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STATE-OF-THE-ART REVIEW

Effects of Environmental Exposures on Fetal and Childhood Growth Trajectories

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Abstract

Delayed fetal growth and adverse birth outcomes are some of the greatest public health threats to this generation of children worldwide because these conditions are major determinants of mortality, morbidity, and disability in infancy and childhood and are also associated with diseases in adult life. A number of studies have investigated the impacts of a range of environmental conditions during pregnancy (including air pollution, endocrine disruptors, persistent organic pollutants, heavy metals) on fetal and child development. The results, while provocative, have been largely inconsistent. This review summarizes up to date epidemiologic studies linking major environmental pollutants to fetal and child development and suggested future directions for further investigation.

KEY WORDS prenatal exposure, environmental pollutants, fetal growths, adverse birth outcomes, low birth weight, catch-up growth, child development

INTRODUCTION

Impaired fetal growth represents one of the greatest public health threats to this generation of children. More than 30 million low-birth-weight (LBW; <2500 g) infants are born annually worldwide. It is now widely accepted that altered fetal growth, LBW, and rapid growth in early childhood (catch-up growth) are associated with an increased risk for multiple diseases in adulthood, including hypertension, obesity, cardiovascular diseases, diabetes, and cancers. Thus, identification of the risk factors for impaired fetal growth, LBW, and catch-up growth will help to not only improve children's health but also to provide etiologic insight and inform prevention strategies for many adult diseases. Although tremendous efforts have been made to understand these risk factors, results from epidemiologic studies have been inconsistent, and the environmental factors that may induce this human suboptimal fetal growth and rapid catch-up growth are currently unclear.

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EFFECTS OF ENVIRONMENTAL EXPOSURES ON FETAL AND CHILDHOOD GROWTH

A better understanding of the potential effects of environmental exposures on fetal and childhood growth is of marked public health significance because of increasing exposure levels of a variety of pollutants resulting from increased industrialization; the known capability of environmental pollutants to readily transport across the placenta; plausible mechanisms linking environmental exposures to impaired fetal and childhood growth; and the influence of early-life exposures on the risk for both childhood and adult diseases. In this review, we provide a brief but thorough overview of the studies linking 4 major environmental pollutants (perfluorinated compounds [PFCs], heavy metals, polyhalogenated aromatic hydrocarbons [PHAHs], and air pollutants) to perturbations in fetal and childhood growth and development.

Effects of Prenatal Exposure to Perfluorinated Compounds on Fetal and Childhood Growth.

Definition

PFCs, also known as perfluorinated alkylated substances (PFAS), are a class of man-made organofluorine compounds. Fluorocarbons are both lipophobic and hydrophobic. The 2 most extensively used and studied PFCs are perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), each of which have an 8-carbon backbone and are hence also known as C8. Because of their strong C-F covalent bonds, PFOA/PFOS are resistant to degradation processes, which allow them to persist indefinitely in the environment as some of the most widespread persistent emerging environmental contaminants.[1,2]

Exposure

Humans are exposed to PFCs on a daily basis through intake of contaminated food, water, air, and dermal exposure due to widespread use in consumer and industrial products since the 1950s as surfactants and emulsifiers.[1,3,4] Their unique water- and oil-repelling characteristics make them suitable for diverse applications in manufacturing of food packaging and containers (eg, microwave popcorn bags), nonstick cookware, textiles, carpet and carpet cleaning liquids, upholstered furniture, cosmetics, household cleaners, refrigerants, adhesives, construction materials, electronic and photographic devices, fire retardants, and insecticides. During the past decade, efforts have been made to eliminate these persistent chemicals from the US market. As such, PFOA production has been reduced and PFOS is no longer manufactured in the United States. However, because of their widespread presence in the environment, their resistance to degradation, their ability to bioaccumulate in humans, and their wide production and use in developing countries (eg, PFOS production alone reached >250 tons a year in China in 2006),[5] these pollutants have been detected worldwide in the environment, wildlife, and humans. In the US general population, PFOA/PFOS can be detected in almost all serum samples. These compounds are stored in the blood with high affinity for albumin or liver and kidney,[6] can cross the placental barrier reaching the fetal circulation, and pass to infants through breastfeeding.

Epidemiologic Studies and Potential Mechanisms of PFC Exposure, Fetal Development, and Birth Size

Despite the fact that PFCs have been extensively used in industrial and consumer products since the 1950s and exposure to PFCs has been clearly demonstrated to result in developmental toxicity in animal studies,[7-10] their potential adverse effect on human health threat, especially the association of prenatal exposure and fetal growth, has only recently received much attention. Our knowledge of PFC-induced developmental effects in humans is still in its infancy.[11] We are not aware of any published studies to date that have directly investigated the relationship between prenatal exposure to PFCs and fetal growth based on ultrasound measures of fetal development. Instead, previous studies have used birth size as a marker for fetal growth and development and several epidemiologic studies have reported an association between maternal serum or cord blood PFOA/PFOS concentrations and lower birth weight,[12-20] with some of them reporting a statistically significantly reduced birth weight associated with exposure to PFOA[12,13,15,18,21] and/or PFOS (Table 1).[16,19,21] Two studies also reported a significant inverse association with birth weight for maternal exposure to perfluorohexane sulfonate (PFHxS).[11,21] Exposure to both PFOA and PFOS[12] or PFOS alone[11] was also associated with a significant inverse association with ponderal index. Several studies, however, found no association between prenatal exposure to PFCs and birth weight, birth length, or ponderal index.[15,20,22-25]

Table 1. Prenatal PFCs Exposure and Selected Birth Outcomes*

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes			
									BW/LBW	BL	PB	PI
PFOA	Significant results											
	Fei et al. 2007[13]	Danmark	Cohort	1400	1996-2002	Maternal blood	5.6 ng/m†	1st trimester	BW: β = −10.63 g; 95% CI, −20.79 to −0.47 g	NS	OR, 2.94; 95% CI, 1.05-8.28 at second quartile	NS
	Hamm et al. 2010[15]	Canada	Cohort	252	2005-2006	Maternal blood	1.5 ng/m‡	2nd trimester	BW: β = −37.4 g; 95% CI, −86 to 11.2 g			
	Maisonet et al. 2012[21]	UK	Cohort	447	1991-1992	Maternal blood	3.7 ng/m‡	During pregnancy	BW: β = −133 g; 95% CI, −237 to −30 g	NS		NS
	Apelberg et al. 2007[12]	US	Cross-sectional	293	2004-2005	Cord blood	1.6 ng/m§	At birth	BW: β = −104 g; 95% CI, −213 to 5 g/ln-unit	NS		β = −0.070 g/cm^3 * 100, 95% CI, −0.138 to −0.001 per ln-unit
	Wu et al. 2012[18]	China	Cohort	167	2007	Maternal blood	Guiyu: 16.95 ng/mL‡ Chaonan: 8.7 ng/mL‡	At birth	BW: β = −267.3 g; 95% CI, −573.27 to −37.18 g/lg-unit	β = −1.91 cm, 95% CI, −3.31 to −0.52 cm/lg-unit		NS
	Insignificant results											
	Monroy et al. 2008[22]	Canada	Cohort	101	2004-2005	Maternal blood	2.13 ng/mL‡	24-28 wk of pregnancy	NS			
						Maternal blood	1.81 ng/mL‡	At birth	NS			
						Cord blood	1.58 ng/mL§	At birth	NS			
	Washino et al. 2009[19]	Japan	Cohort	428	2002-2005	Maternal blood	1.4 ng/mL	2nd trimester	NS	NS		
	Nolan et al. 2009[20]	US	Cross-sectional	1555	2003-2005	Drinking water	LHWA: 6.78 ug/L Belpre: 0.21 ug/L Marietta: 0.0065 ug/L Warren: 0.007 ug/L	NA	NS			

(*continued on next page*)

Table 1. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes			
									BW/LBW	BL	PB	PI
	Savitz et al. 2012[23]	US	Case–control	4534	1990-2004	Estimated PFOA	WV: 10.2 ng/mL OH: 6.3 ng/mL	At birth			NS	
	Savitz et al. 2012[24]	US	Case–control	11,737	2005-2006	Estimated PFOA	1990-1994: 6 ng/mL 1995-1999: 10.7 ng/mL 2000-2005: 15.9 ng/mL	At birth	NS		NS	
	Lee et al. 2013[11]	South Korea	Cross-sectional	70	2011	Maternal blood	2.73 ng/m†	At birth	NS	NS		NS
						Cord blood	2.09 ng/m‖	At birth	NS	NS		NS
	Darrow et al. 2013[16]	US	Cohort	1665	2005-2010	Maternal blood	31 ng/m†	NA	NS		NS	
PFOS	Significant results											
	Washino et al. 2009[19]	Japan	Cohort	428	2002-2005	Maternal blood	5.6 ng/m†	2nd trimester	BW: $\beta = -148.8$ g; 95% CI, −297 to −0.5 g/$\log_{10}$ unit	NS		
	Hamm et al. 2010[15]	Canada	Cohort	252	2005-2006	Maternal blood	7.8 ng/mL‡	2nd trimester	BW: $\beta = 31.3$ g; 95% CI, −43.3 to 105.9 g			
	Fei et al. 2011[13]	Danmark	Cohort	1400	1996-2002	Maternal blood	35.3 ng/m†	2nd trimester	NS	NS	OR, 2.83; 95% CI, 1.10-7.30 at third quartile	NS
	Apelberg et al. 2007[12]	USA	Cross-sectional	293	2004-2005	Cord blood	5 ng/mL§	At birth	BW: $\beta = -69$ g; 95% CI, −149 to 10 g/ln-unit	NS		B = −0.074 g/cm^3 * 100, 95% CI, −0.123 to −0.025
	Maisonet et al. 2012[21]	UK	Cohort	447	1991-1992	Maternal blood	19.6 ng/m†	During pregnancy	BW: $\beta = -140$ g; 95% CI, −238 to −42 g at upper tertile	B = −0.63 cm; 95% CI, −1.11 to −0.15 cm		
	Lee et al. 2013[11]	South Korea	Cross-sectional	70	2011	Maternal blood	10.77 ng/mL†	At birth	NS	NS		OR, 0.22; 95% CI, 0.05-0.90

(*continued on next page*)

Table 1. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes			
									BW/LBW	BL	PB	PI
						Cord blood	3.44 ng/mL[|]	At birth	NS	NS		
	Darrow et al. 2013[16]	US	Cohort	1665	2005-2010	Maternal blood	15.6 ng/mL[†]	NA	BW: β = −49 g; 95% CI, −90 to −8 g/log unit		NS	
	Insignificant results											
	Monroy et al. 2008[22]	Canada	Cohort	101	2004-2005	Maternal blood	16.6 ng/mL[‡]	24-28 wk of pregnancy	NS			
						Maternal blood	14.54 ng/mL[‡]	At birth	NS			
						Cord blood	6.08 ng/mL[§]	At birth	NS			
PFHxS	Significant results											
	Hamm et al. 2010[15]	Canada	Cohort	252	2005-2006	Maternal blood	0.97 ng/mL[‡]	2nd trimester	BW: β = 21.9 g; 95% CI, 23.4-67.2 g			
	Maisonet et al. 2012[21]	UK	Cohort	447	1991-1992	Maternal blood	1.6 ng/mL[‡]	During pregnancy	BW: β= −108 g; 95% CI, −206 to −10 g	β= −0.82 cm; 95% CI, −1.29 to −0.34 cm		
	Lee et al. 2013[11]	South Korea	Cross-sectional	70	2011	Maternal blood	1.35 ng/mL[†]	At birth	LBW: OR, 0.26; 95% CI, 0.08-0.85	OR, 0.33; 95% CI, 0.09-1.17		NS
						Cord blood	0.67 ng/mL[|]	At birth	NS			
	Insignificant results											
	Monroy et al. 2008[22]	Canada	Cohort	101	2004-2005	Maternal blood	1.82 ng/mL[‡]	24-28 wk of pregnancy	NS			
						Maternal blood	1.62 ng/mL[‡]	At birth	NS			
						Cord blood	2.07 ng/mL[§]	At birth	NS			

BL, birth length; BW, birth weight; IQR, interquartile change; LBW, low birth weight; LHWA, Little Hocking Water Association; PB, preterm birth; PFOA, perfluorooctanoic acid; PI, ponderal index; NA, not available.

* The studies included in Table 1 focus on those articles published since 1990 (sample size >50). The table lists exact ORs or β-values for results reaching statistical significance (*$P < 0.05$). Blank spaces in the table indicate that these variables were not investigated by the studies. The birth outcomes listed are restricted to major birth outcomes due to space limitation (BW, BW, BL, PB, and PI).

† Mean levels in maternal blood.

‡ Median levels in maternal blood.

§ Median levels in cord blood.

| Mean levels in cord blood.

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Although the nature of the mechanisms underlying these associations have not been established, several potential pathways have been proposed linking prenatal PFC exposure to impaired fetal development and birth size in humans, including hormone disruption, altered lipid metabolism, immunotoxicity in pregnant women, and direct fetal toxicity.

Hormone disruption. Thyroid hormones are pivotal for normal fetal growth and development. PFOA/PFOS exposure is able to alter thyroid hormone signaling and interfere with thyroid hormone function and homeostasis.[6,19,20] This could trigger developmental and maternal hypothyroidism, which is associated with LBW and human development.[6]

Estrogen has been demonstrated to be important in promoting fetal growth. PFCs affect the expression of estrogen-responsive genes and cause changes in estrogen synthesis. To date, the only demonstrated mode of action by which the health effects of PFOA are mediated is via the activation of the peroxisome proliferator-activated receptor (PPAR)α.[26] Recent studies suggest that PFCs may alter steroid hormone production or act indirectly, via ovarian effects, as a novel means of endocrine disruption.[1] As endocrine disruptors, PFCs could interfere with estrogen receptors.[27,28]

Lipid metabolism disruption. The fetus is sensitive to the availability of cholesterol and tricylglycerol, which support cellular growth, differentiation, and adipose accumulation.[12] PFC exposure has been associated with expression of genes involved in both cholesterol mobilization and transport.[11,29,30] The PPAR family also plays an important role in control of cellular differentiation and in the transcriptional control of lipids and carbohydrate metabolism. An experimental study showed that mice prenatally exposed to PFOA who express the *PPARα* gene had lower postnatal body weights than exposed knockout mice that do not express the *PPARα* gene.[30] Human studies show that exposure to PFOA, and possibly to PFOS, may be associated with increased low-density lipoprotein cholesterol.[31] A significant negative trend was observed in workers between PFOA exposure and blood levels of high-density lipoprotein, the good cholesterol that transports cholesterol back to the liver for excretion.[32]

Other potential mechanisms. Potential mechanisms linking PFC exposure to impaired fetal growth and reduced birth weight may include immunotoxicity, resulting in increased susceptibility to infection in pregnant women; reduced fetal nutrient intake through interference with regular transplacental transfer[13,20]; and direct fetal toxicity (such as adverse effects on the fetal immune system or fetal thyroid development).[6,20]

Epidemiologic studies and potential mechanisms of PFC exposure and rapid catch-up growth. Rapid growth in early childhood is an accelerated growth that occurs after reduced intrauterine growth and development. A recent systematic review of 39 publications supports rapid postnatal catch-up growth of LBW neonates as a more important factor than LBW alone in the genesis of risk for cardiovascular disease later in life.[33] Thus, identification of risk factors for rapid catch-up growth in early childhood is important for prevention of adult diseases and may provide additional insight into disease etiology.

Several epidemiologic studies have examined the relationship between prenatal PFC exposure and neonatal and childhood growth trajectories or body mass index (BMI) during childhood or adulthood. Data from the Danish National Birth Cohort showed that PFOA and PFOS levels in maternal blood were inversely associated with weight at birth in girls, but by 12 months of age, there was no clear difference in weight in girls between the high- and low-exposure groups.[34] An extended analysis of this study population also found no significant differences in weight and height at 7 years of age based on prenatal serum PFCs levels.[35] Another study from Great Britain found that, although girls with higher prenatal exposure to PFOS, PFOA, and PFHxS were significantly smaller at birth, they were 580 g heavier at 20 months of age than those with lower exposure.[21] In a prospective birth cohort study, higher prenatal PFOA concentrations were associated with elevated BMI and risk for overweight in 20-year-old women.[36] A cross-sectional study of US adults reported no association between serum PFCs levels and obesity.[37] An experimental study reported higher body weights in midlife in female offspring of mice with prenatal exposure to PFOA.[38] Thus, limited laboratory and human studies suggest that prenatal PFCs exposure may accelerate child growth trajectories.

Several potential mechanisms have been suggested to support the hypothesis that prenatal PFCs exposure may affect offspring postnatal growth. Maternal exposure to PFCs could disturb the hypothalamus-adrenal (HPA) axis function in the offspring, potentially affecting pathways such as those controlling corticosteroid blood levels.[39,40] The activity of the HPA axis plays a vital role in fetal and childhood growth, and inappropriate corticosterone levels could lead to significant impairment of linear growth and then catch-up growth in childhood.[41] Maternal PFC exposure could disrupt

thyroid hormone functions,[9,42] and impaired maternal thyroid function is almost invariably associated with adverse birth outcomes such as LBW, which is usually followed by accelerated postnatal growth.

