R, Dunford J, Mehran R, Robson S, and Kunadian V. 2014 Pre-eclampsia and future cardiovascular risk among women: A review. J Am Coll Cardiol 63:1815–1822. doi: 10.1016/j.jacc.2014.02.529. [PubMed: 24613324]

Ananth CV, Savitz DA, and Bowes WA, Jr. 1995 Hypertensive disorders of pregnancy and stillbirth in North Carolina, 1988 to 1991. Acta Obstet Gynecol Scand 74:788–793. [PubMed: 8533561]

Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, and Giannone PJ. 2011 Maternal preeclampsia and neonatal outcomes. J Pregnancy 2011 doi: 10.1155/2011/214365.

Banu SK, Stanley JA, Sivakumar KK, Arosh JA, Taylor RJ, and Burghardt RC. 2017 Chromium VI – induced developmental toxicity of placenta is mediated through spatiotemporal dysregulation of cell survival and apoptotic proteins. Reprod Toxicol 68:171–190. doi: 10.1016/j.reprotox.2016.07.006. [PubMed: 27443218]

Barbosa F, Jr. 2017 Toxicology of metals and metalloids: Promising issues for future studies in environmental health and toxicology. J Toxicol Environ Health A 80:137–144. doi: 10.1080/15287394.2016.1259475. [PubMed: 28277036]

Bechi N, Sorda G, Spagnoletti A, Bhattacharjee J, Vieira Ferro EA, de Freitas Barbosa B, Frosini M, Valoti M, Sgaragli G, Paulesu L, and Ietta F. 2013 Toxicity assessment on trophoblast cells for some environment polluting chemicals and 17beta-estradiol. Toxicol In Vitro 27:995–1000. doi: 10.1016/j.tiv.2013.01.013. [PubMed: 23337911]

Benachour N, and Aris A. 2009 Toxic effects of low doses of bisphenol-A on human placental cells. Toxicol Appl Pharmacol 241:322–328. doi: 10.1016/j.taap.2009.09.005. [PubMed: 19769995]

Berg V, Nost TH, Huber S, Rylander C, Hansen S, Veyhe AS, Fuskevag OM, Odland JO, and Sandanger TM. 2014 Maternal serum concentrations of per- and polyfluoroalkyl substances and their predictors in years with reduced production and use. Environ Int 69:58–66. doi: 10.1016/j.envint.2014.04.010. [PubMed: 24815340]

Bjerregaard-Olesen C, Long M, Ghisari M, Bech BH, Nohr EA, Uldbjerg N, Henriksen TB, Olsen J, and Bonefeld-Jorgensen EC. 2017 Temporal trends of lipophilic persistent organic pollutants in serum from Danish nulliparous pregnant women 2011–2013. Environ Sci Pollut Res Int 24:16592–16603. doi: 10.1007/s11356-017-8992-7. [PubMed: 28432626]

Branco V, Caito S, Farina M, Teixeira da Rocha J, Aschner M, and Carvalho C. 2017 Biomarkers of mercury toxicity: Past, present, and future trends. J Toxicol Environ Health B 20:119–154. doi: 10.1080/10937404.2017.1289834.

Brosens IA, Robertson WB, and Dixon HG. 1972 The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu 1:177–191. [PubMed: 4669123]

Brosens I, Robertson WB, and Dixon HG. 1967 The physiological response of the vessels of the placental bed to normal pregnancy. J Pathol Bacteriol 93:569–579. doi: 10.1002/path.1700930218. [PubMed: 6054057]

Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, and Bell R. 2013 Cardiovascular disease risk in women with pre-eclampsia: Systematic review and meta-analysis. Eur J Epidemiol 28:1–19. doi: 10.1007/s10654-013-9762-6. [PubMed: 23397514]

Burton GJ, Woods AW, Jauniaux E, and Kingdom JC. 2009 Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta 30:473–482. doi: 10.1016/j.placenta.2009.02.009. [PubMed: 19375795]

Calafat AM, Koch HM, Swan SH, Hauser R, Goldman LR, Lanphear BP, Longnecker MP, Rudel RA, Teitelbaum SL, Whyatt RM, and Wolff MS. 2013 Misuse of blood serum to assess exposure to bisphenol A and phthalates. Breast Cancer Res 15:403. doi: 10.1186/bcr3494.

Cantonwine DE, Meeker JD, Ferguson KK, Mukherjee B, Hauser R, and McElrath TF. 2016 Urinary concentrations of bisphenol A and phthalate metabolites measured during pregnancy and risk of preeclampsia. Environ Health Perspect 124:1651–1655. doi: 10.1289/ehp188. [PubMed: 27177253]

Carwile JL, Mahalingaiah S, Winter MR, and Aschengrau A. 2014 Prenatal drinking-water exposure to tetrachloroethylene and ischemic placental disease: A retrospective cohort study. Environ Health 13:72. doi: 10.1186/1476-069x-13-72. [PubMed: 25270247]

Centers for Disease Control and Prevention. 2003 Glossary of Classes of Non-persistent Pesticides 1600 Clifton Road, Atlanta, GA 30333: U.S. Department of Health and Human Services.

Centers for Disease Control and Prevention. 2015 Arsenic and Drinking Water from Private Wells U.S. Department of Health and Human Services [cited May 2, 2018]. Available from https://www.cdc.gov/healthywater/drinking/private/wells/disease/arsenic.html.

Centers for Disease Control and Prevention. 2017 Phthalates Factsheet U.S. Department of Health and Human Services [cited June 1, 2018]. Available from https://www.cdc.gov/biomonitoring/Phthalates_FactSheet.html.

Centers for Disease Control and Prevention. 2018 Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables 1600 Clifton Road, Atlanta GA 30329: U.S. Department of Health and Human Services.

Chen J, Thirkill TL, Lohstroh PN, Bielmeier SR, Narotsky MG, Best DS, Harrison RA, Natarajan K, Pegram RA, Overstreet JW, Lasley BL, and Douglas GC. 2004 Bromodichloromethane inhibits human placental trophoblast differentiation. Toxicol Sci 78:166–174. doi: 10.1093/toxsci/kfh046. [PubMed: 14691210]

da Cunha Martins A, Jr., Carneiro MFH, and Grotto D. 2018 Arsenic, cadmium, and mercury-induced hypertension: Mechanisms and epidemiological findings. J Toxicol Environ Health B 21:61–82. doi: 10.1080/10937404.2018.1432025.

Dadvand P, Ostro B, Amato F, Figueras F, Minguillon MC, Martinez D, Basagana X, Querol X, and Nieuwenhuijsen M. 2014 Particulate air pollution and preeclampsia: A source-based analysis. Occup Environ Med 71:570–577. doi: 10.1136/oemed-2013-101693. [PubMed: 24683010]

Damiano AE, Zotta E, and Ibarra C. 2006 Functional and molecular expression of AQP9 channel and UT-A transporter in normal and preeclamptic human placentas. Placenta 27:1073–1081. doi: 10.1016/j.placenta.2005.11.014. [PubMed: 16480766]

Dubey RK, Rosselli M, Imthurn B, Keller PJ, and Jackson EK. 2000 Vascular effects of environmental oestrogens: Implications for reproductive and vascular health. Human Reprod Update 6:351–363.

