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Air Pollution and Adverse Pregnancy Outcome

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1. Introduction

Air pollution is known to be associated with increased total mortality, including cardiovascular and respiratory mortality. People with chronic disease in adulthood, such as cardiovascular disease, metabolic syndrome and respiratory diseases, are very susceptible with air pollutants (Kwon HJ et al., 2003). However, air pollution adversely impacts not only adults and the elderly but also fetuses and children. In fact, fetuses are the most vulnerable group to air pollution because vulnerability and susceptibility to air pollution are formed at early ages. Low birth weight (LBW), pre-term delivery (PTB), intrauterine growth restriction, and post-neonatal infant mortality are such undesirable outcomes.

LBW affects 20 million infants worldwide (UNICEF, 2004). LBW is comprised of two overlapping etiologies: PTB and intrauterine growth retardation (IUGR). In particular, LBW is associated with a higher risk of infant and childhood mortality, coronary heart disease, and other health problems. LBW additionally has a well-established association with early-onset insulin resistance and a later risk of adulthood diseases, including all aspects of the metabolic syndrome.

PTB remains the leading cause of perinatal mortality and occurs in approximately 4-10% of pregnancies (Reagan and Salsberry 2005). Known risk factors for PTB include lower social class, less education, single marital status, low income, younger maternal age, low body weight, ethnicity, smoking, and poor housing, along with medical factors such as induction, premature rupture of membranes, infection, multiple pregnancy, intrauterine death, fetal and uterine abnormalities and chorioamnionitis (Bibby and Stewart 2004).

LBW and PTB are both significantly associated with infant mortality and an array of infant morbidities that range from pulmonary to neurologic outcomes. These associations form the basis for the "fetal origins" or the "Barker hypothesis" which postulates that "fetal growth retardation consequent to malnutrition has long-term structural and physiologic impacts that predispose an individual to chronic diseases in adulthood" (Barker, 2007).

Is there the association between air pollution and adverse pregnancy outcomes, such LBW, and PTB? In this chapter, we will review the association between air pollution and adverse pregnancy outcomes(APO), such as LBW and PTB. We also will estimate the disease burden of LBW and PTB caused by air pollution, and discuss how to decrease these APOs.

2. Air pollution and adverse pregnancy outcomes

2.1 Air pollution and low birth weight

Fifteen (Alderman et al., 1987; Bell et al., 2007; Bobak and Leon, 1999; Bobak, 2000; Dugandzic et al., 2006; Gouveia et al., 2004; Ha et al., 2001; Lee et al., 2003; Lin et al., 2004; Liu et al., 2003; Maisonet et al., 2001; Morello-Frosch et al., 2010; Ritz and Yu, 1999; Rogers et al., 2000; Salam et al., 2005) studies reported data on birth outcomes following SO_2 exposure (Table1): ten reported increased odds of LBW births following SO_2 exposure, five reported no association with LBW, and one reported significant association with extreme LBW (Rogers et al., 2000).

Little is known about the association between nitrous oxide (NO) and APO. But in natural condition, NO is converted into nitrogen dioxide (NO_2), which is 5~10 times more toxic than NO. NO_2 is known to be associated with APO by several studies. The association between NO_2 exposure and LBW was explored in 11 studies (Bell et al., 2007; Bobak, 2000; Gouveia et al., 2004; Ha et al., 2001; Lee et al., 2003; Lin et al., 2004; Liu et al., 2003; Madsen et al., 2010; Maroziene and Grazuleviciene, 2002; Morello-Frosch et al., 2010; Salam et al., 2005) (Table 1). Increased LBW risk with increased NO_2 exposure was reported by Ha et al. (2001) (first trimester), Lee et al. (2003) (second trimester), Bell et al. (2007) (during the entire gestation) and Morello-Frosch et al. (2010). However, other reports did not identify significant increases in LBW births.

The association between carbon monoxide(CO) exposure and birth outcomes was explored in 13 studies (Alderman et al., 1987; Bell et al., 2007; Chen et al., 2002; Gouveia et al., 2004; Ha et al., 2000; Huynh et al., 2006; Lee et al., 2003; Lin et al., 2000; Liu et al., 2003; Maisonet et al., 2001; Morello-Frosch et al., 2010; Salam et al., 2000; Ritz and Yu, 1999) (Table 1). Of these, five studies (Ritz and Yu, 1999; Ha et al., 2000; Maisonet et al., 2001; Lee et al., 2003; Morello-Frosch et al., 2010) reported an increased risk of LBW births.