The most remarkable characteristic of catch-up growth is a disproportionately higher rate of fat gain relative to lean tissue gain.[43] Children who are growth restricted during fetal life but subsequently grow rapidly and achieve a higher body weight are the most affected and show an increased adiposity in childhood and later adult life.[44-49] In addition to changes in adipose tissue mass, LBW individuals have a tendency to store this excess adipose tissue centrally. There is growing evidence that the in utero and neonatal environments program the developing fetus and infant for obesity risk. Childhood obesity increases the risk for type 2 diabetes, cardiovascular disease, and metabolic syndrome, and has adverse effects on pulmonary, musculoskeletal, and psychosocial functioning.[50,51] Thus, identifying and developing interventions for modifiable risk factors for reduced fetal growth and rapid catch-up is a public health priority because there are few generally effective interventions to reduce excess adiposity once it is established. It has been suggested that the influence of prenatal exposure to PFCs on weight homeostasis may persist after birth. Environmental stressors, such as PCF exposure, may result in a "thrifty phenotype" that stores excess calories too efficient.[52]

Effects of Prenatal Heavy Metal Exposures on Fetal Growth and Birth Outcomes

Definition

A heavy metal is any metal or metalloid of environmental health concern. Heavy metals include both toxic and essential trace minerals. For toxic heavy metals, some have suggested that the effect of heavy metal exposure on fetal development and pregnancy outcomes may have no thresholds and that even trace levels confer additional risk.[53] Essential minerals, on the other hand, are important for metabolism, growth, and normal function in humans. However, overexposure to essential minerals in humans can produce adverse effects including adversely affecting pregnancy outcomes.[54,55]

Exposure

Heavy metals are ubiquitous environmental pollutants. With the worldwide increase of industrialization and urbanization, humans are increasingly exposed either voluntarily or involuntarily to various heavy metals through occupational and environmental exposures.[56] The most common sources of exposure for the general population are through air inhalation and dietary intake. Airborne heavy metals come from gasoline and coal combustion, industrial emissions, and the spraying of metal-based pesticides, with exposure levels varying by season. Tobacco smoking is an additional relevant source of exposure to heavy metals such as cadmium (Cd) and lead (Pb).[57,58] Heavy metals have different half-lives; for example, Cd has a half-life of about 3 months, whereas chromium (Cr) has a half-life of 50 to 60 days in humans.[59,60] Heavy metals reach the fetus by trans-placental transfer.[61,62] Notably, we demonstrated in a study conducted in China that the median urinary levels of nearly all 12 metals that were evaluated were higher than in Western populations, with considerable overlap with distributions typically reported in Western populations. This pattern of overlapping but heightened exposure levels is consistent with the industrialization and resulting metal pollution across many Chinese cities and provides insight into the contribution of heavy metal exposures on human development relevant to public health worldwide.

Epidemiologic Studies of Metals, Fetal Growth, and Birth Outcomes

Cadmium. Cd is one of the heavy metals that has recently received the most attention and also one of the few toxic metals that showed an increased risk for adverse birth outcomes in the majority of studies (Table 2). A recent birth cohort study from North Carolina reported that Cd levels in maternal blood at birth were associated with increased risk for delivering small-for-gestational-age (SGA) infants (odds ratio, [OR] for high versus low exposure = 1.71; 95% confidence interval [CI], 1.10-2.64).[71] Of the several studies having both maternal blood and cord blood at birth, 4 reported an increased risk for adverse pregnancy outcomes associated with maternal or cord blood levels of Cd. A study from Saudi Arabia reported that maternal Cd levels >0.976 μg/L were associated with a 5.94-fold increased risk for SGA at birth.[70] A study conducted in China reported that LBW occurred more frequently in infants with higher Cd levels in cord blood than in those exposed to lower levels of Cd in cord blood.[67] This result was consistent with a study from Taiwan, which also reported that Cd levels in cord blood were inversely

Table 2. Prenatal Heavy Metals Exposure and Selected Birth Outcomes*

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
Cd	Significant results												
	Nishijo et al. 2010[63]	Japan	Cross-sectional	55	NA	Maternal blood	9.29 nmol/L†	GW 30-32	NS	β = −0.590 cm; P = 0.001*	NS		
	Menai et al. 2012[64]	France	Cohort	901	2002	Maternal blood	0.8 μg/L‡	2nd trimester	LBW: OR, 1.41; 95% CI, 1.00-1.99				
						Cord blood	0.5 μg/L§	At birth	NS				
	Kippler et al. 2012[65]	Bangladesh	Prospective cohort	1,616	2001-2003	Maternal urine	0.63 μg/L‖	GW 8	BW: β = −31.0 g; 95% CI, −59 to −2.8 g	NS	β = −0.15 cm; 95% CI, −0.27 to −0.026 cm	NS	
	Ikeh-Tawari et al. 2013[66]	Nigeria	Cross-sectional	160	NA	Maternal blood	0.02-0.03 μmol/L	3rd trimester	r = −0.708; P = 0.0000	r = −0.332; P = 0.013	r = −0.499; P = 0.001		
	Sun et al. 2014[67]	China	Cross-sectional	209	NA	Maternal blood	0.48 μg/L¶	3rd trimester	BW: β = −284.72 g; P = 0.03*	β = −0.16 cm; P = .10			
						Maternal urine	0.13 μg/L‖	3rd trimester	NS	NS			
						Cord blood	0.09 μg/L§	At birth	NS	NS			
	Tian et al. 2009[68]	China	Cohort	109	2002-2007	Maternal blood	1.80 μg/L‡	1 wk before delivery	NS	NS			
						Cord blood	0.60 μg/L§	At birth	BW: t = −2.05; P < 0.05*	t = −2.79; P < 0.05*			
						Placenta	0.15 μg/g dry wt.	At birth	NS	NS			
	Lin et al. 2011[69]	Taiwan	Cohort	486	2004-2005	Maternal blood	1.05 μg/L‡	At birth	NS	NS	NS		
						Cord blood	0.31 μg/L§	At birth	NS	NS	β = −0.78 cm; 95% CI, −1.38 to −0.19 cm		
	Al-Saleh et al. 2014[70]	Saudi Arabia	Cross-sectional	1578	2005-2006	Maternal blood	0.986 μg/L†	At birth	NS				NS
						Cord blood	0.780 μg/L¶	At birth	LBW: OR, 1.894; 95% CI, 1.266-2.834				OR, 1.728; 95% CI, 1.146-2.606
						Placenta	0.045 μg/g dry wt.	At birth	NS				NS
	Johnston et al. 2014[71]	US	Cohort	1027	2005-2010	Maternal blood	0.46 μg/L†	At birth	LBW: OR, 1.07; 95% CI, 0.67-1.73	NS	NS	OR, 1.17; 95% CI, 0.74-1.87	OR, 1.71; 95% CI, 1.10-2.64
	Insignificant results												
	Loiacono et al. 1992[72]	Yugoslavia	Cohort	1502	1985-1986	Placenta	0.50-0.73 μmol/L	At birth	NS				
		France		102	2005-2008	Cord blood		At birth	NS				

(continued on next page)

Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
	Frery et al. 1993[73]		Cross-sectional				3-35.4 ng/g wet wt.						
						Neonatal hair	4-47 ppm (median)	At birth	NS				
	Odland et al. 1999[74]	Norway and Russia	Cross-sectional	262	1993-1994	Maternal blood	1.8 nmol/L‡	At birth	NS				
						Cord blood	2.2 nmol/L§	At birth	NS				
	Nishijo et al. 2002[75]	Japan	Cross-sectional	57	1999	Maternal urine	NA	At birth	NS	NS	NS		
	Falcon et al. 2003[76]	Spain	Cross-sectional	96	NA	Placenta Smokers	51 ng/g dry tissue	At birth	NS				
						Nonsmokers	33.6 ng/g dry tissue mean	At birth	NS				
	Dwivedi et al. 2013[77]	India	Cross-sectional	1000	NA	Maternal blood	0.95 µg/L†	At birth	NS				
						Cord blood	0.51 µg/L¶	At birth	NS				
	García-Esquinas et al. 2013[78]	Spain	Cross-sectional	145	2003-2004	Maternal blood	0.53 µg/L‡	At birth	NS	NS			
						Cord blood	0.27 µg/L§		NS	NS			
						Father blood	0.49 µg/L#		NS	NS			
	Zheng et al. 2014[79]	China	Cross-sectional	1106	2010	Cord blood	0.42 µg/L¶	At birth	NS				
Pb	Awasthi et al. 2002[80]	India	Cohort	500	1994-1995	Maternal blood	143.4 µg/L	1st trimester 2nd trimester 3rd trimester	LBW: OR, 0.17; 95% CI, 0.04-0.75				
	Jelliffe-Pawlowski et al. 2006[81]	US	Cross-sectional	262	1996-2002	Maternal blood	10-1300 µg/L	1st trimester 2nd trimester 3rd trimester				OR, 3.2; 95% CI, 1.2-7.4 @ PbB ≥10 µg/L	OR, 4.2; 95% CI, 1.3-13.9* @ PbB ≥10 µg/L
	Cantonwine et al. 2010[82]	Mexico	Cohort	235	1997-1999	Maternal blood	72 µg/L †	1st trimester				NS	
						Maternal blood	63 µg/L †	2nd trimester				OR, 1.75; 95% CI, 1.02-3.02	
						Maternal blood	68 µg/L†	3rd trimester				NS	
						Cord blood	59 µg/L¶	At birth				NS	
	Gundacker et al. 2010[83]	Austria	Longitudinal	53	2005	Maternal blood	24.9 µg/L‡	GW 34-38	BW: $\beta = -0.258$ g; $P = 0.007$	NS			
						Cord blood	13.4 µg/L§	At birth	NS	NS			
						Placenta	25.8 µg/kg	At birth	NS	NS			

(continued on next page)

Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
						Meconium	15.5 μg/kg	The first 5 postnatal days	NS	β = −0.385 cm; $P = 0.012$			
	González-Cossío et al. 1997[84]	Mexico	Cross-sectional	272	NA	Maternal blood	81 μg/L[‡]	At birth	NS				
						Cord blood	62 μg/L[§]	At birth	NS				
						Maternal tibia	9.8 Pb/g (mean)	1-mo postpartum	BW: β = −7.29 g; $P = 0.003$[*]				
						Patella	14.2 Pb/g (mean)	1-mo postpartum	NS				
	Irgens et al. 1998[85]	Norway	Cross-sectional	37,816	1970-1993	Occupational record	NA	Records	LBW: RR, 1.34; 95% CI, 1.12-1.60				
	Odland et al. 1999[74]	Norway and Russia	Cross-sectional	262	1993-1994	Maternal blood Norway	0.06 μmol/L[‡]	At birth	BW: β = −1068 g; 95% CI, −2134 to −2 per g/unit				
						Maternal blood Russia	0.14 μmol/L[‡]	At birth	NS				
						Cord blood Norway	0.05 μmol/L[§]	At birth	NS				
						Cord blood Russia	0.10 μmol/L[§]	At birth	NS				
	Berkowitz et al. 2006[86]	US	Ecological	169,878	1970-1981	Registration	NA	NA	LBW: OR, 2.4; 90% CI, 1.6-3.6				OR, 1.9; 90% CI, 1.3-2.8
	Zentner et al. 2006[87]	Brazil	Cross-sectional	55	2002	Cord blood	39 μg/L[¶]	At birth	BW: β = −0.275; $P = 0.048$	β = −0.460; $P = 0.003$			
	Atabek et al. 2007[88]	Turkey	Cross-sectional	54	NA	Cord blood	144 μg/L[¶]	At birth	BW: β = −0.81 g; $P = 0.01$	β = 0.41 cm; $P = 0.05$			
	Zhu et al. 2010[89]	US	Retrospective cohort	43,288	2003-2005	Maternal blood	20 μg/L	HMR PbB reports in New York State	β = −27.4 g; 95% CI, −17.1 to −37.8 g/log unit			OR, 1.04; 95% CI, 0.89-1.22/log unit	OR, 1.07; 95% CI, 0.93-1.23/log unit
	Xie et al. 2013[5]	China	Cross-sectional	252	2010-2011	Maternal blood	32 μg/L[‡]	Within 3 d before delivery	BW: β = −148.99 g; 95% CI, −286.33 to −11.66 g				
						Cord blood	25.2 μg/L[§]	At birth	NS	β = −0.84 cm; 95% CI, −1.52 to −0.16 cm			
	Taylor et al. 2015[90]	UK	Prospective birth cohort	4285	1991-1992	Maternal blood	36.7 μg/L[†]	During pregnancy	BW: β = −13.23 g; 95% CI, −23.75 to −2.70 g		β = 0.04 cm; 95% CI, −0.07 to −0.06 cm	OR, 2; 95% CI, 1.35-3.00 @ PbB ≥5 lg/dL	

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
	Insignificant results												
	Loiacono et al. 1992[72]	Yugoslavia	Cohort	1502	1985-1986	Maternal blood	0.25-1.05 µmol/L	Mid-pregnancy	NS				
						Cord blood	0.27-0.98 µmol/L	At birth	NS				
	Sowers et al. 2002[91]	US	Cross-sectional	705	NA	Maternal blood	12 µg/L[†]	1st trimester 2nd trimester 3rd trimester at birth	NS				NS
						Cord blood	13 µg/L[§]	At birth	NS				
	Sun et al. 2014[67]	China	Cross-sectional	209	NA	Maternal blood	39.50 µg/L[‡]	3rd trimester	NS	NS			
						Maternal urine	0.48 µg/L[‖]	3rd trimester	NS	NS			
						Cord blood	31.62 µg/L[§]	At birth	NS	NS			
	Mirghani et al. 2010[92]	Saudi Arabia	Cross-sectional	176	NA	Maternal blood	200 µg/L[‡]	At birth	NS				
	Xu et al. 2011[93]	China	Cross-sectional	142	2006-2007	Maternal blood	6.68 µg/L[†]	Before delivery	NS				
						Cord blood	4.25 µg/L[¶]	At birth	NS				
	Rahman et al. 2012[94]	Kuwait	Cross-sectional	194	NA	Maternal blood	57.7 µg/L[†]	At birth	NS		NS		
						Cord blood	109.2 µg/L[¶]	At birth	NS		NS		
	Garcíasquinas et al. 2013[78]	Spain	Cross-sectional	145	2003-2004	Maternal blood	19.80 µg/L[‡]	At birth	NS	NS			
						Cord blood	14.09 µg/L[§]		NS	NS			
						Father blood	33 µg/L[**]		NS	NS			
	Dwivedi et al. 2013[77]	India	Cross-sectional	1,000	NA	Maternal blood	110.8 µg/L[†]	At birth	NS				
						Cord blood	73.7 µg/L[†]	At birth	NS				
	Al-Saleh et al. 2014[70]	Saudi Arabia	Cross-sectional	1578	2005-2006	Maternal blood	28.97 µg/L[†]	At birth	NS				
						Cord Blood	25.51 µg/L[¶]	At birth	NS				
						Placenta	0.579 µg/g dry wt.	At birth	NS				
As	Significant results												
	Rahman et al. 2009[95]	Bangladesh	Cohort	1,578	2002-2003	Maternal urine	79 µg/L[‖]	GW 8	BW: β = −1.68 g; 95% CI, −1.06 to −2.30 g	NS	β = −0.05 cm; 95% CI, −0.02 to −0.08 cm		