Duley L 1992 Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. Br J Obstet Gynaecol 99: 547–553. [PubMed: 1525093]

Duley L 2009 The global impact of pre-eclampsia and eclampsia. Semin Perinatol 33: 130–137. doi: 10.1053/j.semperi.2009.02.010. [PubMed: 19464502]

Elongi Moyene JP, Scheers H, Tandu-Umba B, Haufroid V, Buassa-Bu-Tsumbu B, Verdonck F, Spitz B, and Nemery B. 2016 Preeclampsia and toxic metals: A case-control study in Kinshasa, DR Congo. Environ Health 15:48–59. doi: 10.1186/s12940-016-0132-1. [PubMed: 27044488]

Environmental Protection Agency. 2009 Persistent Organic Pollutants: A Global Issue, A Global Response U.S. Environmental Protection Agency [cited July 15, 2018]. Available from https://www.epa.gov/international-cooperation/persistent-organic-pollutants-global-issue-global-response.

Environmental Protection Agency. 2010 Toxicological Review of Hexavalent Chromium Washington, D.C.: U.S. Environmental Protection Agency.

Environmental Protection Agency. 2013 America's Children and the Environment, Third Edition. Washington, D.C.: U.S. Environmental Protection Agency.

Environmental Protection Agency. 2017 Technical Fact Sheet - Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) Washington, D.C.: U.S. Environmental Protection Agency.

Environmental Protection Agency. 2018 Criteria Air Pollutants. U.S. Environmental Protection Agency [cited July 18, 2018]. Available from https://www.epa.gov/criteria-air-pollutants.

Eskenazi B, Fenster L, Sidney S, and Elkin EP. 1993 Fetal growth retardation in infants of multiparous and nulliparous women with preeclampsia. Am J Obstet Gynecol 169:1112–1118. [PubMed: 8238169]

Eslami B, Malekafzali H, Rastkari N, Rashidi BH, Djazayeri A, and Naddafi K. 2016 Association of serum concentrations of persistent organic pollutants (POPs) and risk of pre-eclampsia: A case-control study. J Environ Health Sci Eng 14:17–24. doi: 10.1186/s40201-016-0256-9. [PubMed: 27904751]

Esteban-Vasallo MD, Aragones N, Pollan M, Lopez-Abente G, and Perez-Gomez B. 2012 Mercury, cadmium, and lead levels in human placenta: A systematic review. Environ Health Perspect 120:1369–1377. doi: 10.1289/ehp.1204952. [PubMed: 22591711]

Evans GW, and Kantrowitz E. 2002 Socioeconomic status and health: The potential role of environmental risk exposure. Annu Rev Public Health 23:303–331. doi: 10.1146/annurev.publhealth.23.112001.112349. [PubMed: 11910065]

Fang J, Nyberg E, Winnberg U, Bignert A, and Bergman A. 2015 Spatial and temporal trends of the Stockholm Convention POPs in mothers' milk -- A global review. Environ Sci Pollut Res Int 22:8989–9041. doi: 10.1007/s11356-015-4080-z. [PubMed: 25913228]

Ferguson KK, McElrath TF, Cantonwine DE, Mukherjee B, and Meeker JD. 2015 Phthalate metabolites and bisphenol-A in association with circulating angiogenic biomarkers across pregnancy. Placenta 36:699–703. doi: 10.1016/j.placenta.2015.04.002. [PubMed: 25913709]

Ferguson KK, O'Neill MS, and Meeker JD. 2013 Environmental contaminant exposures and preterm birth: A comprehensive review. J Toxicol Environ Health B 16:69–113. doi: 10.1080/10937404.2013.775048.

Fowler PA, Bellingham M, Sinclair KD, Evans NP, Pocar P, Fischer B, Schaedlich K, Schmidt JS, Amezaga MR, Bhattacharya S, Rhind SM, and O'Shaughnessy PJ. 2012 Impact of endocrine-disrupting compounds (EDCs) on female reproductive health. Mol Cell Endocrinol 355:231–239. doi: 10.1016/j.mce.2011.10.021. [PubMed: 22061620]

Gerretsen G, Huisjes HJ, and Elema JD. 1981 Morphological changes of the spiral arteries in the placental bed in relation to pre-eclampsia and fetal growth retardation. Br J Obstet Gynaecol 88: 876–881. [PubMed: 7272259]

Gladen BC, Longnecker MP, and Schecter AJ. 1999 Correlations among polychlorinated biphenyls, dioxins, and furans in humans. Am J Ind Med 35: 15–20. [PubMed: 9884741]

Goldman-Wohl D, and Yagel S. 2002 Regulation of trophoblast invasion: From normal implantation to pre-eclampsia. Mol Cell Endocrinol 187:233–238. [PubMed: 11988332]

Gopal K, Tripathy SS, Bersillon JL, and Dubey SP. 2007 Chlorination byproducts, their toxicodynamics and removal from drinking water. J Hazard Mater 140:1–6. doi: 10.1016/j.jhazmat.2006.10.063. [PubMed: 17129670]

Hanssen L, Dudarev AA, Huber S, Odland JO, Nieboer E, and Sandanger TM. 2013 Partition of perfluoroalkyl substances (PFASs) in whole blood and plasma, assessed in maternal and umbilical cord samples from inhabitants of arctic Russia and Uzbekistan. Sci Total Environ 447:430–437. doi: 10.1016/j.scitotenv.2013.01.029. [PubMed: 23410865]

Hassan I, Kumar AM, Park HR, Lash LH, and Loch-Caruso R. 2016 Reactive oxygen stimulation of interleukin-6 release in the human trophoblast cell line HTR-8/SVneo by the trichlorethylene metabolite S-(1,2-dichloro)-l-cysteine. Biol Reprod 95:1–11. doi: 10.1095/biolreprod.116.139261. [PubMed: 27387869]

Hauser R, and Calafat AM. 2005 Phthalates and human health. Occup Environ Med 62: 806–818. doi: 10.1136/oem.2004.017590. [PubMed: 16234408]

Henson MC, and Chedrese PJ. 2004 Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction. Exp Biol Med (Maywood) 229: 383–392. [PubMed: 15096650]

Hettfleisch K, Bernardes LS, Carvalho MA, Pastro LDM, Vieira SE, Srdm Saldiva Saldiva P, and Francisco RPV. 2017 Short-term exposure to urban air pollution and influences on placental vascularization indexes. Environ Health Perspect 125:753–759. doi: 10.1289/ehp300. [PubMed: 27384326]

Hu H, Ha S, Roth J, Kearney G, Talbott EO, and Xu X. 2014 Ambient air pollution and hypertensive disorders of pregnancy: A systematic review and meta-analysis. Atmos Environ 97:336–345. doi: 10.1016/j.atmosenv.2014.08.027.