Seven studies (Chen et al., 2002; Dugandzic et al., 2006; Gouveia et al., 2004; Ha et al., 2001; Lin et al., 2004; Liu et al., 2003; Morello-Frosch et al., 2010) investigated the association between exposure to ozone and LBW (Table 1). None of these studies reported a statistically significant increase in LBW with higher exposure to ozone.

The effects of $PM_{2.5}$ (Particulate matter less than 2.5 μm in aerodynamic diameter) on LBW were evaluated in four studies (Bell et al., 2007; Huynh et al., 2006; Madsen et al., 2010; Morello-Frosch et al., 2010) *(*Table 1*)*. Huynh et al. (2006) reported an association between high levels of $PM_{2.5}$ and LBW when the exposure was measured at any time during the gestation, and particularly in the last 2 weeks of pregnancy and the first month of gestation. Bell et al. (2007) and Morello-Frosch et al. (2010) also reported that high levels of $PM_{2.5}$ were associated with LBW. But Madsen et al. (2010) did not report any association between exposure to high levels of $PM_{2.5}$ and LBW.

Twelve studies (Bell et al., 2007; Chen et al., 2002; Dugandzic et al., 2006; Gouveia et al., 2004; Lee et al., 2003; Maisonet et al., 2001; Lin et al., 2004; Salam et al., 2005; Seo et al., 2010; Madsen et al., 2010; Morello-Frosch et al., 2010; Xu et al., 2011) assessed the effects of PM_{10} (Particulate matter less than 10 μm in aerodynamic diameter) on LBW (Table 1). Lee et al. (2003) and Xu et al. (2011) reported on a possible association between LBW and an increase of more than an interquartile range in PM_{10} exposure during the first and second trimesters, and Gouveia et al. (2004) reported higher odds of LBW among mothers in the highest quartile of exposure during the second trimester. Seo et al. (2010) reported that among seven Korean cities, two had higher odds of LBW births with incremental exposure to PM_{10}, whereas five had no association. Other studies have reported no association between PM_{10} and LBW births.

Of five studies (Bobak, 2000; Bobak and Leon, 1999; Ha et al., 2001; Rogers et al., 2000; Wang et al., 1997) that reported on the association between total suspended particles and LBW (Table 1), three (Ha et al., 2001; Rogers et al., 2000; Wang et al., 1997) reported an increased risk of LBW births with higher concentrations. The other two (Bobak, 2000; Bobak and Leon, 1999) reported no association between TSP (total suspended particle) and LBW births.

Pollutants or exposure variable	**Results**	**Reference**
SO_2	NE*	Alderman et al ,1987
	AOR**=1.22(95% CI, 1.03–1.44) for > 5.5 ppm during the last trimester	Ritz and Yu,1999
	AOR=1.10(95% CI, 1.02–1.17) for 50 µg/m^3 increase	Bobak and Leon, 1999
	NE	Bobak, 2000
	AOR=2.88(95% CI, 1.16–7.13) for > 56.75 µ/m^3 in annual exposure for very LBW infant outcome	Rogers et al.,2000
	ARR=1.06(95% CI, 1.02–1.10) for IQR increase in the first trimester	Ha et al.,2001
	Second trimester exposures falling within the 25 and < 50th (AOR 1.21; CI 1.07,1.37), the 50 to < 75th (AOR 1.20; CI 1.08,1.35), and the 75 to < 95th (AOR 1.21; CI 1.03,1.43) percentiles were also at increased risk for term LBW when compared to those in the reference category (< 25th percentile).	Maisonet et al. 2001
	OR=1.14(95% CI, 1.04–1.24) for IQR increase in all trimesters OR=1.06(95% CI, 1.02–1.11) for IQR increase in the second trimester.	Lee et al. 2003
	AOR=1.11(95% CI, 1.01–1.22) for 5 ppb increase in the first month	Liu et al. 2003
	NE	Gouveia et al. 2004
	AOR=1.16(95% CI, 1.02–1.33) for 7.1-11.4 ppb increase in entire pregnancy AOR=1.26(95% CI, 1.04–1.53) for >11.4 ppb increase in entire pregnancy AOR=1.20(95% CI, 1.01–1.41) for >12.4 ppb increase in third trimester	Lin et al. 2004
	NE	Salam et al., 2005
	ARR=1.15(95% CI, 1.00–1.31) increase in the first trimester	Dugandzic et al. 2006
	NE	Bell et al. 2007
	AOR=1.01(95% CI, 1.00- 1.02) for ppb increase at 10 km monitor distance	Morello-Frosch et al. 2010
NO_2	NE	Bobak. 2000
	ARR=1.07(95% CI, 1.03–1.11) for IQR increase in the	Ha et al. 2001