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
							80 μg/L[‖]	GW 30	NS	NS	NS		
	Hopenhayn et al. 2003[96]	Chile	Ecological	844	1998-2000	Drinking water	42 μg/L <1 μg/L	1998	BW: β = −57 g; 95% CI, −123 to 9 g				
	Yang et al. 2003[97]	Taiwan	Ecological	18,259	1983-1997	Drinking water	>0.9 ppm	Na	BW: β = −29.05; 95% CI, −13.55 to −44.55g			OR, 1.1; 95% CI, 0.91-1.31	
	Huyck et al. 2007[98]	Bangladesh	Cohort	57	2004-2005	Maternal hair	0.14-3.28 μg/g	First prenatal visit	BW: β = −193.5 g; 95% CI, −103.5 to −283.5 g				
						Newborn hair and toenail	<0.001-0.78 μg/g	After birth	NS				
	Xu et al. 2011[93]	China	Cross-sectional	142	2006-2007	Maternal blood	4.13 μg/L[†]	Before delivery	BW: β = −354.405 g; 95% CI, −677.527 to −31.284 g @ male				
	Guan et al. 2012[99]	China	Cross-sectional	125	2006-2007	Maternal blood	5.3 μg/L[‡]	At birth	BW: β = −0.19 g; $P = 0.015$	β = −0.20 cm; $P = 0.017$	NS		
						Cord blood	3.71 μg/L[§]	At birth	NS	NS	β = −0.19 cm; $P = 0.021$		
	McDermott et al. 2014[100]	US	Cohort	9920	1996-2002	Soil sample	NA	NA	LBW: OR, 1.04; 95% CI, 1.02-1.07				
	Insignificant Results												
	Kwok et al. 2006[101]	Bangladesh	Cross-sectional	2006	2003	Drinking water	24-139 ppb	During pregnancy	NS				
	Shirai et al. 2010[102]	Japan	Prospective cohort	78	2007-2008	Maternal urine	76.9 ug/g	GW 9-40	NS	NS	NS		
	Kippler et al. 2012[103]	Bangladesh	Prospective cohort	1929	2001-2003	Maternal urine	79 μg/L[‖]	GW 8	NS	NS	NS		
							85 μg/L[‖]	GW 30	NS	NS			
	Zheng et al. 2014[79]	China	Cross-sectional	1106	2010	Cord blood	(Case) 6.15 μg/L[§]	At birth	NS				
						Cord blood	(Control) 5.72 μg/L [§]						
Hg	Significant results												
	Lee et al. 2010[104]	South Korea	Cohort	417	2006-2008	Maternal blood	3.67 μg/L[‡]	GW 2-20	BW: β = −68.6 g; 95% CI, −138.6 to 1.5 g				
						Maternal blood	3.30 μg/L[‡]	GW8-42	BW: β = −65.5 g; 95% CI, −138.6 to 4.5 g				

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
						Cord blood	5.53 μg/L[§]	At birth	BW: β = −86.4 g; 95% CI, −135.6 to −9.7 g				
	Burch et al. 2014[105]	US	Ecological	362,625	1995-2005	Fish	Ref: ≤0.17 ppm High >0.62 ppm	Registration	LBW: OR, 1.04; 95% CI, 1.00-1.09; upper quartile; lowest quartile			OR, 1.02; 95% CI, 0.98-1.06	
	Vejrup et al. 2014[106]	Norway	Cohort	62,941	1999-2009	Dietary intake	0.6-2.29 μg/kg body weight per week	Questionnaire	BW: β = −34 g; 95% CI, −46 to −22 g				OR, 1.19; 95% CI, 1.08-1.30
	Insignificant results												
	Hujoel et al. 2005[107]	US	Case−control	4468	1993-2000	Dental filling placement	NA	Registration	NS				
	Gundacker et al. 2010[83]	Austria	Cohort	53	2005	Maternal blood	0.7 μg/L[‡]	GW 34-38	NS	NS			
						Cord blood	1.1 μg/L[§]	At birth	NS	NS			
						Maternal hair	184 μg/kg	GW 34-38	NS	NS			
	Drouillet-Pinard et al. 2010[108]	France	Cohort	2002	NA	Maternal hair	0.52 μg/kg	NA	NS	NS	NS		
	Guo et al. 2013[109]	China	Prospective cohort	213	2009-2010	Placentas	3.58 μg/kg	At birth	NS	NS	NS		
						Cord blood	1.54 μg/L[§]	At birth	NS	NS	NS		
						Maternal hair	496.76 μg/kg	3 d postdelivery	NS	NS	NS		
						Fetal hair	233.94 μg/kg	3 d postdelivery	NS	NS	NS		
	Ding et al. 2013[110]	China	Cohort	258	2010-2011	Maternal blood	0.84 μg/L[‡]	Within 3 d before delivery	NS	NS	NS		
						Cord blood	1.46 μg/L[§]	At birth	NS	NS	NS		
	García-Esquinas et al. 2013[78]	Spain	Cross-sectional	145	2003-2004	Maternal blood	3.90 μg/L[‡]	At birth	NS	NS			
						Cord blood	6.72 μg/L[§]	At birth	NS	NS			
						Father blood	5.38 μg/L[#]	At birth	NS	NS			
Zn	Neggers et al. 1990[111]	US	Cohort	476	1984	Maternal blood	11.4-14.0 μmol/L[†]	GW 6-31	BW: β = +37.9 g; 95% CI, +28.8-39 g				
	Kirksey et al. 1994[112]	Egypt	Cohort	476	1982-1987	Maternal blood	10 μmol/L[†]	2nd trimester	BW: β = +45.63 g; 95% CI, 27.95-63.31 g				
	Goldenberg et al. 1995[113]	US	Cohort	580	1991	Maternal blood	9.5 μmol/L[‡]	GW 19	BW: β = +126 g; $P = 0.03$[*]		β = +0.4 cm, $P = 0.02$		

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
	Shirai et al. 2010[102]	Japan	Prospective cohort	78	2007-2008	Maternal urine	393 ug/g-cre g	GW 9-40	$r = 0.247$; $P < 0.05$	NS	NS		
	Ghebremeskel et al. 1994[114]	UK	Cross-sectional	79	1993	Cord blood	13.19 µmol/L ¶	At birth	$r = 0.12$; $P = 0.025$				
	Rwebembera et al. 2006[115]	Tanzania	Case–control study	Cases (81) Control (84)	2002	Maternal blood	(LBW) 10.007 µmol/L†	At birth	LBW: OR, 2.62; 95% CI, 1.36-5.73; low/normal				
						Maternal blood	(Normal) 11.345 µmol/L†						
						Cord blood	(LBW) 9.485 µmol/L¶	At birth	NS				
						Cord blood	(Normal) 10.872 µmol/L¶						
	Abass et al. 2014[116]	Sudan	Case–control	Case (50) Control (50)	2010	Maternal blood	(LBW) 629 µg/L†	At birth	$r = 0.27$; $P = 0.005$				
						Maternal blood	(Normal) 962 µg/L†						
	Insignificant results												
	Lee et al. 2011[104]	South Korea	Cross-sectional	918	NA	24-h recall method	9.9 mg/d	GW 12-28	NS				
	Gebreedhi et al. 2012[117]	Ethiopia	Prospective cohort	575	2011	Maternal blood	7.91 µmol/L†	2nd trimester or 3rd trimester	NS				
	Negandhi et al. 2014[118]	India	Nested case-control	384	NA	Dietary interview	Cases 5.39 mg/dL	GW 26-30	LBW: OR, 0.96; 95% CI, 0.94-0.97				
						Controls 6.77 mg/dL							
	Mistry et al. 2014[119]	UK	Cross-sectional	126	2006	Maternal blood	(SGA) 708.1 µg/L†	3rd trimester	NS				
						Maternal blood	(AGA) 634.4 µg/L†						
	Srivastava et al. 2002[120]	India	Cross-sectional	54	NA	Maternal blood	5.67-6.47 µg/mL†	At birth	NS				
						Cord blood	7.86-9.46 µg/m ¶	At birth	NS				
	Marriott et al. 2004[121]	UK	Cross-sectional	68	1998-1999	Cord blood	12 µmol/L¶	At birth	NS	NS	NS		
	Badakhsk et al. 2011[122]	Iran	Cross-sectional	140	NA	Maternal blood	566 µg/L†	At birth	NS				
		India			2009-1020				NS				

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
	Agarwal et al. 2013[123]		Case–control	Case (220) Control (119)		Maternal blood	(LBW) 460 μg/L[†]	within 48 h of birth					
					Maternal blood	(Normal) 450 μg/L[†]							
					Cord blood	(LBW) 638 μg/L[¶]	At birth	NS					
						Cord blood	(Normal) 674 μg/L[¶]						
	Zheng et al. 2014[79]	China	Cross-sectional	1,106	2010	Cord blood case	2608.68 μg/L[§]	At birth	NS				
						Cord blood control	2504.48 μg/L[§]						
Se	Bogden et al. 2006[124]	US	Nested case-control	233	1996-2002	Maternal blood	106.9 μg/L[†]	1st or 2nd trimester	BW: β = −259 g; 95% CI, −159 to −359 g; $P = 0.01$				
	Sun et al. 2014[67]	China	Cross-sectional	209	NA	Maternal blood	143.53 μg/L[‡]	3rd trimester	NS				
						Maternal urine	4.78 μg/L[‖]	3rd trimester	NS				
						Cord blood	124.61 μg/L[§]	At birth	BW: β = +653.80 g; $P = 0.01$				
	Mistry et al. 2014[119]	UK	Cross-sectional	126	2006	Maternal blood	(SGA) 49.4 μg/L[†]	3rd trimester					OR, 1.16; 95% CI, 1.08-1.24
						Maternal blood	(AGA) 65.1 μg/L[†]						
	Klapec et al. 2008[125]	Croatia	Case–control	Case (49) Control (36)	2003-2004	Placenta	0.14-0.15 μg/g	At birth	β = 6954.92 g; 95% CI, 508.25-11125.61 g/unit				
	Iranpour et al. 2009[126]	Iran	Case–control	Case (49) Control (36)	2008	Maternal blood	(Preterm) 110.56 μg/L[†]	At birth	NS				
						Maternal blood	(Term) 117.03 μg/L[†]						
						Cord blood	(Preterm) 100.30 μg/L[¶]	At birth	$r = 0.59$; $P <$ 0.0001				
						Cord blood	(Term) 124.80 μg/L [¶]						
	Tsuzuki et al. 2013[127]	Japan	Cohort	44	2012	Maternal blood	(Premature) 793 μg/L[¶]	Day of admission	BW: β = +10.985 g; 95% CI, 2.391-19.578 g				
						Maternal blood	(Term) 941 μg/L[¶]						

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
						Cord blood	(Premature) 528 μg/L[†]	At birth	NS				
						Cord blood	(Term) 594 μg/L[†]						
	Al-Saleh et al. 2014[70]	Saudi Arabia	Cross-sectional	250	2006	Cord blood	67.618 μg/L[§]	At birth	BW: β = +0.172 g; $P = 0.028$				
						Placenta	1.053 μg/g dry wt.	At birth					
	Insignificant results												
	Marriott et al. 2004[121]	UK	Cross-sectional	68	NA	Cord blood	19.2 μmol/L[¶]	At birth	NS	NS	NS		
	Shirai et al. 2010[102]	Japan	Prospective cohort	78	2007-2008	Maternal urine	37.6 ug/g-cre	GW9-40	NS				
Mn	Significant results												
	Zota et al. 2009[54]	US	Cross-sectional	470	2002-2007	Maternal blood	24 μg/L[‡]	At birth	U shape				
						Cord blood	42 μg/L[‡]	At birth	NS				
	Guan et al. 2014[128]	China	Cross-sectional	125	2006-2007	Maternal blood	54.98 μg/L[†]	At birth	NS	NS	U shape		
						Cord blood	78.75 μg/L[¶]	At birth	U shape	NS	U shape		
	Chen et al. 2014[55]	China	Cross-sectional	172	2006-2007	Maternal blood	53.8 μg/L[‡]	At birth	U shape				
						Cord blood	76.6 μg/L[§]	At birth	NS				
	Eum et al. 2014[129]	Korea	Cohort	331	2007-2009	Maternal blood	22.5 μg/L[†]	At birth	Curvilinear				
	Insignificant results												
	Takser et al. 2004[130]	Canada	Cohort	149	NA	Maternal blood	8.5-15.6 μg/L[‡]	2nd trimester	NS				
						Cord blood	32.3 μg/L[§]	At birth	NS				
						placenta	0.05 μg/L	At birth	NS				
Cu	Significant results												
	Ghebremeskel et al. 1994[114]	UK	Cross-sectional	79	1993	Cord blood	6.17 μmol/L[¶]	At birth	$r = -0.350$; $P = 0.023$		$r = -0.512$; $P = 0.001$		
	Marriott et al. 2004[121]	UK	Cross-sectional	68	1998-1999	Cord blood	10.1 μmol/L[¶]	At birth	NS	NS	$r = 0.31$; $P = 0.05$		
	Abass et al. 2014[116]	Sudan	Case-control	Case (50) Control (50)	2010	Maternal blood	(LBW) 816 μg/L[†]	At birth	$r = 0.19$; $P = 0.05$				
						Maternal blood	(Normal) 1398 μg/L[†]						

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
						Cord blood	(LBW) 1080 μg/L[¶]	At birth	NS				
						Cord blood	(Normal) 1475 μg/L[¶]						
	Insignificant results												
	Srivastava et al. 2002[120]	India	Cross-sectional	54	NA	Maternal blood	2170-2420 μg/L[†]	At birth	NS				
						Cord blood	1280-1410 μg/L[¶]	At birth	NS				
	Shirai et al. 2010[102]	Japan	Prospective cohort	78	2007-2008	Maternal urine	12.8 μg/g[‖]	GW9-40	NS				
	Tsuzuki et al. 2013[127]	Japan	Cohort	44	2012	Maternal blood	(Premature) 2184 μg/L[†]	Day of admission	NS				
						Maternal blood	(Term) 2292 μg/L[†]						
						Cord blood	(Premature) 283 μg/L [¶]	At birth	NS				
						Cord blood	(Term) 364 μg/L [¶]						
	Mistry et al. 2014[119]	UK	Cross-sectional	126	2006	Maternal blood	(SGA) 1960.2 μg/L[†]	3rd trimester	NS				
						Maternal blood	(AGA) 2059.6 μg/L[†]						
	Zheng et al. 2014[79]	China	Cross-sectional	1,106	2010	Cord blood	Case 909.69 μg/L[§]	At birth	NS				
						Cord blood	Control 905.64 μg/L[§]						
Ni	Pedersen et al. 2015[130]	Europe	Cohort	34,923	1994-2008	Air sample	1.6 ng/m^3	NA	LBW: OR, 1.14; 95% CI, 1.00-1.29				
	Odland et al. 1999[132]	Russia and Norway	Cross-sectional	50	1993-1994	Maternal urine	5-2108 nmol/L	GW20	NS				
	McDermott et al. 2014[100]	US	Retrospective cohort	9920	1996-2002	Soil sample	NA	NA	NS				
	Zheng et al. 2014[79]	China	Cross-sectional	1106	2010	Cord blood	Case 12.65 μg/L[§]	At birth	NS				
						Cord blood	Control 11.63 μg/L[§]						
Cr	Zheng et al. 2014[79]	China	Cross-sectional	1106	2010	Cord blood	Case 4.04 μg/L[§]	At birth	NS				
						Cord blood	Control 4.76 μg/L[§]						

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Table 2. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes				
									BW/LBW	BL	HC	PB	SGA
	McDermott et al. 2014[100]	US	Cohort	9920	1996-2002	Soil sample	NA	NA	NS				
Ti	Bellinger et al. 2012[133]	US	Cross-sectional	76,788	NA	Air sample	NA	NA	LBW: OR, 1.121; 95% CI, 1.0355-1.214 per IQR				
	Laurent et al. 2014[134]	US	Cross-sectional	960,945	2001-2008	Air sample	NA	NA	LBW: OR, 1.003; 95% CI, 1.000-1.006				
	Zheng et al. 2014[79]	China	Cross-sectional	1106	2010	Cord blood	Case 58.74 μg/L[§]	At birth	LBW: OR, 2.38; 95% CI, 1.20-4.73				
						Cord blood	Control 53.07 μg/L[§]						
Tl	Zheng et al. 2014[79]	China	Cross-sectional	1106	2010	Cord blood	Case 0.31 μg/L[§]	At birth	NS				
						Cord blood	Control 0.33 μg/L[§]						
	Xia et al. 2015[135]	China	Case—control	816	2012-2014	Urine	0.32 μg/g	At birth	LBW: OR, 1.90; 95% CI, 1.01-3.58 highest vs lowest tertile				

AGA, appropriate for gestational age; PbB, blood lead level; BL, birth length; BW, birth weight; GW, gestational week; HC, head circumference; HMR, Heavy Metals Registry; IQR, interquartile change; LBW, low birth weight; NA, not available; NS, not significant; PB, preterm birth; SGA, small for gestational age.

* The studies included in Table 2 focus on those articles published since 1990 (sample size more than 50). The table lists exact ORs or β values for results reaching statistical significance (*$P < 0.05$). Blank spaces in the table indicate that these variables were not investigated by the studies. The birth outcomes listed in the table are restricted to major birth outcomes due to space limitation (BW, LBW, BL, HC, birth, and SGA).

† Mean levels in maternal blood.

‡ Median levels in maternal blood.

§ Median levels in cord blood.

‖ Median levels in maternal urine.

¶ Mean levels in cord blood.

Mean levels in father blood.

** Median levels in father blood.

associated with newborn head circumference and height, weight, and head circumference up to 3 years of age.[69] A study conducted in Italy including 45 healthy, nonsmoking pregnant women found that birth weight was inversely correlated with Cd levels in both maternal blood and cord blood.[136]

Several studies using urine samples,[65] or maternal blood samples only,[66] reported an increased risk for adverse birth outcomes associated with Cd exposure. However, some studies did not find any relationship between Cd levels in maternal or cord blood and size at birth.[72,73,75-79,132] To our knowledge, there are currently no epidemiologic studies that have evaluated the association between Cd exposure during the early pregnancy period and fetal development and birth outcomes.