Hu H, Ha S, and Xu X. 2017 Ozone and hypertensive disorders of pregnancy in Florida: Identifying critical windows of exposure. Environ Res 153:120–125. doi: 10.1016/j.envres.2016.12.002. [PubMed: 27940104]

Hu XC, Andrews DQ, Lindstrom AB, Bruton TA, Schaider LA, Grandjean P, Lohmann R, Carignan CC, Blum A, Balan SA, Higgins CP, and Sunderland EM. 2016 Detection of poly- and perfluoroalkyl substances (PFASs) in U.S. drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. Environ Sci Technol Lett 3: 344–350. doi: 10.1021/acs.estlett.6b00260. [PubMed: 27752509]

Hughes MF 2006 Biomarkers of exposure: A case study with inorganic arsenic. Environ Health Perspect 114: 1790–1796. doi: 10.1289/ehp.9058. [PubMed: 17107869]

Hung H, Kallenborn R, Breivik K, Su Y, Brorstrom-Lunden E, Olafsdottir K, Thorlacius JM, Leppanen S, Bossi R, Skov H, Mano S, Patton GW, Stern G, Sverko E, and Fellin P. 2010 Atmospheric monitoring of organic pollutants in the Arctic under the Arctic Monitoring and Assessment Programme (AMAP): 1993–2006. Sci Total Environ 408: 2854–2873. doi: 10.1016/j.scitotenv.2009.10.044. [PubMed: 20004462]

Irgens HU, Reisaeter L, Irgens LM, and Lie RT. 2001 Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. Br Med J 323: 1213–1217. [PubMed: 11719411]

Jaishankar M, Tseten T, Anbalagan N, Mathew BB, and Beeregowda KN. 2014 Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol 7: 60–72. doi: 10.2478/intox-2014-0009. [PubMed: 26109881]

Johns LE, Cooper GS, Galizia A, and Meeker JD. 2015 Exposure assessment issues in epidemiology studies of phthalates. Environ Int 85:27–39. doi: 10.1016/j.envint.2015.08.005. [PubMed: 26313703]

Kahn LG, and Trasande L. 2018 Environmental toxicant exposure and hypertensive disorders of pregnancy: Recent findings. Curr Hypertens Rep 20:87–96. doi: 10.1007/s11906-018-0888-5. [PubMed: 30090982]

Kales SN, Huyck KL, and Goldman RH. 2006 Elevated urine arsenic: Un-speciated results lead to unnecessary concern and further evaluations. J Anal Toxicol 30:80–85. [PubMed: 16620536]

Kanter D, Lindheimer MD, Wang E, Borromeo RG, Bousfield E, Karumanchi SA, and Stillman IE. 2010 Angiogenic dysfunction in molar pregnancy. Am J Obstet Gynecol 202:184e1-e5. doi: 10.1016/j.ajog.2009.09.005. [PubMed: 19922899]

Kestenbaum B, Seliger SL, Easterling TR, Gillen DL, Critchlow CW, Stehman-Breen CO, and Schwartz SM. 2003 Cardiovascular and thromboembolic events following hypertensive pregnancy. Am J Kidney Dis 42:982–989. [PubMed: 14582042]

Khan KS, Wojdyla D, Say L, Gulmezoglu AM, and Van Look PF. 2006 WHO analysis of causes of maternal death: A systematic review. Lancet 367: 1066–1074. doi: 10.1016/s0140-6736(06)68397-9. [PubMed: 16581405]

Klemmensen AK, Olsen SF, Osterdal ML, and Tabor A. 2007 Validity of preeclampsia-related diagnoses recorded in a national hospital registry and in a postpartum interview of the women. Am J Epidemiol 166:117–124. doi: 10.1093/aje/kwm139. [PubMed: 17556761]

Lain KY, and Roberts JM. 2002 Contemporary concepts of the pathogenesis and management of preeclampsia. J Am Med Assoc 287:3183–3186.

Laine JE, Ray P, Bodnar W, Cable PH, Boggess K, Offenbacher S, and Fry RC. 2015 Placental cadmium levels are associated with increased preeclampsia risk. PLoS One 10: e0139341. doi: 10.1371/journal.pone.0139341. [PubMed: 26422011]

Leclerc F, Dubois MF, and Aris A. 2014 Maternal, placental and fetal exposure to bisphenol A in women with and without preeclampsia. Hypertens Pregnancy 33: 341–348. doi: 10.3109/10641955.2014.892607. [PubMed: 24724919]

Lee PC, Roberts JM, Catov JM, Talbott EO, and Ritz B. 2013 First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Matern Child Health J 17: 545–555. doi: 10.1007/s10995-012-1028-5. [PubMed: 22544506]

Lerberghe WV, Manuel A, Matthews Z, and Wolfheim C. 2005 Make every mother and child count. In The World Health Report Geneva, Switzerland: World Health Organization.

Liu L, Wang Y, Shen C, He J, Liu X, Ding Y, Gao R, and Chen X. 2016 Benzo(a)pyrene inhibits migration and invasion of extravillous trophoblast HTR-8/SVneo cells via activation of the ERK and JNK pathway. J Appl Toxicol 36: 946–955. doi: 10.1002/jat.3227. [PubMed: 26359795]

Lyall F 2002 The human placental bed revisited. Placenta 23: 555–562. [PubMed: 12361674]

Madsen C, Haberg SE, Aamodt G, Stigum H, Magnus P, London SJ, Nystad W, and Nafstad P. 2017 Preeclampsia and hypertension during pregnancy in areas with relatively low levels of traffic air pollution. Matern Child Health J 22: 512–519. doi: 10.1007/s10995-017-2417-6.

Maduray K, Moodley J, Soobramoney C, Moodley R, and Naicker T. 2017 Elemental analysis of serum and hair from pre-eclamptic South African women. J Trace Elem Med Biol 43: 180–186. doi: 10.1016/j.jtemb.2017.03.004. [PubMed: 28325649]

Mannetje A, Coakley J, Bridgen P, Brooks C, Harrad S, Smith AH, Pearce N, and Douwes J. 2013 Current concentrations, temporal trends and determinants of persistent organic pollutants in breast milk of New Zealand women. Sci Total Environ 458–460: 399–407. doi: 10.1016/j.scitotenv.2013.04.055. [PubMed: 23410868]

Marti-Cid R, Llobet JM, Castell V, and Domingo JL. 2008 Evolution of the dietary exposure to polycyclic aromatic hydrocarbons in Catalonia, Spain. Food Chem Toxicol 46: 3163–3171. doi: 10.1016/j.fct.2008.07.002. [PubMed: 18675309]

Matteucci F, Ercole C, and del Gallo M. 2015 A study of chlorinated solvent contamination of the aquifers of an industrial area in central Italy: A possibility of bioremediation. Front Microbiol 6. doi: 10.3389/fmicb.2015.00924.

Meekins JW, Pijnenborg R, Hanssens M, McFadyen IR, and van Asshe A. 1994 A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. Br J Obstet Gynaecol 101: 669–674. [PubMed: 7947500]

Mendola P, Wallace M, Liu D, Robledo C, Männistö T, and Grantz KL. 2016 Air pollution exposure and preeclampsia among US women with and without asthma. Environ Res 148:248–255. doi: 10.1016/j.envres.2016.04.004. [PubMed: 27085496]

Miles AM, Singer PC, Ashley DL, Lynberg MC, Mendola P, Langlois PH, and Nuckols JR. 2002 Comparison of trihalomethanes in tap water and blood. Environ Sci Technol 36:1692–1698. [PubMed: 11993865]

Mongraw-Chaffin ML, Cirillo PM, and Cohn BA. 2010 Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertension 56:166–171. doi: 10.1161/hypertensionaha.110.150078. [PubMed: 20516394]

Moran Michael J., Zogorski John S., and Squillace Paul J.. 2007 Chlorinated solvents in groundwater of the United States. Environ Sci Technol 41:74–81. doi: 10.1021/es061553y. [PubMed: 17265929]

Moran P, Lindheimer MD, and Davison JM. 2004 The renal response to preeclampsia. Semin Nephrol 24: 588–595. [PubMed: 15529294]

Mueller R, and Yingling V. 2017 History and Use of Per- and Polyfluoroalkyl Substances (PFAS) Washington, DC 20001: Interstate Technology and Regulatory Council.