	first trimester	
	NE	Maroziene and Grazuleviciene. 2002
	OR=1.04(95% CI, 1.00–1.08) for IQR increase in all trimester OR=1.03(95% CI, 1.01–1.06) for IQR increase in the second trimester	Lee et al. 2003
	NE	Liu et al. 2003
	NE	Gouveia et al. 2004
	NE	Lin et al. 2004
	NE	Salam et al. 2005
	AOR=1.03(95% CI, 1.00–1.05) for IQR increase	Bell et al. 2007
	NE	Madsen et al. 2010
	AOR=1.03(95% CI, 1.01–1.05) for ppm increase at 3 km monitor distance AOR=1.04(95% CI, 1.03–1.05) for ppm increase at 5 km monitor distance AOR=1.03(95% CI, 1.02–1.04) for ppm increase at 10 km monitor distance	Morello-Frosch et al. 2010
CO	NE	Alderman et al., 1987
	AOR=1.22(95% CI, 1.03–1.44) for > 5.5 ppm increase during the last trimester	Ritz and Yu, 1999
	AOR=1.08(95% CI, 1.04-1.12) for IQR increase in the first trimester	Ha et al. 2001
	AOR=1.31(95% CI, 1.06–1.62) for 1 ppm increase in the third trimester	Maisonet et al. 2001
	NE	Chen et al. 2002
	OR=1.05(95% CI, 1.01–1.09) increase in all trimesters OR=1.04(95% CI, 1.01–1.07) for IQR increase in the first trimester OR=1.03(95% CI, 1.00–1.08) increase in the second trimester	Lee et al. 2003
	NE	Liu et al. 2003
	NE	Gouveia et al. 2004
	NE	Lin et al. 2004
	NE	Salam et al. 2005
	NE	Huynh et al. 2006
	NE	Bell et al. 2007
	AOR=1.06(95% CI, 1.03–1.09) for ppm increase at 5 km monitor distance AOR=1.04(95% CI, 1.02–1.06) for ppm increase at 10 km monitor distance	Morello-Frosch et al. 2010
Ozone(O_3)	NE	Ha et al. 2001
	NE	Chen et al. 2002
	NE	Liu et al. 2003

	NE	Gouveia et al. 2004
	NE	Lin et al. 2004
	NE	Dugandzic et al. 2006
	NE	Morello-Frosch et al. 2010
$PM_{2.5}$	AOR=1.14(95% CI, 1.07-1.23) for 17.7–22.1 μg/m^3 increase at any time during the gestation AOR=1.15(95% CI, 1.07–1.24) for > 22.1 μg/m^3 increase at any time during the gestation AOR=1.09(95% CI, 1.01–1.17) for 12.5–18.2 μg/m^3 increase in the first month AOR=1.14(95% CI, 1.06–1.22) for 18.2–23.0 μg/m^3 increase in the first month AOR=1.21(95% CI, 1.12–1.30) for > 23.0 μg/m^3 increase in the first month AOR=1.11(95% CI, 1.04–1.19) for 10.2–15.6 μg/m^3 increase in the last 2 weeks AOR=1.18(95% CI, 1.10–1.19) for 15.6–23.3 μg/m^3 increase in the last 2 weeks AOR=1.17(95% CI, 1.09–1.27) for > 23.3 μg/m^3 increase in the last 2 weeks	Huynh et al. 2006
	OR=1.05(95% CI, 1.02–1.09) for IQR increase	Bell et al. 2007
	NE	Madsen et al. 2010
	AOR=1.05(95% CI, 1.02–1.08) for 10 μg/m^3 increase at 5 km monitor distance AOR=1.04(95% CI, 1.02–1.07) for 10 μg/m^3 increase at 10 km monitor distance	Morello-Frosch et al. 2010
PM_{10}	NE	Maisonet et al. 2001
	NE	Chen et al., 2002
	OR=1.06(95% CI, 1.01–1.10) for IQR increase in all trimesters OR=1.03(95% CI, 1.00–1.07) for IQR increase in the first trimester OR=1.04(95% CI, 1.00–1.08) for IQR increase in the second trimester	Lee et al. 2003
	AOR=1.25(95% CI, 1.03–1.53) for highest quartile of exposure increase in the second trimester	Gouveia et al. 2004
	NE	Lin et al. 2004
	NE	Salam et al. 2005
	NE	Dugandzic et al. 2006
	NE	Bell et al. 2007
	AOR=1.24(95% CI, 1.02–1.52) for increments (difference between the maximum and minimum concentrations) increase in Pusan AOR=1.19(95% CI, 1.04–1.37) increase in Daegu	Seo et al. 2010
	NE	Madsen et al. 2010