Lead. Early studies of Pb exposure and adverse birth outcomes have been inconsistent (Table 2), but animal models showed that Pb exposure during pregnancy could retard fetal growth. A study from Mexico with 235 pregnant women investigated maternal Pb exposure across all 3 trimesters and birth outcomes and reported that a 1 SD increase in blood Pb levels measured during the second trimester was associated with an OR of preterm birth of 1.75 (95% CI, 1.02-3.02).[82] A study in California reported a similar result as women with maximum pregnancy blood Pb levels >10 μg/dL were at 3.2 times increased risk for preterm birth (95% CI, 1.2-7.4) and 4.2 times increased risk for delivering a SGA newborn (95% CI, 1.3-13.9). The second-trimester maximum blood Pb levels were additionally associated with decreased gestation days in that study.[81]

Most of the studies were conducted based on cross-sectional analyses of Pb exposures measured at birth and specific birth outcomes obtained from birth certificate data. Three record-linkage based studies involving large sample sizes from the United States have all found that maternal blood Pb levels were associated with the risk for decreased birth weight.[85,86,89] Of the studies that analyzed associations with birth outcomes in relation to both maternal blood and cord blood at birth, one found an increased risk for adverse birth outcomes for both maternal and cord blood levels.[137] A cohort study in Austria found maternal blood Pb and meconium Pb was inversely related to birth weight and birth size,[83] and similar results were reported by 2 other studies.[74,84] Nevertheless, the other studies did not find an association in either type of biosamples.[67,72,77,78,138] Among the studies that only measured Pb levels in 1 type of biosample, 5 reported an increased risk for adverse birth outcomes with Pb levels in placental samples,[139] cord blood,[87,88] and maternal blood,[90,140] whereas the other studies found no association between Pb levels in the sample measured.[92]

Arsenic. Recent studies of arsenic (As) and pregnancy outcomes did not find an association between prenatal As exposure and adverse pregnancy outcomes,[79,102] whereas 3 studies conducted in Bangladesh where higher levels of As were found in the drinking water reported an increased risk for adverse birth outcomes (Table 2).[95,98,141] One of the studies found that the influence of As on fetal growth appeared to be sex-dependent with an inverse association with fetal size in boys.[141] The results from earlier studies of maternal As exposure and pregnancy outcomes were not consistent, but most of the studies did not assess individual exposure or control for major confounders.[93,96,99,100,142]

Mercury. A considerable number of epidemiologic studies have examined the association between prenatal exposure to mercury (Hg) and birth size (Table 2). Recent studies from China,[109,110] Austria,[83] Spain,[78] and France[108] did not find an association. However, a cohort study in Korea measured maternal blood Hg levels at early gestational age, and found an inverse relationship between birth weight and maternal and cord blood Hg levels.[104] Similar findings have been previously described in countries that are attributed to maternal consumption of fish species high in Hg. A large cohort study in Norway including 62,941 pregnant women reported that dietary Hg exposure had a significant negative association with the birth weight of offspring, with those in the highest exposure group having an increased risk for giving birth to babies being SGA.[106] An ecological study found that term LBW was more likely among women residing in areas in the upper quartile of predicted total Hg in fish (OR, 1.04; 95% CI, 1.00-1.09) than in the lowest quartile.[105]

Zinc. Three studies using blood samples collected in early pregnancy showed an increased risk for delivering LBW infants associated with maternal blood zinc (Zn) levels (Table 2).[111-113] A retrospective cohort study in Alabama involving 476 women who had maternal serum Zn concentrations measured at 16 weeks of gestation found that women with serum Zn levels in the lowest quartile had 8 times higher the prevalence of LBW than women with serum Zn in the highest quartile after controlling for major confounders.[111] A study that measured Zn levels at 14 weeks gestation also reported a significant association between lower serum Zn concentrations and

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reduced birth weight and other adverse pregnancy outcomes.[143] A clinical trial reported that daily Zn supplementation in women with relatively low plasma Zn concentrations at 19 weeks gestation is associated with higher infant birth weights and larger head circumferences.[113] Conversely, studies using blood samples collected at birth or in late pregnancy have produced inconsistent results, with 8 studies[79,117,119-123] showing no association and 3 studies[114-116] observing an increased risk between maternal serum Zn levels and risk for delivering LBW infants.

Selenium. A similar pattern as related to the potential greater importance of metal exposures early in pregnancy on risk for adverse birth outcomes have been observed for selenium (Se; Table 2). A case-control study from the United States reported that low-normal Se in blood serum collected in early pregnancy (around 16 weeks of gestation) was associated with LBW among full-term pregnancies.[124] Another study from the United Kingdom using blood collected between 28 and 32 weeks also found that low plasma Se levels in adolescent mothers was associated with an increased risk for delivering SGA infants.[119] Studies using blood collected at delivery, however, have reached contrasting conclusions. One study from Japan with both maternal and cord blood reported that maternal blood levels of Se at birth were significantly associated with birth weight, whereas cord blood levels of Se were not.[127]

Manganese. No conclusion can be drawn regarding the association between manganese (Mn) exposure and risk for delivering LBW infants based on current epidemiologic evidence (Table 2). Two studies found an association between maternal Mn levels at birth and LBW but did not find such an association for the cord blood Mn levels from the same population.[54,55] Contrarily, a Chinese study found reduced birth weight with cord blood Mn levels, but not with the maternal blood Mn levels.[99] A Korean study also reported an increased risk for LBW with high levels of maternal blood Mn.[129] The only study that collected blood samples at the first, second, and third trimesters of gestation involving 149 mothers from Canada did not find significant associations between Mn levels in any point in pregnancy and birth outcomes.[62]

Copper. One study reported that, of the 4 essential minerals that were studied (Zn, Cu, Se, and Mn), only maternal blood copper (Cu) levels at term were associated with head circumference (Table 2).[121] Of studies that collected both maternal blood at birth and cord blood, 1 found that only maternal blood levels of Cu were associated with gestational age of the baby,[116] whereas the other 3 studies did not find any relationship between birth outcomes and serum Cu levels in either maternal or cord blood samples.[119,120,127] Other studies that used either cord blood[79] or maternal urine[102] did not find an association between levels of Cu and adverse pregnancy outcomes.

Other metals. Prenatal exposure to nickel (Ni),[73,81,100,130] chromium (Cr),[81,100] thallium (Tl),[81,131] and titanium (Ti)[81,133,135] have been inconsistently associated with adverse birth outcomes from previous studies. However, none of the studies have evaluated the association between exposure to these metals and fetal development and birth outcomes over the entire course of pregnancy.

Mechanisms

Specific metals have varied toxicities and different essential minerals have different biological functions. This suggests that the effects of maternal exposure on fetal growth involve biological mechanisms that are metal-specific. Exposure to toxic metals in early pregnancy could affect the fertilized egg or zygote implantation into the lining of the uterus; or disrupt early pregnancy placentation resulting in poor placental growth and impaired placental function.[119,120,134,144] Healthy growing placental cells are fundamentally important for the embryo to attach to the uterine wall and for fetal development. Toxic heavy metals could accumulate in placental transfer cells,[138] causing a decrease in uterine blood flow, and decrease the transfer of nutrients to the fetus, and thus affect fetal growth and development.[111,113,143]

Toxic metals reaching the fetus could impair or alter the uterine environment and dysregulate the fetal epigenome, given that the embryo and fetus are highly susceptible to epigenetic dysregulation by environmental pollutants,[117,121] may affect gene expression and enzyme activity in placental trophoblast cells,[129] act as endocrine disruptors,[118,124,145-147] and/or develop persistent vulnerabilities in immune system function that would affect fetal development.[147,148] Trace minerals could lead to adverse health effects at too high levels.[125,148,149] Imbalanced levels of trace minerals (such as Se, Cu, Mn, and Zn), for example, can affect antioxidant protection culminating in poor fetal growth, or result in reduced glutathione peroxidase activity culminating in reduced antioxidant protection of biological membranes and DNA during the early stage of embryonic development.[150] The result of

Table 3. Prenatal Polyhalogenated Aromatic Hydrocarbon Exposure and Selected Birth Outcomes*

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes			
									BW/LBW	BL	HC	SGA/IUGR
PBDEs	Significant results											
	Harley et al. 2011[153]	US	Cohort	286	1999-2000	Maternal blood	BDE-47 14.57 ng/g liquid†	26th week of pregnancy	BW: β = −115 g; 95% CI, −229 to −2 g per 10-fold increase	NS	NS	
							BDE-99 3.85 ng/g liquid†		BW: β = −114 g; 95% CI, −225 to −4 g per 10-fold increase	NS	NS	
							BDE-100 2.45 ng/g liquid†		BW: β = −122 g; 95% CI, −235 to −9 g per 10-fold increase	NS	NS	
	Wu et al. 2009[154]	China	Cross-sectional	153	2007	Cord blood	13.84 ng/g liquid‡	At birth	$P = 0.004$ *t* test			
	Insignificant results											
	Tan et al. 2009[155]	Singapore	Cross-sectional	41	2006	Cord blood	3.3 ng/g liquid‡	At birth	NS	NS	NS	
PCB	Significant results											
	Rylander et al. 1998[156]	Sweden	Case–control	192	1973-1991	Maternal blood	940 pg/g†	During pregnancy	LBW: OR, 2.1; 95% CI, 1-4.7 above 300 ng/g liquid			
	Patandin et al. 1998[157]	Netherland	Cohort	207	1990-1992	Maternal blood	2.04 ug/L§	36th-40th week of pregnancy	BW: β = −123.1 g; 95% CI, −58.7 to −187.5 g per lnΣPCB			
						Cord blood	0.40 ug/L‖	At birth	BW: β = −119.4 g; 95% CI, −65.7 to −173.1 g per lnΣPCB			
	Murphy et al. 2010[158]	US	Cohort	99	1995-1996	Maternal blood	5.3 ng/g†	Preconception	BW: β = −429.3 g; 95% CI, −807.2 to −51.4 g high/low			
						Maternal blood	4.5 ng/g†	Prenatal	BW: β = −248.9 g; 95% CI, −628.2 to 130.5 g			

(*continued on next page*)

Table 3. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes			
									BW/LBW	BL	HC	SGA/IUGR
	Dar et al. 1992[159]	US	Cohort	1112	1987-1989	Maternal blood	0.6-2.0 ppm	First prenatal visit	$r = 11.06$; $P = 0.004$			
	Insignificant results											
	Sonneborn et al. 2008[160]	Slovakia	Cohort	1057	2002-2004	Maternal blood	6.3 ng/mL[§]	At birth	NS			
	Weisskopf et al. 2005[161]	US	Cohort	143	1993-1995	Maternal blood	1.76 ng/mL[§]	NA	BW: β = 29g; 95% CI, −110 to 168 g per ln (PCB)			
	Longnecker et al. 2005[162]	US	Cohort	1034	1959-1965	Maternal blood	2.8 µg/L[†]	3rd trimester	NS	NS		SGA: OR, 1.6; 95% CI, 0.7-3.7 per 1 µg/L
	Gladen et al. 2003[163]	Ukraine	Cross-sectional	197	1993-1994	Maternal milk	14-149 ng/g milk fat	4-5 d after birth	NS			
	Vartiainen et al. 1998[164]	Finland	Cross-sectional	167	1987	Maternal milk	78-1624 ng/g milk fat	4 wk after birth	NS			
Pesticide	Significant results											
	Longnecker et al. 2001[165]	US	Cohort	2380	1959-1965	Maternal blood	DDE 25µg/L[†]	3rd trimester				SGA: OR, 1, 1.9, 1.7, 1.6, 2.6 trend $P = 0.04$ per µg /L
	Weisskopf et al. 2005[161]	US	Cohort	143	1993-1995	Maternal blood	2.20 ng/mL[†]	NA	BW: β = −146 g; 95% CI, −35 to −257 g per unit increase in ln (DDE)			
	Siddiqu et al. 2003[166]	India	Case−control	54	NA	Maternal blood p,p′-DDE	IURG 8.79 ppb[§]	At birth				IUGR $r = -0.25$; $P < 0.05$
						p,p′-DDE	Normal BW 6.32 ppb[§]					
						Cord blood d-HCH	IURG 26.61 ppb[‖]	At birth				IUGR $r = -0.27$; $P < 0.05$
						HCH	Normal BW 15.82 ppb[‖]					
						Cord blood p,p′-DDE	IURG 7.81 ppb[‖]					IUGR $r = -0.26$; $P < 0.05$

(*continued on next page*)

Table 3. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes			
									BW/LBW	BL	HC	SGA/IUGR
						Cord blood p,p′-DDE	Normal BW 5.33 ppb‖					
	Insignificant results											
	Bjerregaard et al. 2000[167]	Greenland	Cross-sectional	180	1994-1996	Maternal blood	Total DDT 3.8 μg l wet wt.	End of pregnancy	NS			
	Farhang et al. 2005[168]	USA	Cohort	420	1959-1967	Maternal blood	DDE 43 μg/L†	1st trimester 2nd trimester 3rd trimester	BW: β = −34 g; (SE: 36); *P* = .34			OR, 0.75; 95% CI, 0.44-1.26 per IQR
							DDT 11 μg/L†	β = 21 g; (SE: 35); *P* = .55				OR, 0.76; 95% CI, 0.48-1.20 per IQR
	Ribas-Fit et al. 2002[169]	Spain	Cross-sectional	70	1997-1999	Cord blood	p,p′-DDE 0.85 ng/mL†	At birth	NS			NS
	Gladen et al. 2003[163]	Ukraine	Cross-sectional	197	1993-1994	Maternal milk	p,p′-DDE 2457 ng/g milk fat p,p′-DDT 336 ng/g milk fat (median)	4 or 5 d after birth	NS			
BHC	Significant Results											
	Siddiqu et al. 2003[166]	India	Case–control	54	NA	Maternal blood			*r* = −0.27; *P* < 0.05			
	Schade et al. 1998[170]	Germany	Case–control	1553	1986-1997	Maternal milk	0.036 mg/kg median	3 and 6 mo after delivery	BW: β = 0.05 g; *P* < 0.05 per log unit			
	Insignificant results											
	Gladen et al. 2003[163]	Ukraine	Cross-sectional	197	1993-1994	Maternal milk	731 ng/g milk fat	4 or 5 d after birth	NS			
	Bjerregaard et al. 2000[167]	Greenland	Cross-sectional	180	1994-1996	Maternal blood	0.2 μg/L wet wt.§	End of pregnancy	NS			
HCB	Schade et al. 1998[170]	Germany	Case–control	1553	1986-1997	Maternal milk	0.065 mg/kg median	3 and 6 mo after delivery	BW: β = 0.05 g; *P* < 0.05 per log BHC			
	Ribas-Fit et al. 2002[169]	Spain	Cross-sectional	70	1997-1999	Cord blood	1.13 ng/mL‡	At birth			β = −0.46 cm; SE = 0.22 cm	
	Gladen et al. 2003[163]	Ukraine	Cross-sectional	197	1993-1994	Maternal milk	168 ng/g milk fat	4-5 d after birth	NS			

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Table 3. continued

Species	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Level of Exposure	Time of Measurement	Adverse Birth Outcomes			
									BW/LBW	BL	HC	SGA/IUGR
	Bjerregaard et al. et al. 2000[167]	Greenland	Cross-sectional	180	1994-1996	Maternal blood	0.9 µg/L wet wt.[§]	End of pregnancy	NS			
	Lackmann et al. 1999[171]	Germany	Cross-sectional	80	1994-1995	Neonatal blood	0.61 µg/L	First 12 h of life	NS			
Other OC	Bjerregaard et al. 2000[167]	Greenland	Cross-sectional	180	1994-1996	Maternal blood	Trans-nonachlor 1 µg/L wet wt.	End of pregnancy	NS			
	Gladen et al. 2003[163]	Ukraine	Cross-sectional	197	1993-1994	Maternal milk	16 ng/g milk fat (heptachlor epoxide neg)	4-5 d after birth	NS			

BL, birth length, BW, birth weight; GW, gestational week; HC, head circumference; IQR, interquartile change; IUGR, intrauterine growth restriction; LBW, low birth weight; NA, not available; NS, not significant; SGA, small for gestational age.
* The studies included in Table 3 focus on those articles published since 1990 (sample size >50). The table lists exact ORs or β values for results reaching statistical significance (*$P < 0.05$). Blank spaces in the table indicate that these variables were not investigated by the studies. The birth outcomes listed in the table are restricted to major birth outcomes due to space limitation (BW, LBW, BL, HC, SGA, and IUGR).
† Median levels in maternal blood.
‡ Median levels in cord blood.
§ Mean levels in maternal blood.
‖ Mean levels in cord blood.

this could compromise the protection against placental oxidative stress, which may detrimentally affect fetal growth.

Effects of Prenatal PHAH Exposures on Fetal and Childhood Growth.