Murray J, Eskenazi B, Bornman R, Gaspar FW, Crause M, Obida M, and Chevrier J. 2018 Exposure to DDT and hypertensive disorders of pregnancy among South African women from an indoor residual spraying region: The VHEMBE study. Environ Res 162:49–54. doi: 10.1016/j.envres.2017.12.006. [PubMed: 29287179]

Nahidi F, Gholami R, Rashidi Y, and Majd HA. 2014 Relationship between air pollution and pre-eclampsia in pregnant women: A case-control study. East Mediterr Health J 19 Suppl 3:S60–S66. [PubMed: 24995762]

National Institute of Environmental Health Sciences. 2016 Perfluorinated Compounds (PFCs) U.S. Department of Health and Human Services [cited May 4 2018]. Available from https://www.niehs.nih.gov/health/topics/agents/pfc/index.cfm.

National Institute of Environmental Health Sciences. 2018 Bisphenol A (BPA) U.S. Department of Health and Human Services [cited April 25 2018]. Available from https://www.niehs.nih.gov/health/topics/agents/sya-bpa/index.cfm.

Nickerson K 2006 Environmental contaminants in breast milk. J Midwifery Womens Health 51: 26–34. doi: 10.1016/j.jmwh.2005.09.006. [PubMed: 16399607]

Nieuwenhuijsen MJ, Toledano MB, Eaton NE, Fawell J, and Elliott P. 2000 Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: A review. Occup Environ Med 57:73–85. [PubMed: 10711274]

Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, and Austgulen R. 2000 Risk factors and clinical manifestations of pre-eclampsia. Br J Obstet Gynaecol 107: 1410–1416.

Park HR, Kamau PW, and Loch-Caruso R. 2014 Involvement of reactive oxygen species in brominated diphenyl ether-47-induced inflammatory cytokine release from human extravillous trophoblasts in vitro. Toxicol Appl Pharmacol 274:283–292. doi: 10.1016/j.taap.2013.11.015. [PubMed: 24296301]

Pedersen M, Halldorsson TI, Olsen SF, Hjortebjerg D, Ketzel M, Grandstrom C, Raaschou-Nielsen O, and Sorensen M. 2017 Impact of road traffic pollution on pre-eclampsia and pregnancy-induced hypertensive disorders. Epidemiology 28: 99–106. doi: 10.1097/ede.0000000000000555. [PubMed: 27648591]

Pedersen M, Stayner L, Slama R, Sorensen M, Figueras F, Nieuwenhuijsen MJ, Raaschou-Nielsen O, and Dadvand P. 2014 Ambient air pollution and pregnancy-induced hypertensive disorders: A systematic review and meta-analysis. Hypertension 64: 494–500. doi: 10.1161/hypertensionaha.114.03545. [PubMed: 24935943]

Phipps E, Prasanna D, Brima W, and Jim B. 2016 Preeclampsia: Updates in pathogenesis, definitions, and guidelines. Clin J Am Soc Nephrol 11:1102–1113. doi: 10.2215/cjn.12081115. [PubMed: 27094609]

Piasek M, Mikolic A, Sekovanic A, Sulimanec Grgec A, and Jurasovic J. 2014 Cadmium in placenta- a valuable biomarker of exposure during pregnancy in biomedical research. J Toxicol Environ Health A 77:1071–1074. doi: 10.1080/15287394.2014.915779. [PubMed: 25072893]

Pijnenborg R, Vercruysse L, and Hanssens M. 2006 The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 27:939–958. doi: 10.1016/j.placenta.2005.12.006. [PubMed: 16490251]

Pollack AZ, Ranasinghe S, Sjaarda LA, and Mumford SL. 2014 Cadmium and reproductive health in women: A systematic review of the epidemiologic evidence. Curr Environ Health Rep 1: 172–184. doi: 10.1007/s40572-014-0013-0. [PubMed: 27453808]

Poropat AE, Laidlaw MAS, Lanphear B, Ball A, and Mielke HW. 2018 Blood lead and preeclampsia: A meta-analysis and review of implications. Environ Res 160: 12–19. doi: 10.1016/j.envres.2017.09.014. [PubMed: 28938191]

Powers RW, Roberts JM, Plymire DA, Pucci D, Datwyler SA, Laird DM, Sogin DC, Jeyabalan A, Hubel CA, and Gandley RE. 2012 Low placental growth factor across pregnancy identifies a subset of women with preterm preeclampsia: Type 1 versus type 2 preeclampsia? Hypertension 60: 239–246. doi: 10.1161/hypertensionaha.112.191213. [PubMed: 22647886]

Redman CW, and Sargent IL. 2005 Latest advances in understanding preeclampsia. Science 308: 1592–1594. doi: 10.1126/science.1111726. [PubMed: 15947178]

Redman CW, and Staff AC. 2015 Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. Am J Obstet Gynecol 213: S9.e1, S9–11. doi: 10.1016/j.ajog.2015.08.003. [PubMed: 26428507]

Roberts JM, and Cooper DW. 2001 Pathogenesis and genetics of pre-eclampsia. Lancet 357:53–56. [PubMed: 11197372]

Roberts JM, and Hubel CA. 2009 The two stage model of preeclampsia: Variations on the theme. Placenta 30 Suppl A: S32–S37. doi: 10.1016/j.placenta.2008.11.009. [PubMed: 19070896]

Roberts JM, and Von Versen-Hoeynck F. 2007 Maternal fetal/placental interactions and abnormal pregnancy outcomes. Hypertension 49: 15–16. doi: 10.1161/01.hyp.0000251523.44824.02. [PubMed: 17116760]

Sandoval-Carrillo A, Mendez-Hernandez EM, Antuna-Salcido EI, Salas-Pacheco SM, Vazquez-Alaniz F, Tellez-Valencia A, Aguilar-Duran M, Barraza-Salas M, Castellanos-Juarez FX, La Llave-Leon O, and Salas-Pacheco JM. 2016 Arsenic exposure and risk of preeclampsia in a Mexican mestizo population. BMC Pregnancy Childbirth 16:153–157. doi: 10.1186/s12884-016-0946-4. [PubMed: 27401918]

Savitz DA, Elston B, Bobb JF, Clougherty JE, Dominici F, Ito K, Johnson S, McAlexander T, Ross Z, Shmool JL, Matte TD, and Wellenius GA. 2015 Ambient fine particulate matter, nitrogen dioxide, and hypertensive disorders of pregnancy in New York City. Epidemiology 26: 748–757. doi: 10.1097/ede.0000000000000349. [PubMed: 26237745]