	NE	Morello-Frosch et al. 2010
	AOR=1.13(95% CI, 1.02-1.25) for IQR (7µg/m^3) increase in the first trimester AOR=1.10(95% CI, 1.00-1.22) for IQR (7µg/m^3) increase in the second trimester	Xu et al. 2011
TSP	AOR=1.10(95% CI, 1.05–1.14) for 100 µg/m^3 increase	Wang et al. 1997
	NE	Bobak and Leon 1999
	NE	Bobak. 2000
	AOR=2.88(95% CI, 1.16–7.13) for > 56.75 µ/m^3 increase for very LBW infant outcome	Rogers et al. 2000
	ARR=1.04(95% CI, 1.00–1.08) for IQR increase in the first trimester	Ha et al. 2001

Air pollution and LBW
*NE: No effect, **AOR: Adjusted odds ratio

Table 1. Air pollution and low birth weight

2.2 Air pollution and preterm delivery

An association of higher exposure to SO_2 and PTB was reported in seven (Bobak, 2000; Huynh et al., 2006; Leem et al, 2006; Liu et al., 2003; Mohorovic, 2004; Sagiv et al., 2005; Xu et al., 1995) of the eight studies.

The association of NO_2 exposure and PTB was explored in 10 studies (Bobak, 2000; Gehring et al., 2011; Jalaludin et al., 2007; Leem et al, 2006; Liu et al., 2003; Llop et al. 2010; Maroziene and Grazuleviciene, 2002; Ritz et al.,2000, 2007, 2011) (Table 2). Bobak (2000) (first and third trimester), Maroziene and Grazuleviciene(2002) (first trimester), Leem et al (2006), Bobak (2000) (first and third trimester), Llop et al. (2010) (second and third trimester and entire pregnancy) reported an increased risk of PTB; however, others reported no association.

The association between CO exposure and preterm birth was explored in 6 studies (Ritz et al., 2000; Huynh et al., 2006; Leem et al., 2006; Liu et al., 2003; Wilhelm and Ritz, 2005; Ritz et al., 2007). Liu et al. (2003) (last month of the pregnancy), Wilhelm and Ritz (2005) (first trimester), leem et al (2006) (first and third trimester) and Ritz et al. (2007) (first trimester) reported a higher risk of PTB with higher concentration of CO. 4 of 6 studies reported a higher risk of PTB with CO exposure around 1ppm. In particular, Leem et al's study (2006) showed that the relationships between PTB and exposures to CO was dose dependent ($p<0.001$). But Ritz et al.(2000) and Huynh et al. (2006) did not report the association between CO exposure and preterm birth There was a significant dose-dependent association between gestational age and sulfur dioxide and total suspended particulate concentrations (Xu et al, 1995).

In 3 studies (Ritz et al., 2000; Liu et al., 2003; Ritz et al., 2007, the association between exposure to ozone and PTB was investigated (Table 2). None of these studies reported a statistically significant increase in PTB with higher exposure to ozone.

The effects of $PM_{2.5}$ on PTB were evaluated in three studies (Huynh et al., 2006; Ritz et al., 2007, 2011) *(Table 2)*. Huynh et al. (2006) and Ritz et al. (2007, 2011) reported an association of high levels of $PM_{2.5}$ with PTB when the exposure was measured at any time during the gestation.