Definition

The chemicals that comprise the bulk of PHAH residues found in human tissues that exhibit reproductive and endocrine-disrupting effects, and that have been suggested to be associated with risk for LBW, can be divided into 3 broad categories: polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and organochlorine pesticides. PBDEs are a group of bromide-containing compounds. Although there are potentially 209 PBDE congeners, only 3 major commercial mixtures (which contain a limited number of congeners, present in penta-, octa-, or decabrominated forms) have been used as flame-retardants since 1965. PCBs are a group of man-made organic chemicals that contain 209 individual chlorinated congeners. PCBs were widely used since 1929 mainly as flame-retardants. The global accumulated amount of PCBs is estimated to be around 2 million tons. Organochlorine pesticides are chlorinated hydrocarbons that can be divided into 6 groups: DDT and its analogues; benzene hexachloride (BHC) isomers; cyclodienes and similar compounds; toxaphene and related chemicals; the caged structures, mirex and chlordecone; and hexachlorobenzene. Use of PHAHs has been banned or severely limited in the United States and many other countries since the 1970s, although DDT is still actively used in several countries for malaria control.

Exposure

PHAHs are now ubiquitous environmental pollutants and the levels of PHAHs in humans and in the environment are still significant due to their persistence, stability, and bioaccumulation through the food chain. Humans have been and will continue to be exposed to these chemicals, mainly through foods. Their inefficient metabolism and their high solubility in lipids lead to lifelong sequestration in adipose tissue, resulting in lifelong exposure to these chemicals. Most importantly, PHAHs readily cross the placenta when maternal fat stores during pregnancy are mobilized resulting in transfer of these chemicals to the embryo and fetus through the placenta.[151,152]

Epidemiologic Studies of PHAHs, Fetal Growth, and Birth Outcomes

PBDEs. Studies of the relationship between PBDEs and LBW are only at a pilot stage (Table 3). To date, 5 small epidemiologic studies have examined whether PBDE exposure during pregnancy affects birth weight, with 3 studies[153,154,172] reporting an increased risk for LBW and 2 studies[155,173] reporting no association. A study of 286 pregnant women from California evaluated the levels of 10 PBDE congeners using collected blood samples near the 26th week of pregnancy in 1999-2000, and found that higher levels of PBDEs in maternal serum during pregnancy were associated with LBW in this study population.[153] Each 10-fold increase in the concentrations of BDE-47, -99, and -100 was associated with about a 115-g decrease in birth weight. The California study is consistent with a recent study in China that found that levels of BDE-28, -47, -99, -153, and -183 were higher in the cord blood of infants with adverse birth outcomes,[154] and is also consistent with a study from Taiwan, which found that BDE-47, -99, -100, and -209 were higher in breast milk of mothers delivering lower birth weight infants.[172] These results are, however, different from 2 other epidemiologic studies that have reported no association of PBDE exposure during pregnancy and fetal growth.[155,173] Four of these 5 studies did not control for gestational age at birth to examine fetal growth independent of duration of gestation. Also, the statistical power is a major concern as the largest study only included a sample size of 286 mothers.

PCBs. Although occupationally[174,175] and accidentally poisoned women[176,177] have showed an increased risk for giving birth to LBW infants, studies of prenatal low- level exposure to PCBs and LBW have produced inconsistent results (Table 3). In particular, 7 studies evaluating exposure to low levels of PCBs in relation to LBW have supported an increased risk,[155-158,175,178,179] whereas 5 other studies showed no relationship,[160-164] and 2 other studies showed that increased exposure was associated with having heavier babies.[159,180] One study[158] assessed 76 PCB congeners in maternal serum from 52 US women and found an inverse association between PCB exposure and birth weight, and also provided 3 important observations:

1. The inverse association mainly came from the exposure to antiestrogenic PCBs.
2. The magnitude of the effect is considerably more than that reported for cigarette smoking.[181]
3. The reduction in birth weight is not mediated through gestation, but instead through a pathway directly affecting fetal growth because the study found no significant reduction in gestational age in relation to PCB groupings or concentrations.

This study, although small, underscores the importance of evaluating specific PCB congeners. On the other hand, a US study[165] involving 221 SGA infants and 2148 controls, found that maternal serum levels of PCBs were unrelated to birth weight. The study, however, did not present the results by the purported biologic activity of congener groupings in relation to birth weight as was done in an earlier study.[158] As to the studies that reported increased PCB exposure to be associated with heavier babies,[182] their study population had high fish consumption. High intake of fish oil could improve placental blood flow and thus could be the reason for the increasing birth weight observed in these studies. In support of this argument, results from a controlled trial indicated that fish oil supplementation during pregnancy increases birth weight.[183]

DDT congeners. Findings regarding an association between exposure to DDT and DDE and birth weight have similarly been inconsistent. Several studies reported a negative association between DDT levels and birth weight (Table 3).[161,165,166,184] For example, the US study,[165] which did not find an association between PCBs and birth weight, found that DDE concentration in maternal blood collected at the third trimester was associated with increased odds of LBW with a strong dose-response relationship ($P_{\text{trend}} < 0.0001$). A US study involving 143 children born to mothers who ate Great Lakes sport-caught fish showed that each unit increase in the natural log of maternal serum DDE concentration was significantly associated with an estimated 146 g reduction in birth weight after adjustment for potential confounders.[161] A study from India involving 54 participants also reported a significant negative correlation between body weight of newborn babies and p,p'-DDE in maternal blood ($r = -0.25$; $P < 0.05$) and in the cord blood ($r = -0.26$; $P < 0.05$) after accounting for gestational age.[166]

On the other hand, several studies did not find increased levels of DDT and DDE to be significantly associated with infant birth weight.[163,167-169,179,185,186] For example, a recent US study[168] involving 420 participants reported that neither maternal serum (drawn mainly in the postpartum period) levels of DDT nor levels of DDE were significantly associated with birth weight, or any other adverse birth outcomes such as preterm birth and SGA. A study involving 197

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singleton infants in Ukraine also did not find a significant association between birth weight and p,p'-DDE levels in breast milk collected at the fourth or fifth day after birth after adjusting for gestational age and other major potential confounders.[163]

BHC congeners. Four small studies reported that increased body BHC levels are associated with an increased risk for lowered birth weight (Table 3). For example, an India study[166] involving 54 participants reported a significant negative correlation between body weight of newborn babies and δ-BHC in the cord blood ($r = -0.27$; $P < 0.05$) after accounting for gestational age. Studies conducted in Germany, India, and Israel also reported an inverse relationship between body levels of BHC and birth weight.[170,187-189] Four other studies from India, Ukraine, and Greenland, however, reported no significant association between exposure to low-level BHC and LBW.[163,167,190,191]

Other OC pesticides. A study from Germany reported an inverse association between exposure to background concentrations of the fungicide HCB and birth weight (Table 3).[170] A study including serum samples from 72 mothers at delivery and 70 cord serum samples found that HCB levels in both cord and maternal serum were inversely associated with birth length but not birth weight.[169] Several other studies have reported no relationship between HCB exposure and LBW.[163,167,171,186]

For other organochlorine pesticides, previous human literature on birth weight is sparse. Trans-nonachlor, one of the components of the insecticide chlordane, and oxychlordane have been evaluated in 2 studies. both of which reported no effects.[163,167] For heptachlor epoxide, the stable metabolite of the insecticide heptachlor, 1 study reported a negative relationship with birth weight,[189] whereas 3 others reported none.[163,186,191]

Mechanisms

Studies have suggested at least 2 pathways by which PHAHs may exert their effect on birth outcomes:

1. They accumulate in the placenta where they may interact with hormones and nutrient transport systems resulting in insufficient supply of nutrients to the developing fetus, thereby affecting the normal development of the child and the pregnancy outcome[192]; and/or
2. They are transferred from mothers to the offspring through the placental barrier during gestation resulting in prenatal exposure to the developing fetuses,[152] and the fetuses are more vulnerable to the effects of these pollutants as their detoxification systems are relatively immature.[193]

PBDEs, PCBs, and organochlorine pesticides have endocrine-disrupting activities and may resemble human hormones such as thyroid and sex hormones, which may ultimately play a role in interfering with the action of key hormones that regulate early development and disruption of normal fetal development.

Effects of Prenatal Exposures to Air Pollutants on Fetal and Childhood Growth.

Definition

Air pollution consists of a complex mixture of gases, liquids, and particulate matter (PM; component of air pollution).[194,195] There has been increasing concern regarding the health effects of air pollutants, with evidence implicating PM as the chief perpetrator of harmful health outcomes. PM is normally expressed as the mass of particles within a cubic meter of air (micrograms per cubic meter [$\mu g/m^3$]). In general, PM include coarse particles (PM 2.5-10 μm or PM_{10}), fine (PM <2.5 μm or $PM_{2.5}$), and ultrafine (PM <0.1 μm or $PM_{0.1}$) particles.[196] The other pollutants of concern include polycyclic aromatic hydrocarbons (PAHs), carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides as the combination of NO and NO_2 (NO_x), ground-level ozone (O_3), and sulfur dioxide (SO_2).

Exposure Despite multiple air-quality guidelines, air pollutants are ubiquitous contaminants that continue to be steadily produced due to increasing industrialization and urbanization. Air pollutants are mainly emitted via anthropogenic sources, although some air pollutants are emitted naturally. Motor vehicle emissions, power plants, various industrial combustions, indoor cooking, and construction and demolition activities all contribute as major sources of air pollutants.[197] The main path of exposure is through inhalation of the polluted air, although one can also ingest these pollutants due to subsequent contamination of the environment.[198] Hence, all humans are exposed to ambient air pollutants occupationally and non-occupationally, and low- and middle-income countries are affected by air pollutants more heavily, especially in southeast Asia and in western Pacific areas.

Table 4. Prenatal Air Pollutants Exposure and Selected Birth Outcomes*

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
CO	Bell et al. 2007[199]	US	Prospective cohort	358,504	1999-2002	Estimated	Each trimester and entire pregnancy	656 ppb (IQR = 303)	BW: β = −16.2 g; 95% CI −19.7 to −12.6 g		
	Brauer et al. 2008[200]	Canada	Prospective cohort	70,249	1999-2002	Estimated via IDW and LUR model	Each month	IDW: 613.8 μg/m^3 (IQR = 100)	NS	OR, 1.16; 95% CI, 1.01-1.33	OR, 1.06; 95% CI, 1.03-1.08
	Darrow et al. 2011[201]	US	Prospective cohort	406,627	1994-2004	Estimated via distributed lag models	Each month, 3rd trimester	1st month of gestation: 0.9 ppm (IQR = 0.3) 3rd trimester: 0.8 ppm (IQR, 0.3)	BW: 3rd trimester Hispanic: β = −14.4 g; 95% CI, −23.4 to −5.5 g		
	Geer et al. 2012[202]	USA	Prospective cohort	1,548,904	1998-2004	Estimated residentially	Each trimester	451 ppb (IQR, 98)	NS		
	Gouveia et al. 2004[203]	Brazil	Prospective cohort	179,460	1997	Estimated via regression models	Each trimester	3.7 ppm (results from 4th quartile)	BW: β = −23.1 g; 1st trimester: 95% CI, −41.3 to −4.9g		
	Jalaludin et al. 2007[204]	Australia	Prospective cohort	123,840	1998-2000	Estimated	1st trimester 1 mo before birth, first month after estimated date of conception	0.9 ppm (IQR = 0.73)		1st mo: Sydney OR, 0.90; 95% CI, 0.84-0.95; 1st trimester: Sydney OR, 0.77; 95% CI, 0.72-0.84	
	Laurent et al. 2014[133]	US	Prospective cohort	70,000	1997-2006	Measured via ambient monitoring stations, estimated via CALINE4	Entire pregnancy	Measured: 0.73 ppm (IQR = 0.48) CALINE 4: 0.10 ppm (IQR = 0.08)	BW measured: β = +22.79 g; 95% CI, 18.23-27.35 CALINE4: β = +15.09 g; 95% CI, 11.27-18.91		
	Le et al. 2012[205]	US	Prospective cohort	164,905	1990-2001	Measured	First and last month and each trimester of pregnancy	Month: 0.66 ppm Trimester: 0.66 ppm (results from 4th quartile)		1st mo: OR, 0.89; 95% CI, 0.83-0.97	1st mo: OR, 1.20; 95% CI, 1.09-1.33 1st trimester: OR, 1.16; 95% CI, 1.04-1.28

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Lee et al. 2003[206]	South Korea	Prospective cohort	388,105	1995-1998	Estimated	Each month and trimester during pregnancy	1.2 ppm	LBW 1st trimester: OR, 1.04; 95% CI, 1.01-1.07 3rd trimester: OR, 0.96; 95% CI, 0.93-0.99; All trimesters: OR, 1.05; 95% CI, 1.01-1.09		
	Liu et al. 2003[207]	Canada	Prospective cohort	229,085	1995-1998	Estimated	Entire Pregnancy	1 ppm (IQR = 1)	NS	Last month: OR, 1.08; 95% CI, 1.01-1.15	
	Maisonet et al. 2001[17]	US	Prospective cohort	89,557	1994-1996	Estimated using air monitoring data	Each trimester	(IQR = 1 ppm)	LBW 3rd trimester: OR, 1.31; 95% CI, 1.06-1.62		
	Mannes et al. 2014[208]	Australia	Prospective cohort	138,056	1998-2000	Estimated via monitoring stations	Each trimester	0.8 ppm (IQR = 1)	BW 1 mo before birth: $\beta = -15.28$ g; 95% CI, −25.59 to −4.97		1st and 2nd trimester: ↓ 3rd trimester and 1 mo before birth: ↑
	Morello-Frosch et al. 2010[209]	US	Prospective cohort	3,545,177	1996-2006	Estimated	Entire pregnancy	0.87 ppm (IQR = 1)	BW At 5 km: $\beta = -5.9$ g; 95% CI, −7.8 to −3.9 g At 10 km: $\beta = -5.4$ g; 95% CI, −6.8 to −4.1 g LBW At 5 km: OR, 1.06; 95% CI, 1.03-1.09 At 10 km: OR, 1.04; 95% CI, 1.02-1.06		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Rich et al. 2009[210]	US	Prospective cohort	199,221	1999-2003	Measured	Each trimester	0.925-0.946 ppm (IQR = 0.5)			NS
	Ritz et al. 2007[211]	US	Case-control	58,316	2003	Estimated via logistic regression and 2-phase models	1st trimester	>1.25 ppm		1st trimester: OR, 1.25; 95% CI, 1.12-1.38	
	Rudra et al. 2011[212]	US	Prospective cohort	3509	1996-2000	Estimated regression models based on regional air pollutant monitoring data	Prepregnancy, first 2 trimesters, last 3 mo, last month	(IQR = 0.1 ppm)		NS	
	Trasande et al. 2013[213]	US	Cross-sectional	222,359	2000, 2003, 2006	Estimated based on birth hospital address	Month of birth	0.58 ppm (IQR = 0.43)	VLBW OR, 1.35; 95% CI, 1.09-1.65 Term LBW OR, 2.07; 95% CI, 1.10-3.59 Preterm LBW OR, 1.48; 95% CI, 1.03-2.14		
	Wilhelm et al. 2002[214]	US	Prospective cohort	37,433	1994-1996	Estimated residentially	Each month	(IQR = 1 ppm)	LBW: OR, 1.22; 95% CI, 1.03-1.44	NS	
	Wilhelm et al. 2005[215]	US	Prospective cohort	840,472	1994-2000	Estimated residentially	Each month, trimester, 6 wk before birth, and entire pregnancy	1st trimester: 1.42 ppm 3rd trimester: 1.21 ppm 6 wk before birth: 1.42 ppm (IQR = 1)	LBW 3rd trimester: OR, 1.12; 95% CI, 1.05-1.19	1st trimester: OR, 1.04; 95% CI, 1.01-1.07	
	Wu et al. 2011[216]	US	Prospective cohort	81,186	1997-2006	Estimated via LUR and CALINE4	1st trimester, 2nd trimester, Last Month, Entire Pregnancy	Measured: 0.7 ppm (IQR = 0.5)		LA: OR, 1.13; 95% CI, 1.08-1.19 Orange County: OR, 1.14; 95%	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
										CI, 1.04-1.26 Very preterm birth LA: OR, 1.34; 95% CI, 1.20-1.49 Orange County: OR, 1.76; 95% CI, 1.27-2.44	
	Yu et al. 1999[217]	US	Cross-sectional	125,573	1989-1993	Measured	3rd trimester	2.45 ppm (results $\geq$5.5 ppm)	LBW OR, 1.22; 95% CI, 1.03-1.44		
NO	Brauer et al. 2008[200]	Canada	Prospective cohort	70,249	1999-2002	Estimated via IDW and LUR model	Each month	IDW: 22.1 $\mu g/m^3$ LUR: 30.7 $\mu g/m^3$ (IQR = 10)	NS	IDW: OR =1.26; 95% CI, 1.08-1.47	IDW: OR, 1.05; 95% CI, 1.03-1.08
	Ghosh et al. 2012[218]	US	Prospective cohort	379,103	1995-2006	Estimated via LUR and measured	3rd trimester, last month of pregnancy, entire pregnancy	LUR 32.9 ppb (IQR = 11.2) Measured 41.6 ppb (IQR = 24.1)	LBW LUR entire pregnancy: OR, 1.02; 95% CI, 1.01-1.04		
	Laurent et al. 2014[133]	US	Prospective cohort	70,000	1997-2006	Measured via ambient monitoring stations, estimated via LUR, Gaussian dispersion model, and traffic density and proximity to roads models	Entire pregnancy	Measured: 30.69 ppb (IQR = 17.90)	BW measured: $\beta = +20.27$ g; 95% CI, 16.23-24.32		
	Wilhelm et al. 2011[219]	US	Prospective cohort	241,415	2004-2006	Estimated via LUR	1st trimester, 2nd trimester, 30 d before birth, entire pregnancy	27.3 ppb (IQR = 27.3)		OR, 1.03; 95% CI, 1.01-1.05	
	Wilhelm et al. 2012[220]	US	Prospective cohort	241,415	2004-2006	Estimated via LUR	Each trimester, entire pregnancy	32.2 ppb (IQR = 10.5)	NS		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Wu et al. 2011[216]	US	Prospective cohort	81,186	1997-2006	Estimated via LUR and CALINE4	1st trimester, 2nd trimester, last month, entire pregnancy	Measured: 30.9 ppb (IQR = 18.3) LUR: 30.9 ppb (IQR = 11.6)		Measured: LA: OR, 1.11; 95% CI, 1.06-1.16 Very preterm birth: Measured: LA: OR, 1.27; 95% CI, 1.15-1.40	
NO_x	Bobak et al. 2000[221]	Czech Republic	Prospective cohort	108,173	1991	Estimated	Each trimester	Median 38 $\mu g/m^3$ (IQR = 50)	NS	NS	
	Ghosh et al. 2011[218]	US	Prospective cohort	379,103	1995-2006	Estimated via LUR and measured	3rd trimester, last month of pregnancy, entire pregnancy	LUR 60.4 ppb (IQR = 15.5) Measured 76.3 ppb (IQR = 31.2)	NS		
	Laurent et al. 2013[222]	US	Prospective cohort	70,000	1997-2006	Measured via ambient monitoring stations, estimated via LUR, Gaussian dispersion model, and traffic density and proximity to roads models	Entire pregnancy	Measured: 55.42 ppb (IQR = 27.70) LUR: 59.93 ppb (IQR = 25.24) CALINE 4: 7.18 ppb (IQR = 5.65)	BW Measured: $\beta = +25.31$ g; 95% CI, 20.84-29.78 LUR: $\beta = +9.42$ g; 95% CI, 5.25-13.59 CALINE4: $\beta = +14.10$ g; 95% CI, 10.29-17.9		
	Malmqvist et al. 2011[223]	Sweden	Prospective cohort	81,110	1999-2005	Estimated via residential models	Each month and trimester	16.4 $\mu g/m^3$ (results > 22.7 $\mu g/m^3$)	NS	OR, 0.85; 95% CI, 0.77-0.94	For girls: OR, 1.12; 95% CI, 1.01-1.24 For mothers who had not changed residency during pregnancy: OR, 1.09; 95% CI, 1.01-1.18