Savitz DA, Klebanoff MA, Wellenius GA, Jensen ET, and Longnecker MP. 2014 Persistent organochlorines and hypertensive disorders of pregnancy. Environ Res 132: 1–5. doi: 10.1016/j.envres.2014.03.020. [PubMed: 24742720]

Savitz DA, Stein CR, Bartell SM, Elston B, Gong J, Shin HM, and Wellenius GA. 2012 Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community. Epidemiology 23:386–392. doi: 10.1097/EDE.0b013e31824cb93b. [PubMed: 22370857]

Schuster JK, Gioia R, Moeckel C, Agarwal T, Bucheli TD, Breivik K, Steinnes E, and Jones KC. 2011 Has the burden and distribution of PCBs and PBDEs changed in European background soils between 1998 and 2008? Implications for sources and processes. Environ Sci Technol 45:7291–7297. doi: 10.1021/es200961p. [PubMed: 21819101]

Shaw GM, Yang W, Roberts EM, Aghaeepour N, Mayo JA, Weber KA, Maric I, Carmichael SL, Winn VD, Stevenson DK, and English PB. 2018 Residential agricultural pesticide exposures and risks of preeclampsia. Environ Res 164:546–555. doi: 10.1016/j.envres.2018.03.020. [PubMed: 29614386]

Shen M, Smith GN, Rodger M, White RR, Walker MC, and Wen SW. 2017 Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia 12: e0175914. doi: 10.1371/journal.pone.0175914.

Shin HM, Vieira VM, Ryan PB, Steenland K, and Bartell SM. 2011 Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project. Environ Health Perspect 119: 1760–1765. doi: 10.1289/ehp.1103729. [PubMed: 21813367]

Siddiqi MA, Laessig RH, and Reed KD. 2003 Polybrominated eiphenyl ethers (PBDEs): New pollutants-old diseases. Clin Med Res 1: 281–290. [PubMed: 15931321]

Silva LM, Coolman M, Steegers EA, Jaddoe VW, Moll HA, Hofman A, Mackenbach JP, and Raat H. 2008 Low socioeconomic status is a risk factor for preeclampsia: The Generation R Study. J Hypertens 26: 1200–1208. doi: 10.1097/HJH.0b013e3282fcc36e. [PubMed: 18475158]

Starling AP, Engel SM, Richardson DB, Baird DD, Haug LS, Stuebe AM, Klungsoyr K, Harmon Q, Becher G, Thomsen C, Sabaredzovic A, Eggesbo M, Hoppin JA, Travlos GS, Wilson RE, Trogstad LI, Magnus P, and Longnecker MP. 2014 Perfluoroalkyl substances during pregnancy and validated preeclampsia among nulliparous women in the Norwegian Mother and Child Cohort Study. Am J Epidemiol 179: 824–833. doi: 10.1093/aje/kwt432. [PubMed: 24557813]

Stasenko S, Bradford EM, Piasek M, Henson MC, Varnai VM, Jurasovic J, and Kusec V. 2010 Metals in human placenta: Focus on the effects of cadmium on steroid hormones and leptin. J Appl Toxicol 30: 242–253. doi: 10.1002/jat.1490. [PubMed: 19847775]

Steegers EA, von Dadelszen P, Duvekot JJ, and Pijnenborg R. 2010 Pre-eclampsia. Lancet 376: 631–644. doi: 10.1016/s0140-6736(10)60279-6. [PubMed: 20598363]

Stein CR, Savitz DA, and Dougan M. 2009 Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. Am J Epidemiol 170: 837–846. doi: 10.1093/aje/kwp212. [PubMed: 19692329]

Suh CH, Cho NK, Lee CK, Lee CH, Kim DH, Kim JH, Son BC, and Lee JT. 2011 Perfluorooctanoic acid-induced inhibition of placental prolactin-family hormone and fetal growth retardation in mice. Mol Cell Endocrinol 337: 7–15. doi: 10.1016/j.mce.2011.01.009. [PubMed: 21241770]

Tachibana T, Wakimoto Y, Nakamuta N, Phichitraslip T, Wakitani S, Kusakabe K, Hondo E, and Kiso Y. 2007 Effects of bisphenol A (BPA) on placentation and survival of the neonates in mice. J Reprod Dev 53: 509–514. [PubMed: 17384489]

Tchounwou PB, Yedjou CG, Patlolla AK, and Sutton DJ. 2012 Heavy metal toxicity and the environment. Mol Clin Environ Toxicol. Experientia Suppl 101: 133–164. doi: 10.1007/978-3-7643-8340-4_6.

United Nations Environment Programme. 2008a The 12 initial POPs under the Stockholm Convention Secretariat of the Stockholm Convention [cited April 9 2018]. Available from http://chm.pops.int/TheConvention/ThePOPs/The12InitialPOPs/tabid/296/Default.aspx.

United Nations Environment Programme. 2008b Guidance for Identifying Populations at Risk From Mercury Exposure. edited by Inter-Organization Programme for the Sound Management of Chemicals Geneva, Switzerland: World Health Organization.

United Nations Environment Programme. 2008c What are POPs? Secretariat of the Stockholm Convention [cited April 9 2018]. Available from http://chm.pops.int/TheConvention/ThePOPs/tabid/673/Default.aspx.

United Nations Environment Programme. 2013 History of the negotiations of the Stockholm Convention Secretariat of the Stockholm Convention [cited April 9 2018]. Available from http://chm.pops.int/TheConvention/Overview/History/Overview/tabid/3549/Default.aspx.

Valenzuela FJ, Pérez-Sepúlveda A, Torres MJ, Correa P, Repetto GM, and Illanes SE. 2012 Pathogenesis of preeclampsia: The genetic component. J Pregnancy 2012: 632732. doi: 10.1155/2012/632732. [PubMed: 22175024]

van den Berg H 2009 Global status of DDT and its alternatives for use in vector control to prevent disease. Environ Health Perspect 117:1656–1663. doi: 10.1289/ehp.0900785. [PubMed: 20049114]

Venier M, and Hites RA. 2010 Time trend analysis of atmospheric POPs concentrations in the Great Lakes region since 1990. Environ Sci Technol 44: 8050–8055. doi: 10.1021/es101656u. [PubMed: 20932001]

Vigeh M, Yokoyama K, Ramezanzadeh F, Dahaghin M, Sakai T, Morita Y, Kitamura F, Sato H, and Kobayashi Y. 2006 Lead and other trace metals in preeclampsia: A case-control study in Tehran, Iran. Environ Res 100: 268–275. doi: 10.1016/j.envres.2005.05.005. [PubMed: 16029873]

Wang F, Fan F, Wang L, Ye W, Zhang Q, and Xie S. 2018a Maternal cadmium levels during pregnancy and the relationship with preeclampsia and fetal biometric parameters. Biol Trace Elem Res 186: 322–329. doi: 10.1007/s12011-018-1312-3. [PubMed: 29651732]

Wang Q, Zhang H, Liang Q, Knibbs LD, Ren M, Li C, Bao J, Wang S, He Y, Zhu L, Wang X, Zhao Q, and Huang C. 2018b Effects of prenatal exposure to air pollution on preeclampsia in Shenzhen, China. Environ Pollut 237: 18–27. doi: 10.1016/j.envpol.2018.02.010. [PubMed: 29466771]

Wesselink AK, Carwile JL, Fabian MP, Winter MR, Butler LJ, Mahalingaiah S, and Aschengrau A. 2017 Residential proximity to roadways and ischemic placental disease in a Cape Cod family health study. Int J Environ Res Public Health 14: 682–695. doi: 10.3390/ijerph14070682.