In 4 studies (Leem et al., 2006; Ritz et al., 2000; Sagiv et al, 2005; Wilhelm and Ritz,2005) , the effects of PM_{10} on PTB were assessed (Table 2). Leem et al. (2006) and Ritz et al. (2000) reported on the association between PTB and high levels in PM_{10} exposure during the first

trimester. But Wilhelm and Ritz (2005) and Sagiv et al(2005) did not report any association between exposure to PM_{10} and PTB.

Three studies (Bobak, 2000; Bobak and Leon, 1999; Xu et al., 1995) reported on total suspended particles and an association with PTB (Table 2), all of which reported an increased risk of PTB births with higher concentrations.

Some studies reported the association between living near petrochemical industrial complexes or living with 500m of freeway, or living 200m of main roads and PTB. Llop et al. reported the association between benzene exposure > 2.7 µg/m^3 and PTB.

Pollutants or exposure variable	**Results**	**Reference**
SO_2	AOR** = 1.21 (95% CI, 1.01–1.45) for 100 µg/m^3 increase	Xu et al. 1995
	NE*	Langren, 1996
	AOR = 1.27 (95% CI, 1.16–1.39) for 50 µg/m^3 increase in the 1st trimester	Bobak 2000
	AOR=1.09(95% CI, 1.01–1.19) for 5.0 ppb increase	Liu et al 2003
	Significantly shorter gestation for SO_2 exposure during the initial two months of pregnancy	Mohorovic 2004
	AOR=1.15(95% CI, 1.00, 1.32) for 15 ppb increase during 6 weeks before birth	Sagiv et al., 2005
	AOR=2.31(95% CI, 1.29-4.15) for 1 hr maximum in the first trimester	Huynh et al. 2006
	AOR=1.21 (95% CI: 1.04-1.42) in the highest quartiles in the 1st trimester	Leem et al., 2006
NO_2	AOR= 1.10(95%CI,1.00-1.21) For 50 µg/m^3 increase above mean level in the 1st trimester AOR= 1.08(95%CI,0.98-1.19) For 50 µg/m^3 increase above mean level in the 1st trimester AOR= 1.11(95%CI,1.00-1.23) For 50 µg/m^3 increase above mean level in the 1st Trimester	Bobak, 2000
	NE	Ritz et al. 2000
	AOR= 1.67(1.28-2.18) for 10 µg/m^3 increase in exposure in the first trimester	Maroziene and Grazuleviciene, 2002
	NE	Liu et al. 2003
	AOR=1.24 (95% CI: 1.09-1.41) for 0.77 1.01 ppm in the 1st trimester AOR=1.21 (95% CI: 1.07-1.37) in the highest quartiles in the 3rd trimester	Leem et al., 2006
	Decreasing PTB risk	Jalaludin et al. 2007
	NE	Ritz et al., 2007
	AOR=1.16 (95% CI: 1.07-1.26) per inter-quartile range	Ritz et al. 2011
	AOR=1.29(95% CI= 1.13- 1.46) NO_2 > 46.2 µg/m^3	Llop et al. 2010