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Olsson et al. 2013[224]	Sweden	Prospective register-based cohort	120,755	1998-2006	Measured	Early pregnancy	IQR = 10 μg/m^3		NS	OR, 0.97; 95% CI, 0.94-0.99
	Schembari et al. 2015[225]	England	Prospective cohort	9,067	2007-2010	Estimated via LUR	Each trimester and entire pregnancy	IQR = 20 μg/m^3	NS		
	Wilhelm et al. 2011[219]	US	Prospective cohort	241,415	2004-2006	Estimated via LUR	1st trimester, 2nd trimester, 30 d before birth, entire pregnancy	52.8 ppb (IQR = 52.8)		OR, 1.03; 95% CI, 1.01-1.05	
	Wilhelm et al. 2012[220]	US	Prospective cohort	241,415	2004-2006	Estimated via LUR	Each trimester, entire pregnancy	59.1 ppb (IQR = 15.1)	NS		
	Wu et al. 2011[216]	US	Prospective cohort	81,186	1997-2006	Estimated via LUR and CALINE4	1st trimester, 2nd trimester, last month, entire pregnancy	Measured: 55.8 ppb (IQR = 28.2) LUR: 59.9 ppb (IQR = 15.6) CALINE4: 7.2 ppb (IQR = 5.6)		Measured: Orange County: OR, 1.13; 95% CI, 1.07-1.19 Very preterm birth: Measured: LA: OR, 1.34; 95% CI, 1.18-1.53 LUR: LA: OR, 1.18; 95% CI, 1.01-1.39 CALINE4: LA: OR, 1.16; 95% CI, 1.04-1.28	
NO_2	Aguilera et al. 2009[226]	Spain	Prospective cohort	570	2004-2006	Estimated via LUR	Each trimester and entire pregnancy	1st trimester: 32.17 μg/m^3 2nd trimester: 31.86 μg/m^3 3rd trimester: 32.67 μg/m^3 entire pregnancy: 32.17 μg/m^3	BW <2 h/d in nonresidential outdoor environments (n = 259) 2nd trimester only significant result: β = −74 g; 95% CI, −140.4 to −9.0 g		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Aguilera et al. 2010[227]	Spain	Prospective cohort	562	2004-2006	Estimated via LUR, ultrasound measurements	12th, 20th, 32nd wk of gestation	Week 1-12: 32.45 μg/m^3 (IQR = 12.19) Week 12-20: 31.68 μg/m^3 (IQR = 11.47) Week 20-32: 32.13 μg/m^3 (IQR = 13.23)	Estimated fetal weight: <2 h/d in nonresidential outdoor environments (n = 255) Week 20-32 only significant result: β = −4.78 g; 95% CI, −9.47 to −0.02 g		
	Ballester et al. 2010[228]	Spain	Prospective cohort	785	2003-2005	Estimated via LUR	Each trimester and entire pregnancy	1st trimester: 37.9 μg/m^3 2nd trimester: 35.9 μg/m^3 3rd trimester: 37.9 μg/m^3 Entire pregnancy: 32.17 μg/m^3 (IQR = 10)	NS		2nd trimester:OR, 1.37; 95% CI, 1.01-1.85
	Bell et al. 2007[199]	US	Prospective cohort	358,504	1999-2002	Estimated	Each trimester and entire pregnancy	17.4 ppb (IQR = 4.8)	BW: β = −8.9 g; 95% CI, 7-10.8 g LBW: OR, 1.027; 95% CI, 1.002-1.051		
	Brauer et al. 2008[200]	Canada	Prospective cohort	70,249	1999-2002	Estimated via Inverse-Distance Weighting (IDW) and Land-Use Regression Model (LUR)	Each month	IDW: 32.5 μg/m^3 LUR: 31.6 μg/m^3 (IQR = 10)	LBW IDW: OR, 1.11; 95% CI 1.01-1.23	NS	IDW: OR, 1.14; 95% CI 1.09-1.18
	Darrow et al. 2011[201]	USA	Prospective cohort	406,627	1994-2004	Estimated via Distributed Lag Models	Each month, 3rd trimester	1st month of gestation: 23.6 ppb (IQR = 5) 3rd trimester: 23.8 ppb (IQR = 5)	3rd trimester: β = −4.5 g; 95% CI, −8.5 to −0.6 g		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Dibben et al. 2015[229]	Scotland	Prospective cohort and occupational	21,843 (LBW) 23,086 (BW)	1994-2008	Estimated residential exposure and combined residential and workplace exposure	Entire Pregnancy	Residential: 17.48 μg/m^3 Residential and Workplace: 17.80 μg/m^3	BW Residential: β = −1.24 g; 95% CI, −2.02 to −0.46g Residential and Workplace: β = −0.92 g; 95% CI −1.66 to −0.18 g LBW Residential: OR, 1.02; 95% CI, 1.00-1.03 Residential and Workplace: OR, 1.07; 95% CI, 1.01-1.13	NS	
	Estarlich et al. 2011[230]	Spain	Prospective cohort	2337	2003-2008	Estimated residentially	Each trimester, entire pregnancy	29.2 μg/m^3 (IQR = 10)	NS		
	Geer et al. 2012[202]	US	Prospective cohort	1,548,904	1998-2004	Estimated residentially	Each trimester	15.0 ppb (IQR = 2.4)	NS		
	Ghosh et al. 2011[218]	US	Prospective cohort	379,103	1995-2006	Estimated via LUR and measured	3rd trimester, last month of pregnancy, entire pregnancy	LUR 27.8 ppb (IQR 5.2) Measured 34.8 ppb (IQR 10.4)	NS		
	Gouveia et al. 2004[203]	Brazil	Prospective cohort	179,460	1997	Estimated via regression models	Each trimester	117.9 μg/m^3 (results from 4th quartile)	NS		
	Hansen et al. 2007[231]	Australia	Prospective cohort	26,617	2000-2003	Estimated based on city-wide average of pollutants	Each month and trimester of pregnancy	8.8 ppb	NS		2nd trimester: OR, 0.80; 95% CI, 0.69-0.94
	Huang et al. 2015[232]	China	Prospective cohort	50,874	2006-2010	Estimated	Each trimester	58.07 μg/m^3 (per 10 μg/m^3 Increase)	BW 3rd trimester: β = −13.78 g; 95% CI, −21.12 to −6.43 g*	NS	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Jalaludin et al. 2007[204]	Australia	Prospective cohort	123,840	1998-2000	Estimated	First trimester, 3 and 1 mo before birth, first month after estimated date of conception	23.4 ppb (IQR = 9.45)		1st mo: Sydney OR, 0.97; 95% CI, 0.96-0.98 At 5 km: OR, 0.59; 95% CI, 0.36-0.96 1st trimester: Sydney OR, 0.97; 95% CI, 0.96-0.98	
	Laurent et al. 2013[222]	US	Prospective cohort	70,000	1997-2006	Measured via ambient monitoring stations, Estimated via LUR, Gaussian dispersion model, and traffic density and proximity to roads models	Entire Pregnancy	Measured: 24.78 ppb (IQR = 11.87) LUR: 28.03 (IQR = 9.34)	BW measured: β = 36.24 g; 95% CI, 30.50-41.98 LUR: β = 16.59 g; 95% CI, 12.01-21.16 LBW measured: OR, 0.85; 95% CI, 0.76-0.94		
	Le et al. 2012[205]	US	Prospective cohort	164,905	1990-2001	Measured	First and last month and each trimester of pregnancy	Month: 21.3 ppb trimester: 21.2 ppb (results from 4th quartile)		NS	1st mo: OR, 1.10; 95% CI, 1.01-1.19
	Lee et al. 2003[206]	South Korea	Prospective cohort	388,105	1995-1998	Estimated	Each month and trimester during pregnancy	32.5 ppb	LBW: 2nd trimester: OR, 1.06; 95% CI, 1.02-1.11		
	Liu et al. 2003[207]	Canada	Prospective cohort	229,085	1995-1998	Estimated	Entire pregnancy	19.4 ppb (IQR = 10.0)	NS	NS	
	Llop et al. 2010[233]	Spain	Prospective cohort	785	2003-2005	Estimated residential exposure via multiple regression models	Entire pregnancy and each trimester	Results >46.2 μg/m^3		2nd trimester: OR, 1.11; 95% CI, 1.03-1.21 Entire pregnancy: OR, 1.29; 95% CI, 1.13-1.46	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Mannes et al. 2014[208]	Australia	Prospective cohort	138,056	1998-2000	Estimated via monitoring stations	Each trimester	23.2 ppb (IQR = 1)	BW 1st trimester: $\beta = -1.07$ g; 95% CI, −2.07 to −0.07 g 3rd trimester: $\beta = -1.48$ g; 95% CI, −2.70 to −0.26g		NS
	Maroziene et al. 2002[234]	Lithuania	Prospective cohort	3988	1998	Estimated residential exposure	Entire pregnancy	11.69 μg/m^3 (IQR = 10)	NS	1st trimester: OR, 1.69; 95% CI, 1.28-2.23 2nd trimester: OR, 1.30; 95% CI, 1.02-1.64	
	Morello-Frosch et al. 2010[209]	US	Prospective cohort	3,545,177	1996-2006	Estimated	Entire pregnancy	2.42 pphm (IQR = 1)	BW At 3 km: −8.3 g; 95% CI, −9.6 to −7.9 g At 5 km: −9.7 g; 95% CI, −10.6 to −8.8 g At 10 km: −9.0 g; 95% CI, −9.6 to −8.4 g LBW At 3 km: OR, 1.03; 95% CI, 1.01-1.05 At 5 km: OR, 1.04; 95% CI, 1.03-1.05 At 10 km: OR, 1.03; 95% CI, 1.02-1.04		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Olsson et al. 2012[235]	Sweden	Prospective cohort	115,588	1987-1995	Estimated	Each trimester and last week of gestation	1st trimester: 38.5 μg/m^3 (IQR = 6) 2nd trimester: 38.9 μg/m^3 (IQR = 5.8) Last week: 38.3 μg/m^3 (IQR = 11)		Last week: OR, 1.07; 95% CI, 1.03-1.11	
	Rahmalia et al. 2012[236]	France	Prospective cohort	801	2003-2006	Estimated via dispersion model	Each trimester and entire pregnancy	Nancy City: 24.8 μg/m^3 Poitiers: 16.1 μg/m^3 (IQR = 10)	NS		
	Rich et al. 2009[210]	US	Prospective cohort	199,221	1999-2003	Measured	Each trimester	25.8-25.9 ppb (IQR = 10)			VSGA 1st trimester: % Change = 7 (95% CI, 1.8-12.4)* 2nd trimester: % change = 7.7 (95% CI, 2.6-13)* 3rd trimester: % change = 7.4 (95% CI, 2.5-12.5)*
	Ritz et al. 2007[211]	US	Case-control	58,316	2003	Estimated via logistic regression and 2-phase models	1st trimester	>3.64 pphm		NS	
	Schembari et al. 2015[225]	England	Prospective cohort	9067	2007-2010	Estimated via LUR	Each trimester and entire pregnancy	IQR = 10 μg/m^3	NS		
	Slama et al. 2007[237]	Germany	Prospective cohort	1,016	1998-1999	Estimated via LUR	Each trimester	35.8 μg/m^3 (IQR = 10)	NS		
	Trasande et al. 2013[213]	US	Cross-sectional	222,359	2000, 2003, 2006		Month of birth	0.017 ppm (IQR = 0.013)		OR, 1.02; 95% CI, 1.01-1.14	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
						Estimated based on birth hospital address			Preterm LBW OR, 1.26; 95% CI, 1.06-1.50		
	van den Hooven et al. 2012[238]	Netherlands	Prospective cohort	7772	2001-2006	Estimated residentially	Each trimester and entire pregnancy	1st trimester: 40.4 μg/m^3 2nd trimester: 40.2 μg/m^3 3rd trimester: 40.0 μg/m^3 Entire pregnancy: 39.8 μg/m^3 (IQR = 1)	BW At birth: $\beta = -3.4$ g; 95% CI, −6.2 to −0.6 g	NS	NS
	Wilhelm et al. 2002[214]	US	Prospective cohort	37,433	1994-1996	Estimated residentially	Each month	(IQR = 1 pphm)	NS	NS	
	Wilhelm et al. 2011[219]	US	Prospective cohort	241,415	2004-2006	Estimated via LUR	1st trimester, 2nd trimester, 30 d before birth, entire pregnancy	25.2 ppb (IQR = 25.2)		OR, 1.04; 95% CI, 1.02-1.07	
	Wilhelm et al. 2012[220]	US	Prospective cohort	241,415	2004-2006	Estimated via LUR	Each trimester, entire pregnancy	26.8 ppb (IQR = 4.9)	NS		
	Wu et al. 2011[216]	US	Prospective cohort	81,186	1997-2006	Estimated via LUR and CALINE4	1st trimester 2nd trimester, last month, entire pregnancy	Measured: 24.9 ppb (IQR = 11.7) LUR: 28.0 ppb (IQR = 5.1)		Measured: Orange County: OR, 1.13; 95% CI, 1.02-1.25 LUR: LA: OR, 0.92; 95% CI, 0.85-0.98 Very preterm birth: Measured: LA: OR, 1.46; 95% CI, 1.11-1.92 Orange County: OR, 1.43; 95% CI, 1.02-2.01	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
O_3	Dugandzic et al. 2006[239]	Canada	Prospective cohort	74,284	1988-2000	Estimated via ambient air pollution data	Each trimester	21 ppb	NS		
	Geer et al. 2012[202]	US	Prospective cohort	1,548,904	1998-2004	Estimated residentially	Each trimester	25.4 ppb (IQR = 5.9)	BW: −2.72 g; 95% CI, −4.33 to −1.11 g Only significant ethnic results Non-Hispanic black mother: −3.89 g; 95% CI, −6.6 to −1.17 g Non-Hispanic white mother: −2.97 g; 95% CI, −5.15 to −0.78 g		
	Gouveia et al. 2004[203]	Brazil	Prospective cohort	179,460	1997	Estimated via regression models	Each trimester	63.0 μg/m^3 (results from 4th quartile)	NS		
	Hansen et al. 2007[231]	Australia	Prospective cohort	26,617	2000-2003	Estimated based on citywide average of pollutants	Each month and trimester of pregnancy	26.7 ppb	BW Highest quartile 3rd trimester only significant result: 25 g; 95% CI, 0.5-49.4 g		3rd trimester: OR, 0.83; 95% CI, 0.71-0.97
	Jalaludin et al. 2007[204]	Australia	Prospective cohort	123,840	1998-2000	Estimated	First trimester, 3 and 1 mo before birth, first month after estimated date of conception	30.9 ppb (IQR = 13.43)		1st mo: 5 km OR, 1.60; 95% CI, 1.27-2.03 1st trimester: Sydney OR, 1.01; 95% CI, 1.01-1.02 At 5 km: OR, 0.81; 95% CI, 0.67-0.98	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Laurent et al. 2013[222]	US	Prospective cohort	70,000	1997-2006	Measured via ambient monitoring stations, estimated via LUR, Gaussian dispersion model, and traffic density and proximity to roads models	Entire pregnancy	Measured: 35.66 ppb (IQR = 11.50)	BW Measured: $\beta = -31.36$ g; 95% CI, −36.82 to −25.89 g LBW Measured: OR, 1.13; 95% CI, 1.02-1.25		
	Le et al. 2012[205]	US	Prospective cohort	164,905	1990-2001	Measured	First and last month and each trimester of pregnancy	Month: 69.78 ppb trimester: 76.56 ppb (results from 4th quartile)		1st mo: OR, 1.09; 95% CI, 1.04-1.15	NS
	Lee et al. 2013[240]	US	Prospective cohort	34,705	1997-2002	Estimated based on residential monitoring data	1st trimester	25.72 ppb (IQR = 16.8)		OR, 1.23; 95% CI, 1.01-1.50	NS
	Liu et al. 2003[207]	Canada	Prospective cohort	229,085	1995-1998	Estimated	Entire pregnancy	13.4 ppb (IQR = 10.0)	NS	NS	
	Mannes et al. 2014[208]	Australia	Prospective cohort	138,056	1998-2000	Estimated via monitoring stations	Each trimester	31.6 ppb (IQR = 1)	BW 2nd trimester: $\beta = -0.75$ g; 95% CI, −1.38 to −0.12 g		NS
	Morello-Frosch et al. 2010[209]	US	Prospective cohort	3,545,177	1996-2006	Estimated	Entire pregnancy	2.35 pphm (IQR = 1)	BW At 3 km: −8.9 g; 95% CI −10.6 to −7.1 g At 5 km: −7.0 g; 95% CI −8.2 to −5.8 g At 10 km: −5.7 g; 95% CI −6.6 to −4.9 LBW At 10 m: OR, 0.98; 95% CI, 0.97-0.99		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Olsson et al. 2012[235]	Sweden	Prospective cohort	115,588	1987-1995	Estimated	Each trimester and last week of gestation	1st trimester: 57.1 μg/m^3 (IQR = 20.4) 2nd trimester: 56.7 μg/m^3 (IQR = 20.9) last week: 59 μg/m^3 (IQR = 25.3)		1st trimester: OR, 1.08; 95% CI, 1.03-1.13	
	Olsson et al. 2013[224]	Sweden	Prospective register-based cohort	120,755	1998-2006	Measured	Early pregnancy	IQR = 10 μg/m^3		OR, 1.04; 95% CI, 1.01-1.08	NS
	Ritz et al. 2007[211]	US	Case-control	58,316	2003	Estimated via logistic regression and 2-phase models	1st trimester	>3.54 pphm		NS	
	Trasande et al. 2013[213]	US	Cross-sectional	222,359	2000, 2003, 2006	Estimated based on birth hospital address	Month of birth	0.026 ppm (IQR = 0.017)	VLBW OR, 2.60; 95% CI, 1.40-4.82		
	Wilhelm et al. 2002[214]	US	Prospective cohort	37,433	1994-1996	Estimated residentially	Each month	IQR = 1 pph)	NS	NS	
	Wu et al. 2011[216]	US	Prospective cohort	81,186	1997-2006	Estimated via LUR and CALINE4	1st trimester, 2nd trimester, last month, entire pregnancy	Measured: 35.6 ppb (IQR = 11.5)		NS	
SO_2	Bell et al. 2007[199]	US	Prospective cohort	358,504	1999-2002	Estimated	Each trimester and entire pregnancy	4.7 ppb (IQR = 1.6)	NS		
	Bobak et al. 2000[221]	Czech Republic	Prospective cohort	108,173	1991	Estimated	Each trimester	Median 32 μg/m^3 (IQR = 50)	NS	1st trimester: OR, 1.27; 95% CI 1.16-1.39 2nd trimester: OR, 1.25; 95% CI 1.14-1.38 3rd trimester: OR, 1.24; 95% CI 1.13-1.36	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Brauer et al. 2008[200]	Canada	Prospective cohort	70,249	1999-2002	Estimated via IDW and LUR model	Each month	IDW: 5.3 μg/m^3 (IQR = 1)	NS	NS	NS
	Darrow et al. 2011[201]	US	Prospective cohort	406,627	1994-2004	Estimated via distributed lag models	Each month, 3rd trimester	1st month of gestation: 10.7 ppb (IQR = 4) 3rd trimester: 9.5 ppb (IQR = 3)	3rd trimester: β = −3.9 g; 95% CI, −7.5 to −0.4 g; Only significant ethnic results: 3rd trimester: Non-Hispanic white: −5.2 g; 95% CI, −9.2 to −1.2 g Hispanic: −5.7 g; 95% CI, −11.4 to −0.1 g		
	Dibben et al. 2015[229]	Scotland	Prospective cohort and occupational	21,843 (LBW) 23,086 (BW)	1994-2008	Estimated residential exposure and combined residential and workplace exposure	Entire pregnancy	Residential: 5.41 μg/m^3 Residential and workplace: 5.44 μg/m^3	NS	NS	
	Dugandzic et al. 2006[239]	Canada	Prospective cohort	74,284	1988-2000	Estimated via ambient air pollution data	Each trimester	10 ppb	NS		
	Geer et al. 2012[202]	US	Prospective cohort	1,548,904	1998-2004	Estimated residentially	Each trimester	2.3 ppb (IQR = 1.6)	BWβ = −4.99 g; 95% CI, −8.11 to −1.87 g Only significant ethnic results Hispanic mother: β = −6.39 g; 95% CI, −9.62 to −3.16 g		
	Gouveia et al. 2004[203]	Brazil	Prospective cohort	179,460	1997	Estimated via regression models	Each trimester	19.6 μg/m^3 (results from 4th quartile)	BW 2nd trimester: β = +33.7 g; 95% CI, 1.6-65.8 g		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Jalaludin et al. 2007[204]	Australia	Prospective cohort	123,840	1998-2000	Estimated	First trimester, 3 and 1 mo before birth, first month after estimated date of conception	3.6 ppb (IQR = 2.24)		1st mo: Sydney OR, 0.86; 95% CI, 0.82-0.89* 1st trimester Sydney OR, 0.83; 95% CI, 0.78-0.90 5 km OR, 2.31; 95% CI, 1.29-4.15 3 mo before birth: 5 km OR, 2.33; 95% CI, 1.34-4.04 1 mo before birth: 5 km OR, 1.56; 95% CI, 1.02-2.38	
	Le et al. 2012[205]	US	Prospective cohort	164,905	1990-2001	Measured	First and last month and each trimester of pregnancy	Month: 5.8 ppb trimester: 5.8 ppb (results from 4th quartile)		Last month: OR, 1.07; 95% CI, 1.02-1.13	1st mo: OR, 1.11; 95% CI, 1.04-1.18* 1st trimester: OR, 1.15; 95% CI, 1.08-1.23* 2nd trimester: OR, 1.12; 95% CI, 1.05-1.20* 3rd trimester: OR, 1.12; 95% CI, 1.05-1.20*