Wikstrom AK, Stephansson O, and Cnattingius S. 2010 Tobacco use during pregnancy and preeclampsia risk: Effects of cigarette smoking and snuff. Hypertension 55:1254–1259. doi: 10.1161/hypertensionaha.109.147082. [PubMed: 20231527]

Williams PJ, and Broughton Pipkin F. 2011 The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 25: 405–417. doi: 10.1016/j.bpobgyn.2011.02.007. [PubMed: 21429808]

Wu M, Ries JJ, Proietti E, Vogt D, Hahn S, and Hoesli I. 2016 Development of late-onset preeclampsia in association with road densities as a proxy for traffic-related air pollution. Fetal Diagn Ther 39: 21–27. doi: 10.1159/000381802. [PubMed: 26088708]

Ye Y, Zhou Q, Feng L, Wu J, Xiong Y, and Li X. 2017 Maternal serum bisphenol A levels and risk of pre-eclampsia: A nested case-control study. Eur J Public Health 27: 1102–1107. doi: 10.1093/eurpub/ckx148. [PubMed: 29186464]

Yorifuji T, Naruse H, Kashima S, Murakoshi T, and Doi H. 2015 Residential proximity to major roads and obstetrical complications. Sci Total Environ 508: 188–192. doi: 10.1016/j.scitotenv.2014.11.077. [PubMed: 25478655]

Table 1.

Persistent organic pollutants and preeclampsia

Study				**Exposure**				**Association**	
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	Modeled Exposure	HR/OR/RR (95% CI)
Eslami 2016	Case-control	Tehran, Iran	N=115 n_{PE}=45	3rd trimester	Serum (ng/g lipid)	Total PCB	PE: 3.72 (2.37) Control: 2.07 (1.66)	Not reported	OR: 1.77 (1.34, 2.32)
						Total PBDE	PE: 2.15 (1.64) Control: 1.20 (0.90)		2.19 (1.39, 3.45)
						Total POP	PE: 5.87 (3.54) Control: 3.28 (2.23)		1.54 (1.26, 1.87)
Murray 2018	Retrospective cohort	South Africa	N=633 n_{PE}=15	Delivery	Serum (ng/g lipid)	p,p'-DDT	52.5 (18.6, 257.1)†	Per ln-unit	OR: 1.26 (0.74, 2.16)
						p,p'-DDE	239.0 (88.7, 878.1)†		1.14 (0.62, 2.10)
						o,p'-DDT	7.0 (3.4, 22.6)†		1.48 (0.86, 2.56)
Savitz 2014	Retrospective cohort	U.S.	N=1,933 n_{PE}=131	Every 8 weeks after enrollment; analysis used 3rd trimester samples	Serum (μg/l)	p,p'-DDT	9.25 (6.22, 14.19)†	Upper vs. lowest quintile	OR: 0.6 (0.2, 1.5)
						p,p'-DDE	24.50 (16.95, 36.73)†		0.8 (0.4, 1.8)
						Total PCB	2.69 (1.85, 3.83)†		0.5 (0.2, 1.3)
						β-HCH	1.39 (1.01, 2.11)†		1.2 (0.5, 3.2)
Savitz 2012	Cross-sectional	Mid-Ohio Valley, US	N=10,189 n_{PE}=730	Measured in 2005–2006 and modeled 15 years prior	Estimated serum (ng/ml)	PFOA	Exposure year 1990–1994: 6.0 (4.5, 27.6)† 1995–1999: 10.7 (5.1, 50.4)† 2000–2005: 15.9 (5.9, 56.2)†	IQR (lnPFOA)	OR: 1.13 (1.00, 1.28)
Stein 2009	Cross-sectional	Mid-Ohio Valley, US	N=1,589 n_{PE}=156 N=4,566 n_{PE}=407	Measured in 2005–2006 and included pregnancies from 2000–2006	Serum (ng/ml)	PFOA	21.2 (10.3, 49.8)†	≥50th percentile vs. <50th percentile	OR: 1.3 (0.9, 1.9)
						PFOS	13.6 (9.4, 18.7)†		1.3 (1.1, 1.7)
Starling 2014	Case-cohort	Norway	N=976 n_{PE}=466	2nd trimester	Plasma (ng/ml)	PFOA	2.78 (2.14, 3.57)†	Per ln-unit	HR: 0.89 (0.65, 1.22)
						PFNA	0.54 (0.39, 0.74)†		0.90 (0.70, 1.16)

Study	Exposure	Association		
	PFDA	0.10 (<LOQ, 0.18)†	0.88 (0.75, 1.04)	
	PFUnDA	0.17 (0.08, 0.27)†	0.78 (0.66, 0.92)	
	PFHxS	0.69 (0.49, 0.95)†	0.91 (0.72, 1.14)	
	PFHpS	0.15 (0.09, 0.23)†	1.03 (0.86, 1.24)	
	PFOS	12.87 (9.69, 17.03)†	1.13 (0.84, 1.52)	

Abbreviations: hazard ratio (HR); odds ratio (OR); risk ratio (RR); confidence interval (CI); interquartile range (IQR); preeclampsia (PE); polychlorinated biphenyls (PCB); polybrominated diphenyl ethers (PBDE); persistent organic pollutants (POP); dichlorodiphenyltrichloroethane (DDT); dichlorodiphenyldichloroethylene (DDE); beta-hexachlorocyclohexane (HCH); perfluorooctanoic acid (PFOA); perfluorooctane sulfonic acid (PFOS); perfluorononanoic acid (PFNA); perfluorodecanoic acid (PFDA); perfluoroundecanoic acid (PFUnDA); perfluorohexane sulfonate (PFHxS); perfluoroheptane sulfonate (PFHpS)

(†)*Note.* Levels represent mean (standard deviation), or median (IQR).

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Table 2.

Drinking water contaminants and preeclampsia

Study				**Exposure**				**Association**	
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	Modeled Exposure	HR/OR/RR (95% CI)
Carwile 2014	Retrospective cohort	MA, U.S.	N=4,836 n_{PE}=49	Year of LMP	Weber and Brown leaching and transport model	PCE	Median cumulative exposure before LMP month and year: 0.57 grams	Any vs. none >50th vs. none	RR: 0.37 (0.17, 0.83) 0.36 (0.12, 1.07)

Abbreviations: hazard ratio (HR); odds ratio (OR); risk ratio (RR); confidence interval (CI); preeclampsia (PE); last menstrual period (LMP); Massachusetts (MA); tetrachloroethylene (PCE)

Table 3.