	NE	Gehring et al., 2011
CO	NE	Ritz et al. 2000
	AOR=1.08(95% CI: 1.01-1.15) for a 1.0 ppm increase	Liu et al 2003
	AOR= 1.27 (95% CI: 1.07–1.50) for 1ppm increase in the 1st trimester	Wilhelm and Ritz 2005
	AOR= 1.25 (95%: 0.81–1.91)	Huynh et al. 2006
	AOR=1.26 (95% CI: 1.11-1.44) for 0.77 1.01 ppm in the 1st trimester AOR=1.16 (95% CI: 1.01-1.34) for 0.79 1.11 ppm in the 3rd trimester	Leem et al., 2006
	AOR= 1.25(95% CI: 1.12- 1.38) for CO more than 1.25 ppm in the 1st trimester	Ritz et al. 2007
$PM_{2.5}$	AOR = 1.15(95% CI: 1.07- 1.24).	Huynh et al. 2006
	AOR= 1.10(95% CI: 1.01- 1.20) for $PM_{2.5}$ more than 21.36 µg/m^3 in the 1st Trimester	Ritz et al. 2007
	AOR= 1.08 (1.02-1.15) per inter-quartile range	Ritz et al. 2011
PM_{10}	RR = 1.16 (95% 1.06–1.26) for 50 µg/m^3 increase in the 1st trimester	Ritz et al. 2000
	AOR=1.00(95% CI, 0.90—1.12) for 10 µg/m^3 increase in the 1st trimester	Wilhelm and Ritz 2005
	NE	Sagiv et al., 2005
	AOR=1.27 (95% CI: 1.04-1.56)) in the highest quartiles in the 1st trimester	Leem et al.,2006
TSP	AOR = 1.10 (95% CI, 1.01–1.20) for 100 µg/m^3 increase	Xu et al. 1995
	AOR= 1.11(95% CI, 1.02-1.22) for each 50 µg/m^3 increase in the 1st trimester AOR= 1.06(95% CI, 0.96-1.16) for each 50 µg/m^3 increase in the 2nd trimester AOR= 1.14(95% CI, 1.03-1.26) for each 50 µg/m^3 increase in the 3rd trimester	Bobak and Leon 1999
	AOR = 1.18 (95% CI, 1.05–1.31) for 50 µg/m^3 increase in the 1st trimester	Bobak 2000
O_3	NE	Ritz et al. 2000
	NE	Liu et al 2003
	NE	Ritz et al. 2007
SO_2 + NO_2 + PM_{10}	AOR = 1.41 (91% CI, 1.08–1.82) comparing petrochemical and control municipalities	Lin et al. 2001
SO_2 + NO_2 + PM_{10}+ CO (Air Polllution Index)	AOR=4.66(95% CI, 1.92-11.32); 95% confidence interval (95% CI), 1.92-11.32 in hispanic mothers	Woodruff et al. 2003
Benzene	AOR=1.29(95% CI= 1.13- 1.46) Benzene > 2.7 µg/m^3	Llop et al. 2010

Living near petrochemical industrial complexes	AOR=1.18 (95% CI=1.04-1.34 for mothers living near petrochemical industrial complexes	Yang et al. 2002
living near industrial districts	AOR=1.11 (95% CI, 1.02-1.21)) for mothers living near industrial districts	Tsai et al. 2003
living near oil refinery plants	AOR=1.14 (95% CI,1.01-1.28) for mothers living near oil refinery plants	Yang et al. 2004
local traffic-generated NO(x) and PM($_{2.5}$).	AOR= 1.42(95% CI, 1.26-1.59) For highest NO(x) and PM(2.5) quartiles	Wu et al. 2009
living within 500 m of the freeway.	AOR=1.30 (95% CI, 1.03, 1.65)	Yang et al. 2003
Living within 200 m of main roads	AOR= 1.5 (95% CI = 1.2-1.8),	Yorifuji et al. 2011

Air pollution and premature births
*NE: No effect, **AOR: Adjusted odds ratio

Table 2. Air pollution and premature births

3. Considerations to reduce bias or measurement errors

Some studies systemically reviewed published articles about air pollution and LBW or PTB (Bobak, 2005; Bonzini et al., 2010; Pope et al., 2010; Leonardi-Bee et al., 2008; Ghosh et al., 2007; Misra et al., 1999; Sram et al., 2011). Because of different exposure assessments, methods of ascertainment, measurement times and collinearity between pollutants, the results about the association showed heterogeneity and/or an absence of association. We summarized our systemic review of these research papers in tables 1 and 2. Exposure to sulphur dioxide was associated with PTB, and exposure to $PM_{2.5}$ was associated with LBW and PTB. The evidence for NO_2, ozone and carbon monoxide was inconclusive.
To investigate the association between air pollutants and adverse birth outcomes is challenging. The following are major issues in clarifying such associations.