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Lee et al. 2003[206]	South Korea	Prospective cohort	388,105	1995-1998	Estimated	Each month and trimester during pregnancy	12.1 ppb	LBW 2nd trimester: OR, 1.06; 95% CI, 1.02-1.11 All trimesters: OR, 1.14; 95% CI, 1.04-1.24		
	Liu et al. 2003[207]	Canada	Prospective cohort	229,085	1995-1998	Estimated	Entire pregnancy	4.9 ppb (IQR = 5.0)	LBW 1st mo: OR, 1.11; 95% CI, 1.01-1.22	Last month: OR, 1.09; 95% CI, 1.01-1.19	
	Maisonet et al. 2001[17]	US	Prospective cohort	89,557	1994-1996	Estimated using air monitoring data	Each trimester	IQR = 10	NS		
	Morello-Frosch et al. 2010[209]	US	Prospective cohort	3,545,177	1996-2006	Estimated	Entire pregnancy	2.10 ppb (IQR = 1)	BW At 5 km: 2.4 g; 95% CI, 1-3.7 At 10 km: 3.1 g; 95% CI, 2.3-3.8 g		
	Rich et al. 2009[210]	US	Prospective cohort	199,221	1999-2003	Measured	Each trimester	5.4 to 5.7 ppb (IQR = 3)			NS
	Sagiv et al. 2005[241]	US	Prospective cohort	187,997	1997-2001	Estimated	6 wk before birth, 3 d before birth	7.9 ppb (IQR = 15)		NS	
	Wang et al. 1997[242]	China	Prospective cohort	74,671	1988-1991	Estimated	Each month	IQR = 100 $\mu g/m^3$	BW $\beta = -7.3$ g; (SE = 1.5; $P < 0.01$)* LBW OR, 1.11; 95% CI, 1.06-1.16		
PAH	Dejmek et al. 1999[243]	Czech Republic	Cross-sectional	4,883	1994-1998	Versatile air pollution sampler	Entire pregnancy	14 $\mu g/m^3$			OR, 1.22; 95% CI, 1.07-1.39 per 10 ng
	Vassilev et al. 2001[244]	US	Cross-sectional	222,997	1990-1991	EPA monitor data	During pregnancy	0.0400 $\mu g/m^3$	LBW: OR, 1.31; 95% CI, 1.21-1.43 with high/low	OR, 1.25; 95% CI, 1.19-1.31 with high/low	

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Perera et al. 2002[245]	US	Cross-sectional	263	NA	Maternal blood	3rd trimester	3.7 ng/m^3	BW: $\beta = -0.09$g, $P = 0.003$ @ for African Americans		
	Wilhelm et al. 2011[219]	US	Case–control	112,915	2004-2006	Air quality management district and chemical mass balance model	1st trimester 2nd trimester 3rd trimester	PAH 221.4 μg/m^3		OR, 1.30; 95% CI, 1.15-1.47 per IQR	
PAH (Benzene)	Slama et al. 2009[246]	France	Prospective cohort	271	2005-2006	Personal air monitor	2nd trimester, 3rd trimester	1.8 μg/m^3 median	BW: $\beta = -68$g; 95% CI, −135 to −1 g per lg-unit		
$PM_{2.5}$	Jedrychowski et al. 2004[247]	Poland	Prospective cohort	362	2001-2003	Personal air monitor	2nd trimester	43 μg/m^3	BW: $\beta = -200.8$ g; $P = 0.03$ per lg-unit		
	Basu et al. 2004[248]	US	Ecological study	16,693	2000	California Air Resources Board	Entire pregnancy	4-34 μg/m^3	BW: $\beta = -4.04$ g; 95% CI, −6.71 to −1.37 per 1 μg/m^3		
	Wilhelm et al. 2005[215]	US	Cross-sectional	136,134	1994-2000	Air monitoring data	Entire pregnancy	21.9 μg/m^3		OR, 0.85; 95% CI, 0.70-1.02 per 10 μg/m^3	
	Brauer et al. 2008[200]	Canada	Cohort	70,249	1999-2002	Air monitor	Entire pregnancy	5.3 μg/m^3	LBW: OR, 1.11; 95% CI, 1.01-1.23 per standardized increase	NS	OR, 1.26; 95% CI, 1.07-1.49 per standardized increase
	Kloog et al. 2012[249]	US	Ecological study	634,844	2000-2008	Satellite remote sensing	Entire pregnancy	9.6 μg/m^3	BW: $\beta = -13.80$ g; 95% CI, −21.10 to −6.05 g per 10 μg/m^3	OR, 1.06; 95% CI, 1.01-1.13 per 10 μg/m^3	
	Geer et al. 2012[202]	US	Cross-sectional	1,548,904	1998-2004	US EPA 2008a	1st trimester 2nd trimester 3rd trimester	12.6 μg/m^3	BW: $\beta = +2.49$ g; 95% CI, 0.58-4.41 g per IQR		

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Gray et al. 2014[250]	US	Cross-sectional	457,642	2002-2006	EPA	1st trimester, 2nd trimester, 3rd trimester	13.6 μg/m^3	LBW: OR, 1.02; 95% CI, 0.99-1.04 per IQR	OR, 1.01; 95% CI, 0.99-1.02 per IQR	OR, 1.03; 95% CI, 1.02-1.05 per IQR
	Silva et al. 2014[251]	Brazil	Retrospective cohort	6,147	2004-2005	SINASC	1st trimester, 2nd trimester, 3rd trimester	18.1-21.7 μg/m^3	LBW: OR, 1.51; 95% CI, 1.04-2.17		
	Rich et al. 2015[252]	China	Cross-sectional	83,672	2007-2010	Air pollution monitoring stations	Each month of gestation	61.3 μg/m^3	BW: β= −18 g; 95% CI, −32 to −3 g per IQR		
	Hao et al. 2015[253]	USA	Ecological	3,389,450	2002	EPA	1st trimester, 2nd trimester, 3rd trimester	12.5 μg/m^3	LBW: OR, 1.02; 95% CI, 1.00-1.03 per 5 μg/m^3		
	Stieb et al. 2015[254]	Canada	Ecological	2,969,380	1999-2008		Entire pregnancy	8.4 μg/m^3	BW: β = −20.5 g; 95% CI, −24.7 to −16.4 g per 10 μg/m^3		OR, 1.04; 95% CI 1.01-1.07 per 10 μg/m^3
PM_{10}	Wilhelm et al. 2005[215]	US	Cross-sectional	136,134	1994-2000	Air monitoring data	1st trimester, 2nd trimester, 3rd trimester	42.2 μg/m^3	LBW: OR, 1.22; 95% CI, 1.05-1.41 per 10 μg/m^3 3rd trimester	OR, 1.00; 95% CI, 0.93-1.09 per 10μg/m^3	
	Dugandzic et al. 2006[239]	Canada	Retrospective cohort study	74,284	1988-2000	NAPS air monitoring data	1st trimester, 2nd trimester, 3rd trimester	17 μg/m^3	LBW: RR, 1.33; 95% CI, 1.02-1.74 per IQR		
	Brauer et al. 2008[200]	Canada	Cohort	70,249	1999-2002		Entire pregnancy	12.7 μg/m^3	LBW: OR, 1.11; 95% CI, 1.01-1.23 per standardized		OR, 1.26; 95% CI, 1.07-1.49 per standardized

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Table 4. continued

Air Pollutant	Author/Year	Location	Type of Study	Sample Size	Study Period	Sample Matrix	Time of Measurement	Mean Level of Exposure	Adverse Birth Outcomes		
									BW/LBW	PB	SGA
	Geer et al. 2012[202]	US	Cross-sectional	1,548,904	1998-2004	US EPA	1st trimester, 2nd trimester, 3rd trimester	27.4 μg/m^3	BW: β = +1.30 g; 95% CI, 0.14-2.46 g per IQR		
	Ramao et al. 2013[265]	Brazil	Ecological	57,392	2000-2006	EPA monitor	1st trimester, 2nd trimester, 3rd trimester	22.74-65.55 μg/m^3	LBW: OR, 1.26; 95% CI, 1.14-1.40 per IQR		

BW, birth weight; EPA, Environmental Protection Agency; GW, gestational week; IDW, inverse-D instance weighting; IQR, interquartile change; LBW, low birth weight; LUR, land-use regression; NA, not available; NAPS, National Air Pollution Surveillance; NS, not significant; PB, preterm birth; SGA, small for gestational age.

* The studies included in Table 4 focus on those articles published since 1990 (sample size >50). The table lists exact ORs or β-values for results reaching statistical significance (*$P < 0.05$). Blank spaces in the table indicate that these variables were not investigated by the studies. The birth outcomes listed in the table are restricted to major birth outcomes due to space limitation (BW, LBW, PB, and SGA).

Epidemiologic Studies of Air Pollutants, Fetal Growth, and Selected Birth Outcomes.