Air pollutants and preeclampsia

Study				**Exposure**				**Association**	
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	Modeled Exposure	HR/OR/RR (95% CI)
Dadvand 2014	Retrospective cohort	Barcelona, Spain	N=3,182 n_{PE}=47	1st trimester, entire pregnancy	PMF source apportionment using urban background monitor	PM_{10} (μg/m^3)	Entire pregnancy: 45.8 (3.1) †	Entire pregnancy, per IQR	OR: 0.57 (0.30, 1.07)
						$PM_{2.5}$ (μg/m^3)	Entire pregnancy: 32.1 (6.5) †		0.55 (0.29, 1.04)
Lee 2013	Retrospective cohort	PA, U.S.	N=34,705 n_{PE}=1,141	1st trimester	Space-Time Ordinary Kriging interpolation	O_3 (ppb)	21.7 (13.3, 30.2) †	Per IQR	OR: 1.12 (0.89, 1.42)
						PM_{10} (μg/m^3)	24.8 (21.7, 29.4) †		1.00 (0.87, 1.15)
						$PM_{2.5}$ (μg/m^3)	15.6 (13.6, 17.6) †		1.15 (0.96, 1.39)
Madsen 2017	Prospective cohort	Norway	N=17,533 n_{PE}=590	Entire pregnancy	Land use regression models	NO_2 (μg/m^3)	13.6 (6.9)	Per 10 μg/m^3	OR: 0.89 (0.74, 1.08)
						Road within 15 miles	46.6% of women		1.16 (0.96, 1.39)
Mendola 2016	Retrospective cohort	U.S.	N=210,508 pregnancies n_{PE}=10,528	Preconception, 1st trimester, 2nd trimester, entire pregnancy	Community Multiscale Air Quality model	CO (ppb)	Entire pregnancy: 548.3 (206.2) †	Per IQR unit increase, non-asthmatics, entire pregnancy	RR: 1.01 (0.96, 1.05)
						NO_x (ppb)	29.1 (24.3) †		0.97 (0.89, 1.04)
						O_3 (ppb)	28.5 (7.9) †		0.95 (0.91, 1.01)
						SO_2 (ppb)	3.3 (2.9) †		0.98 (0.92, 1.05)
						PM_{10} (μg/m^3)	22.0 (4.5) †		1.04 (0.99, 1.08)
						$PM_{2.5}$ (μg/m^3)	11.9 (4.7) †		1.02 (0.94, 1.11)
Nahidi 2014	Case-control	Tehran, Iran	N=195 n_{PE}=65	Entire pregnancy	Air monitoring data and subject interviews	CO	% high exposure: 53.3	At or above median vs. below	OR: 1.92 (0.92, 4.02)
						NO_2	49.7		0.77 (0.37, 1.61)
						SO_2	55.9		0.80 (0.40, 1.60)
						PM_{10}	50.3		0.98 (0.43, 2.19)
						O_3	49.2		1 (0.49, 2.03)
Pedersen 2017	Prospective cohort	Denmark	N=72,745 n_{PE}=1,880	Entire pregnancy	AirGIS dispersion model	NO_2 (μg/m^3)	Entire pregnancy: 11.0 (4.8) †	per 10 μg/m^3 increase	OR: 1.07 (1.01, 1.14)
Savitz 2015	Retrospective cohort	NY, U.S.	N=268,601 n_{PE}=11,166	1st and 2nd trimester	Estimation of spatial variation of air pollutants and temporal adjustment of spatial data to match gestational exposure time windows	$PM_{2.5}$ (μg/m^3)	2nd trimester: 11.67 †	Per 10 μg/m3 increase, 2nd trimester	Mild PEOR: 0.8 (0.7, 0.9) Severe PE: 1.1 (0.93, 1.3)
						NO_2 (ppb)	2nd trimester: 26.44 †	Per 10 ppb increase, 2nd trimester	Mild PE 0.93 (0.89, 0.98) Severe PE: 1.0 (0.97, 1.1)

Study				Exposure				Association	
Wang 2018	Retrospective cohort	Shenzhen, China	N=1.21 million n_{PE}= 14,070	1st trimester, 2nd trimester, entire pregnancy	Daily average measurements	PM_{10} (μg/m^3) SO_2 (μg/m^3) NO_2 (μg/m^3)	Entire pregnancy: 59.1 (7.0) 15.6 (6.4) 45.9 (6.0)	4th vs. 1st quartile, entire pregnancy	OR: 1.32 (1.25, 1.40) 1.16 (1.10, 1.22) 1.10 (1.05, 1.16)
Wesselink 2017	Retrospective cohort	Cape Cod, U.S.	N=3,309 pregnancies n_{PE}=31	Addresses before and during pregnancy	Residential proximity to major roadways	Traffic pollution	Length of major roadways within 500 m buffer of residence: 1008 (592, 1571) † Shortest Euclidean distance between residence and closest major roadway: 188 m (85, 362) †	Length of roads in 500 m buffer: ≥1076 m of road vs. 0 m of road Distance from closest road, <100 m vs. ≥200 m	RR: 0.69 (0.23, 2.06) 0.46 (0.16, 1.29)
Wu 2016	Case-control	Basel, Switzerland	N=100 n_{PE}=50	Address during pregnancy	Surrogate measures of road density	Traffic pollution	Total length of major roads within 500 m of a woman's domicile: PE: ~1550 m Controls: ~2300 m		
Yorifuji 2015	Retrospective cohort	Shizuoka, Japan	N=19,077 n_{PE}=630	Address at time of delivery	Residential proximity to major roads	Traffic pollution	Not reported	Living ≤200 m of a major road vs. >200 m	OR: 1.3 (1.0, 1.8)

Abbreviations: odds ratio (OR); hazard ratio (HR); risk ratio (RR); confidence interval (CI); preeclampsia (PE); interquartile range (IQR); positive matrix factorization (PMF); particulate matter (PM); nitrogen dioxide (NO_2); nitrogen oxides (NO_x); carbon monoxide (CO); ozone (O_3); sulfur dioxide (SO_2); parts per billion (ppb); New York (NY)

(†)*Note.* Levels represent mean (standard deviation), or median (IQR).

Table 4a.

Arsenic and preeclampsia

Study				**Exposure**			**Association**	
Reference	Design	Location	Sample size	Timing	Assessment	Level	Modeled Exposure	HR/OR/RR (95% CI)
Elongi Moyene 2016	Case-control	Kinshasa, Democratic Republic of Congo	N=176 n_{PE}=88	Cases: Admission for diagnosis of PE Controls: not reported	Urine (μg/l)	PE: 46.9 (26.1, 79.9)[§] Control: 26.8 (13.4, 51.6)[§]		
Maduray 2017	Cross-sectional	South Africa	N=66 n_{PE}=43	Not reported	Pubic hair (μg/g)	PE: 7.63 (1.32)[*] Control: 5.47 (2.79)[*]		
					Serum (mg/l)	PE: 0.06 (0.0)[*] Control: 0.49 (0.0)[*]		
Sandoval-Carrillo 2016	Case-control	Mexico	N=306 n_{PE}=104	Before delivery	Urine (μg/l)	PE: 7.1 (5.74) Control: 6.78 (3.48)	High vs. low tertile	OR: 0.788 (0.411, 1.512)

Abbreviations: hazard ratio (HR); odds ratio (OR); risk ratio (RR); confidence interval (CI); preeclampsia (PE); interquartile range (IQR)

(§) *Note.* Levels represent mean (standard deviation), geometric mean (IQR)

(*) or median (SEM).

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Table 4b.