3.1 Exposure assessment: reduction of misclassification

Epidemiological studies for APO often had limited spatial and temporal information on pollution sources and concentrations. Misclassification of exposure is often a source of bias in such environmental epidemiologic studies.
Various exposure assessment methods have been applied in different studies. Exposures were assigned to individual subjects based on residential address at delivery using the nearest ambient monitoring station data [CO, NO_2, NO, nitrogen oxides (NOx), O_3, and $PM_{2.5}$ or less than 10 μm in aerodynamic diameter (PM_{10})], both unadjusted and temporally adjusted land-use regression (LUR) model estimates, line-source air dispersion model

estimates, and a simple traffic-density measure. Proximity to main roads and photochemical industrialized zones was also applied by using geographic information system (GIS).
Reliable measurements of daily SO_2, NO_2, CO, and PM_{10} concentrations were available from several air monitoring stations by using various extrapolation method, such as kriging to predict the spatial distribution of the air pollutants (Pikhart et al. 2001; Mulholland et al., 1998; Jerrett et al. 2005b). The kriging method, unlike proximity models (Jerrett et al. 2005a), uses real pollution measurements in the computation of exposure estimates. In case of many monitoring stations, kriging methods are often preferred to other interpolation methods because they are fairly accurate in a variety of situations and avoid the artifacts that often result from the use of IDW, spline, or global/local polynomials (Jerret et al. 2005a; Ritz et al. 2000; Waller and Gotway, 2004).
Even though exposure models, such as kriging method, attempt to decrease misclassification of individual exposures by enhancing exposure assessment through spatially- and temporally-explicit exposure models, the potential remains for misclassification of exposure due to the use of surrogate ambient air pollution data. The only real way to avoid such potential misclassifications is to conduct personal exposure assessments which are often not feasible. LUR models often produced odds ratios somewhat larger in size than temporally adjusted models (Wu J et al. 2011).
Mobility patterns could introduce possible confounding when examining small-scale variations in exposure by using addresses. This could be of importance in future studies (Madsen C et al., 2010).

3.2 Biological mechanism

Interpretation of epidemiological studies reporting an association between air pollution and birthweight needs caution. Although a range of social and behavioural determinants of birthweight or preterm birth have been identified, the biological mechanisms leading to prematurity are not well understood (Berkowitz and Papiernik, 1993) and it is not clear which mechanisms could provide the link between air pollution and birthweight. The biological mechanisms whereby air pollution might influence birth weight remain unexplained, although several theories have been proposed. The pathways could be similar to those of maternal smoking, which can increase PTB risk through premature rupture of membranes and placental abruption and lower birth weight. Air pollution could affect fetal health either through direct effects on the fetus by exposure through the placenta or from effects on the mother's health and multiple mechanisms may occur simultaneously (Glinianaia et al., 2004).
One hypothesized pathway is that placental inflammation may play an important role in the physiological pathway between air pollution exposure and LBW (Lee BE et al., 2003). Although most published reports focus on genitourinary infections, maternal illness due to respiratory infection in pregnancy may also be involved. It is possible that air pollution during pregnancy leads to placental inflammation, which impairs placental function (Dexter et al., 2000). Salafia et al. (1995) reported that chronic inflammation brought about growth restriction, independently of placental vasculopathy. PM_{10} and SO_2 exposures from first through second trimesters appeared to have the largest effect on LBW. In terms of the biological mechanism on LBW, it is reasonable to consider PM_{10} and SO_2 together rather than separately because they represent fine particles that are believed to be a risk pollutant (Ha et al., 2001). In addition, these pollutants were correlated strongly with each other and exerted an effect on LBW within similar periods.

Coarse PM (PM ≤ 10μM) is emitted from residential heating and power plants, whereas fine PM (PM ≤ 2.5 μM) is emitted from cars, utilities or wood burning. Both types of PM are comprised of primary and secondary particles: primary particles are emitted directly from a source, such as construction work, and secondary particles are formed after the reaction of primary particles in the atmosphere with chemical pollutants such as SO_2 or NO_2. When PM enters the lungs it can be absorbed into the blood and hence dispersed into distant organs. Due to their relatively small size, PM escapes phagocytosis (Ritz et al., 2007). Particle exposure in vitro and in exposed animals causes oxidative stress (Kadiiska et al., 1997) and can increase the permeability of lung epithelium, allowing particles access to the endothelial cells and the blood (Donaldson et al., 2001). PM_{10} and gaseous pollutants such as SO_2 and NO_2 lead to pulmonary inflammation with a systemic release of cytokines (Walters et al., 2001; Nemmar et al., 2002) and increased blood viscosity (Peters et al., 1997; Prescott et al., 2000).