Carbon monoxide. Several epidemiologic studies have been conducted to examine whether prenatal CO exposure has an effect on birth weight (Table 4). Most of the studies have measured exposure levels via monitoring stations and found that maternal exposure to CO has a significantly adverse effect on birth weight.[17,199,201,203,206,208,209,213,219,220,222,255] For example, one study[201] reported a significant decrease of birth weight among an American Hispanic cohort population when exposed during the third trimester. Another study[255] found an increased risk for LBW when the CO exposure exceeded 5.5 ppm during the third trimester. It has also been demonstrated that birth weight would be significantly reduced by 15.3 g for each ppm increase of CO 1 month before birth.[208] Several other studies reported a significantly reduced birth weight based on residential distance from the monitoring stations.[17,209,213] However, one study[206] found that the exposure during the third trimester decreased the risk for LBW, whereas the estimated exposure during the first trimester increased the risk. It has also been reported that birth weight significantly increases with increasing CO exposure.[222]

Results from multiple studies support a significantly increased risk for preterm birth associated with prenatal CO exposure.[200,204,205,207,215,216,255] These associations have varied with respect to the timing of exposure, with some studies reporting associations for exposures during the first trimester,[211,215] last month of gestation,[207] and entire gestational period.[209] However, these findings have not been entirely consistent as some studies have suggested a decreased risk for preterm birth associated with CO exposure during the first month of gestation[205] and during the first trimester.[204]

Some studies found that prenatal CO exposure was related to SGA. One such study[200] reported a significantly increased risk for SGA for CO exposure during the entire gestation. Another study[205] also found a significantly increased risk for SGA for exposure at the highest quartile during the first month of gestation and the first trimester.

Nitrogen oxides (NO, NO_2, NO_x). As shown in Table 4, some studies have indicated that prenatal exposure to nitrogen oxides has an adverse effect on birth weight, although the evidence is inconsistent. Of the studies focusing on NO_2 exposure, some studies determined that NO_2 exposure leads to significantly reduced birth weight specially for

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exposures during the first trimester,[208] second trimester,[226,227] third trimester,[201,232] entire gestational period,[199,200,209,213,229] and at birth.[238] On the contrary, one study[222] found that prenatal NO_2 exposure in fact significantly decreased the risk for LBW. Several epidemiologic studies examined the association between preterm birth and prenatal NO exposure. Specifically, one study[216] reported that the risk for preterm birth rose significantly when exposed to high levels of NO and NO_x. An increased risk was observed for prenatal exposed to NO in other studies.[200,213,219,224,233]

Several studies provided evidence for a significant association between higher levels of NO or NO_2 exposure and SGA for exposures during the first month of gestation,[205] second trimester,[228] and throughout the entire pregnancy period.[210,223] Two other studies, however, reported that NO exposure has decreased the risk for SGA for exposures occurring during gestation[224] or the second trimester specifically.[231]

Ozone. Among the studies that investigated the association between prenatal O_3 exposure and birth weight, some provided evidence for an association between higher levels of O_3 exposure and reduced birth weight, based on exposures during the second trimester,[208] entire pregnancy,[222] and month of birth.[213] On the other hand, one study[231] reported that O_3 exposure significantly increased birth weight for those with the highest exposure during the third trimester.

Epidemiologic findings for the relationship between prenatal O_3 exposure and preterm birth have been mixed (Table 4). Two prospective studies in Sweden[224,235] reported a significantly increased risk for preterm birth for O_3 exposures during the first trimester or early pregnancy period. An increased risk for preterm birth in relation to O_3 exposure was reported in some cohorts conducted in the United States and Australia,[204,205,240] although others reported null findings.[207,211,214,216] Most studies have reported no association between prenatal O_3 exposure and risk for SGA, although a reduced risk for SGA was reported for those exposed to high level of O_3 during the third trimester of gestation.[231]

Sulfur dioxide. Several epidemiologic studies reported statistically significant adverse effects of SO_2 on birth weight. One study[242] found that the birth weight would decrease by 7.3 g per 100 $\mu g/m^3$ SO_2 exposure during each month of gestation and that the risk for LBW would increase by 11%. Another[201] showed that the birth weight decreased by 3.9 g per 3 ppb exposure during the third trimester and noted that Hispanic and non-Hispanic white fetuses had significantly higher risk. A significantly decreased birth weight was associated with SO_2 exposure in the Hispanic infants in another study.[202] However, 2 studies reported a significant increase in birth weight for the highest quartile of SO_2 exposure.[203,209]

One study found a 7% increased risk for preterm birth for those with high SO_2 exposures during the last month of gestation.[205] Another study found a higher risk for preterm birth for exposures during each of the 3 trimesters.[221]

Three studies tested whether heightened SO_2 exposure would increase the risk for SGA, among which only 1 study found a statistically significant increased risk. The study[205] reported an increased risk for SGA for those exposed to the highest quartile of SO_2 level at each of the 3 trimesters, with the first trimester exposure having the strongest impact (OR, 1.15; 95% CI, 1.08-1.23).

PAHs. Epidemiologic studies appear to support prenatal high-level exposure to PAHs having adverse effects on fetal development. One study[244] evaluated annual average polycyclic organic matter (POM) concentrations (of which PAHs are a major constituent) for residents of New Jersey and reported exposure-response relations with very LBW (<1500g), term LBW, SGA, and preterm birth. Two studies[245,256] showed that high prenatal exposures to PAHs in the third trimester were associated with increased risk for reduced birth weight and head circumference. A cross-sectional study showed that PAH-DNA adducts in cord blood were inversely associated with birth weight, length, and head circumference.[257] Similar findings were reported from a cohort study in China.[258]

A study from France found a statistically significant inverse association between 1-OHP in spot urine and birth weight, birth length, and head circumferences.[246] However, the correlation became insignificant when study cohorts were limited to only nonsmokers. Outdoor exposure to PAHs was reported to increase the risk for LBW in a pilot study in the United States.[244] One study[243] reported maternal exposure to PAH was associated with intrauterine growth restriction (IUGR) in the first gestational month. A study in New York[245] found that black mothers exposed to high levels of airborne PAHs were more likely to deliver term infants with symmetric IUGR and with a larger head size relative to birth weights. A case-control study in the United States found a 30% increased risk for preterm birth per interquartile of PAH exposure.[220] Another cross-sectional study reported a significantly increased risk for preterm birth and maternal PAH exposures.[244]

$PM_{2.5}$ and PM_{10}. There is emerging interest in examining the relationship between PM and birth weight, but the results of studies conducted to date have been inconsistent (Table 4). A prospective cohort study conducted in Poland measured $PM_{2.5}$ by personal air monitoring over a 48-hour period during the second trimester of pregnancy and found that $PM_{2.5}$ was significantly inversely associated with birth weight, birth length, and head circumference.[247] One study[259] reported that heavy exposure to PM_{10} was associated with a significant reduction in femur length and head circumference.

A study from Canada found an increased risk for delivering an LBW infant for women in the highest quartile of PM_{10} during the first trimester of gestation.[239] Another study found that first trimester exposure, rather than exposures during the second or third trimester, was associated with adverse birth outcomes.[206] There was one study, however, that only found an increased risk for term LBW from $PM_{2.5}$ or PM_{10} exposure during the third trimester.[220] It should be noted that 2 studies found no association between prenatal PM exposure and birth weight[250,260] and one study found that $PM_{2.5}$ exposure during the first trimester was associated with an increase in birth weight.[202]

Some studies investigated the association between prenatal PM exposure and preterm birth. One study[261] reported that $PM_{2.5}$ exposure in the first trimester had the strongest association with preterm birth. A Massachusetts study[249] reported a significant 6% increased risk for preterm birth per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Two studies showed an increased risk for preterm birth from prenatal exposure to $PM_{2.5}$ or PM_{10}, but the results became insignificant after control of confounders.[260,262] There is evidence indicating that $PM_{2.5}$ and PM_{10} may be associated with IUGR or SGA.[200,254,260]

Proposed Mechanisms

Although several studies have found significant evidence linking air pollution and adverse birth outcomes, only limited information is available on the mechanism of action. Air pollutants can cross the placental barrier to reach the fetus directly and consequentially weaken relevant transplacental functions. Studies also suggest that air pollutants can cause an inflammatory response, oxidative stress,[263] an allergic immune response, and a reduction in heart rate variability. Each of these outcomes can impede fetal growth and development.[264]

GAPS IN THE CURRENT LITERATURE

Although there is clear biological plausibility linking prenatal low-level environmental exposures to impaired fetal development and childhood growth, the epidemiologic results so far have been inconsistent. Suggestive associations are apparent but the inconsistencies dictate further study before any of these relationships can be viewed as established. There are substantial gaps in our knowledge about the relationship between prenatal environmental exposures and fetal and early childhood growth.

Type of Study

Most studies conducted to date have been cross-sectional in design and relied on birth size and blood samples collected at delivery. The reported study findings could be subject to reverse causality if other factors influence exposure levels and birth size, and do not allow for the assessment of whether specific windows of susceptibility exist. As such, longitudinal studies are needed to comprehensively and prospectively investigate the relationship between prenatal environmental exposures and fetal and early childhood growth trajectories.

Study Populations

In many of the evaluated studies, the study population included very few LBW infants. If environmental exposures are indeed associated with impaired fetal growth, exclusion of LBW infants from the study may result in a missed opportunity to observe the association because the results would be biased toward the null by excluding LBW infants.

Exposure of Interest

There is a need to study both the independent and joint effects of environmental exposures. Many studies measured only 1 or 2 or several selected chemicals, which makes it difficult to compare the results across studies. It is plausible that the interaction of a combination of these environmental pollutants may have significant effects on birth outcomes.

Outcome of Interest

Many prior studies relied on birth size as a marker for fetal growth to examine the role of prenatal environmental exposure on fetal growth. Without

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information on fetal growth, the observed relationship between prenatal environmental exposures and birth size may actually reflect underlying causes of fetal growth impairment rather than LBW itself. For instance, we are not aware of any human study so far having directly examined the relationship between prenatal PFC exposure and fetal growth and development during the gestational period using ultrasound measures of fetal development at different periods of pregnancy.

Effect Modification

Few studies have investigated the potential gene-environment interactions or epigenetic effects of environmental exposures on the risk for impaired fetal and childhood growth. Candidate genes have been associated with birth weight, including genes that metabolize environmental pollutants, genes that are involved in the functional activities of endogenous and exogenous hormones, or genes associated with fetal growth. It is well known that gene polymorphisms modify the relationship between environmental exposures and human diseases. Recent studies have demonstrated that epigenetic alterations, particularly DNA methylation status, may have an effect on LBW.

Windows of Vulnerability

To our knowledge, no prospective study has systematically examined windows of vulnerability to environmental exposures for fetal and childhood growth trajectories at different periods of pre- and postnatal development.

Control of Confounding Effects.

Many studies lacked control for some major confounders such as glomerular filtration rate (GFR) and interpregnancy intervals. Some have suggested that lack of control for GFR alone may account for a large proportion of the observed association between prenatal environmental exposures and birth weight. Furthermore, exposure levels and biological samples from the fathers of the index children may be important contributors of fetal growth and development and birth outcomes. Collection of milk from mothers who breastfeed their infants and information on dietary intakes could also be valuable in studies of childhood growth and rapid catch-up growth.

PROSPECTIVE PRENATAL COHORT STUDY IN WUHAN, CHINA

Considering the major gaps in the current literature, many prenatal or birth cohort studies are being built worldwide. In the United States, the much anticipated US National Children Study has been recently closed by the National Institutes of Health. The efforts, however, to elucidate environmental exposures that are associated with fetal and childhood growth trajectories must be pursued in other ways because of their critical public health implications.

Through collaboration between scientists from Tongji School of Public Health, the Wuhan Medical and Health Center for Women-Children, and Brown University School of Public Health, an ongoing prenatal cohort study in the Wuhan Medical and Health Center for Women-Children is being conducted. The study was initiated in 2014. Before starting the prenatal cohort study, we first conducted a birth cohort study investigating in utero exposures and risk for adverse birth outcomes by recruiting 10,000 mother-infant pairs in the same hospital between 2011 and 2013 as a pilot and used the pilot experience gained and the infrastructure established for the birth cohort study to conduct the ongoing prenatal cohort study. The main purposes of building the prenatal cohort was to establish a critical mass for

1. Studying the association between prenatal exposures, fetal growth trajectories, and birth outcomes;
2. Following up the children in the study to assess childhood growth trajectories, neuropsychiatric development, pubertal development, and health-related issues; and
3. Exploring the fetal origin hypothesis of adult diseases.

Eligible pregnant women for this prenatal cohort study are those with signed informed consents to participate in the study satisfying the following conditions:

1. Aged $\geq$20 years;
2. $<$16 weeks pregnant with a single gestation at the time of enrollment;
3. Having 3 prenatal cares and being followed up in the study hospital with completion of in-person interviews, specific biochemical and biophysical measures, and ultrasound measures of fetal development at around 14 to 16 weeks (time 1), 26 to 28 weeks (time 2), and 36 to 38 weeks (time 3) of gestation;

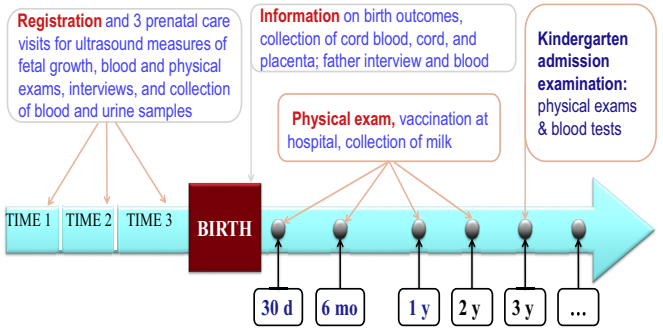

Figure 1. **Illustration of the study design and timeline for the prenatal cohort study in Wuhan, China.**

4. Delivered a singleton live birth without congenital malformation at the study hospital; and
5. Donated maternal blood at each of the 3 prenatal care visits.

The goal of the prenatal cohort study is to recruit 3000 mother-infant pairs who satisfy the study conditions.

As shown in Figure 1, at each of the prenatal care visits, study participants have had ultrasound measures of fetal development, in-person interviews, specific biochemical and biophysical measures, donated maternal blood samples, and urine samples. Taking ultrasound measurements at these 3 points of pregnancy allows us to have the 5 ultrasound measures (biparietal diameter, occipital frontal diameter, head circumference, femur length, and abdominal circumference) for all 3 periods of pregnancy for comparison purposes. This is because the only reliable and valid measure for fetal growth before 14 weeks is the Crown-Rump length for which the measurement is usually made between 7 and 13 weeks. Also, for the purpose of evaluating the exposure effects on fetal growth for a specific trimester, we feel it is better to take the ultrasound measures at the end of the trimester or at the early period of next trimester compared with the ultrasound measures taken too early or in the middle of the trimester, which may not be able to see a lag effect or the effect from whole trimester exposure.

At the time of delivery, we collected umbilical cord and cord blood, placental samples, and recorded information on birth outcomes. During the postnatal follow-up visits, the infants were (or will be) invited back to the hospital at the first month for physical examinations and mothers who breastfeed their babies are asked to donate 10 mL milk.

Our ongoing follow-up at 6 and 12 months, and 2 years of age are arranged at the time of mandated vaccinations to have anthropometry measurements and physical examinations. The study participants are also followed up through an established tracking system at the Wuhan Medical and Health Center for Women-Children. Biospecimens, questionnaires, and anthropometry collected at these visits will be used to characterize prenatal and postnatal exposures and fetal and infant growth trajectories. In-person interviews and blood samples are also solicited from the children's biological father.

Several distinctive features of the study population (almost no Chinese women in Wuhan smoke tobacco products or drink alcohol, the majority were giving birth to their first child, and the relatively high environmental exposure levels due to the rapid industrialization and urbanization), along with longitudinal measures of exposures, fetal development and infant growth, and extensive data on potential confounders provide us with the unique opportunity to identify potentially modifiable risk factors for impaired fetal development, adverse birth outcomes, and rapid catch-up growth in early childhood.

CONCLUSION

It is now widely accepted that impaired fetal growth, reduced birth weight, and rapid catch-up growth in childhood predispose to high morbidity in infants and subsequent risk for adult diseases. Understanding the risk profiles for impaired fetal development and postnatal catch-up growth is thus critical to establish appropriate interventions to prevent childhood and adult diseases, and to further understand the underlying etiology of these

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diseases. Our evaluation of the literature linking environmental exposures to fetal growth, birth size, and childhood growth suggests that the effects of a variety of environmental pollutants, although provocative, have been largely inconsistent with results varying by study population, study design, and timing of exposure. Ongoing and planned longitudinal studies that have the ability to measure exposures across various time points during pregnancy and that comprehensively and prospectively investigate the relationship between exposures and fetal and early childhood growth trajectories are likely to provide increased insight into these associations.

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