Cadmium and preeclampsia

Study				Exposure			Association	
Reference	Design	Location	Sample size	Timing	Assessment	Level	Modeled Exposure	HR/OR/RR (95% CI)
Elongi Moyene 2016	Case-control	Kinshasa, Democratic Republic of Congo	N=176 n_{PE}=88	Cases: Admission for diagnosis of PE Controls: not reported	Urine (μg/l)	PE: 1.78 (0.71, 3.85)[§] Control: 0.53 (0.29, 0.68)[§]		
Laine 2015	Nested case-control	NC, AL, TX, U.S.	N=172 n_{PE}=86	Delivery	Placenta (ng/g)	PE: 3.7 Control: 3.5		OR: 1.5 (1.1, 2.2)
Maduray 2017	Cross-sectional	South Africa	N=66 n_{PE}=43	Not reported	Pubic hair (μg/g)	PE: 3.96 (0.87) [*] Control: 3.75 (0.64) [*]		
					Serum (mg/l)	PE: 0.05 (0.04) [*] Control: 0.10 (0.03) [*]		
Wang 2018	Case-control	Zhejiang, China	N=102 n_{PE}=51	28^{th}-40^{th} week	Maternal blood (μg/l)	Control: 1.09 (0.72, 1.31)[†] PE: 1.21 (0.76, 1.84)[†]	High tertile (≥1.36 μg/L) vs. low (<0.93 μg/L)	OR: 7.83 (1.64, 37.26)
				Delivery	Placenta (μg/kg wet weight)	PE: 4.28 (3.06, 5.71)[†] Control: 3.61 (2.19, 4.37)[†]		
				Delivery	Cord blood (μg/l)	PE: 0.28 (0.17, 0.39)[†] Control: 0.37 (0.19, 0.46)[†]		

Abbreviations: hazard ratio (HR); odds ratio (OR); risk ratio (RR); confidence interval (CI); interquartile range (IQR); preeclampsia (PE); North Carolina (NC); Alabama (AL); Texas (TX)

(†) *Note.* Levels represent mean (standard deviation), median (IQR)

(§) geometric mean (IQR)

(*) or median (SEM).

Table 4c.

Chromium and preeclampsia

Study				Exposure			Association	
Reference	Design	Location	Sample size	Timing	Assessment	Level	Modeled Exposure	HR/OR/RR (95% CI)
Elongi Moyene 2016	Case-control	Kinshasa, Democratic Republic of Congo	N=176 n_{PE}=88	Cases: Admission for diagnosis of PE Controls: not reported	Urine (μg/l)	PE: 4.57 (1.02, 24.3)[§] Control: 0.88 (0.39, 2.46)[§]		
Maduray 2017	Cross-sectional	South Africa	N=66 n_{PE}=43	Not reported	Pubic hair (μg/g)	PE: 13.31 (2.67) [*] Control: 11.05 (7.62) [*]		
					Serum (mg/l)	PE: 0.24 (0.01) [*] Control: 0.05 (0.03) [*]		

Abbreviations: hazard ratio (HR); odds ratio (OR); risk ratio (RR); confidence interval (CI); interquartile range (IQR); preeclampsia (PE).

(†) *Note.* Levels represent mean (standard deviation), median (IQR)

(§) geometric mean (IQR)

(*) or median (SEM)

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Table 4d.

Mercury and preeclampsia

Study				**Exposure**			**Association**	
Reference	Design	Location	Sample size	Timing	Assessment	Level	Modeled Exposure	HR/OR/RR (95% CI)
Vigeh 2006	Case-control	Tehran, Iran	N=396 n_{PE}=31	Within 24 hours after delivery	Maternal whole blood (μg/l)	PE: 1.35 (0.74) Control: 1.34 (1.19)		
					Umbilical cord blood (μg/l)	PE: 1.69 (1.19) Control: 1.70 (1.33)		

Abbreviations: hazard ratio (HR); odds ratio (OR); risk ratio (RR); confidence interval (CI); interquartile range (IQR); preeclampsia (PE).

Note. Levels represent mean (standard deviation), median (IQR) (†), geometric mean (IQR) (§), or median (SEM) (*)

Table 5.

Non-persistent organic pollutants and preeclampsia

Study				Exposure				Association	
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	Modeled Exposure	HR/OR/RR (95% CI)
Cantonwine 2016	Nested case-control	MA, U.S.	N=406 n_{PE}=50	Median sample collection across 4 visits (weeks): 9.7, 17.9, 36.0, 35.1	Urine (ng/ml)	BPA	Visit 1: 1.34 (1.24, 1.45)*	IQR increase, pregnancy average	HR: 1.14 (0.73, 1.79)
						MEHP	12.7 (11.3, 14.3)*		1.40 (1.03, 1.89)
						∑DEHP	0.46 (0.41, 0.51)*		1.79 (1.30, 2.46)
						MBzP	6.9 (6.3, 7.7)*		0.93 (0.64, 1.35)
						MBP	17.9 (16.5, 19.5)*		1.06 (0.74, 1.53)
						MiBP	7.3 (6.8, 7.8)*		0.84 (0.58, 1.21)
						MEP	140.8 (123.2, 160.9)*		1.40 (1.00, 1.95)
						MCPP	2.3 (2.0, 2.5)*		0.95 (0.71, 1.28)
Leclerc 2014	Case-control	Quebec, Canada	N=58 n_{PE}=23	Delivery	Serum (ng/ml)	BPA	PE: 2.80 † Control: 3.00 †		
					Placenta (ng/g)		PE: 9.40 † Control: 3.00 †		
Ye 2017	Nested case-control	Shanghai, China	N=173 n_{PE}=74	16–20 weeks	Serum (μg/l)	BPA	PE: 3.40 (1.85, 6.73) † Controls: 1.50 (0.05, 1.98) †	Per unit increase in BPA	OR: 1.39 (1.19, 1.63)
Shaw 2018	Nested case-control	CA, U.S.	Severe PE, 20–31 weeks N=198,825 n_{PE}=824	One month prior to conception to delivery, every 4 weeks	Estimated	543 pesticides; 69 classes	1st month of pregnancy: 25.8% of women exposed	Exposure to >5 chemical groups vs. no exposure	Severe PE, 20–31 weeks OR: 1.10 (0.84, 1.45)
			Severe PE, 32–36 weeks N=200,108 n_{PE}=2647				26.1%		Severe PE, 32–36 weeks 0.82 (0.70, 0.98)
			Mild PE, 20–31 weeks N=197,668 n_{PE}=207				28.0%		Mild PE, 20–31 weeks 1.10 (0.63, 1.91)

Study	Exposure		Association
	Mild PE, 32–36 weeks N=200,0354 n_{PE}=2573	27.4%	Mild PE, 32–36 weeks 0.85 (0.71, 1.00)

Abbreviations: hazard ratio (HR); odds ratio (OR); risk ratio (RR); confidence interval (CI); preeclampsia (PE); bisphenol a (BPA); interquartile range (IQR); mono(2-ethylhexyl) phthalate (MEHP); summed di(2-ethylhexyl) phthalate (∑DEHP); monobenzyl phthalate (MBzP); mono-n-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); mono-ethyl phthalate (MEP); mono(3-carboxypropyl) phthalate (MCPP); Massachusetts (MA); California (CA)

(†) *Note.* Levels represent mean (standard deviation), median (IQR)

(§) geometric mean (IQR)

(✱) geometric mean (95% CI)

(*) or median (SEM)