Air pollution may affect DNA or its transcription. DNA adducts are more common in areas with higher levels of pollution. Placental DNA adducts were more common among mothers exposed to higher levels of outdoor air pollution(Bobak, 2000). When toxic organic matter such as polycyclic aromatic hydrocarbons (PAH) is adsorbed onto the surface of PM, associated oxidative stress (Leem et al., 2005) and DNA adducts are formed (Perera et al., 1999). High levels of DNA adducts were associated with reduced gestational length (Liu et al., 2003; Perera et al., 1998; Perera et al., 1999), and a correlation has been observed between the adduct levels in the mother's and the newborn's blood (Topinka et al., 2009). Newborns with elevated PAH-DNA adducts (which are used as a proxy to measure individual biologically effective dose to PAH) were found to have significantly reduced birth weight and head circumference suggesting that transplacental exposures to PAHs in ambient air may negatively impact on fetal development. High levels of PAH can interfere with nourishment of the fetus by increasing blood viscosity, and reducing the flow of blood to the placenta and uterus (Liu et al., 2003; Shah PS et al.,2011; Ritz et al., 2000). The effects of air pollution on DNA adducts levels seem similar (although weaker) to the effects of cigarette smoking. There may also be a parallel with maternal smoking, an accepted risk factor for LBW, for which the biologic mechanisms are not well understood. Although the fetal exposures to air pollution are probably lower than to tobacco smoke, the biologic mechanisms (rheologic factors, DNA damage) may be partially similar(Bobak, 2000)

Another potential mechanisms could be related to hematologic factors. Rheologic variables, including blood viscosity, influence the blood perfusion of the placenta. It has been shown that inflammation in the lung caused by air pollutants increases the coagulability of the blood. Production of free radicals induced by pollutants might cause an inflammatory response, contributing to enhanced blood coagulation. Hematologic effects of air pollutants might occur from an initial inflammatory response resulting in increased blood coagulation, and subsequent decreased oxygen supply to the placenta. Human volunteers exposed to diesel particles at 300 $\mu g/m^3$ for an hour had increases in peripheral neutrophils and platelets as well as upregulation of endothelial adhesion molecules. Decreased oxygen supply from blood viscosity changes by increasing coagulability may cause chronic hypoxic injury to fetus. This theory is supported by evidence of the role of elevated blood viscosity for impaired efficiency of maternal blood flow(Ha et al., 2001). Increased blood viscosity is associated with decreased oxygen diffusion (Zondervan et al., 1988) and may interfere with the supply of oxygen and nutrients to the fetus. In addition, some toxicants from air pollutants could cross the placenta with direct effects on fetal development (Dejmek et al., 1999).

Alternatively, placental insufficiency may be an important pathway. Basic concepts of the pathophysiology of IUGR are based on different levels of maternal supply, fetoplacental competition, and fetal adaptations. In recent studies knowledge about placental development and function has been increased. Abnormalities in placental development may occur during its formation, and cellular and molecular functions may be changed leading to inadequate implantation and growth. Abnormalities in placental transport may also develop later on, because of problems in the uteroplacental circulation, exchange at the intervillous space, and umbilical and fetal circulation. All these factors lead to problems with fetal adaptation mechanisms, most importantly decreased fetal growth rate and fetal activities. Biologic mechanisms that have been suggested to support the hypothesis of an effect associated with early pregnancy exposures are related to the etiology of IUGR. Although likely multifactorial, one suggested mechanism for IUGR is abnormal placental development in early pregnancy. Placental insufficiency reduces the oxygen and nourishment supplies to the fetus and leads to growth retardation.

Exposure to air pollution in early pregnancy could cause insufficient trophoblast formation, and lead to insufficient placental vascularization (Duvekot et al., 1995). Chronic reductions of uteroplacental circulation due to the effects of air pollution could result in fetal hypoxia and IUGR (Werler et al., 1985).

CO is well known as a reproductive toxicant that can interfere with oxygen delivery to the fetus. CO shifts the oxyhemoglobin dissociation equilibrium and displaces oxygen from hemoglobin for a given partial pressure of oxygen. CO can also cause oxidative injury due to its effects on the endothelium (Hardy and Thom, 1994). CO has also been shown to cross the placental barrier (Sangalli et al., 2003) and the fetus is particularly vulnerable to CO poisoning because of 10–15% higher accumulation in fetal blood than maternal levels. Its elimination is slower in fetal blood than in maternal circulation. Fetal hemoglobin has greater affinity for binding CO than does adult hemoglobin (Longo, 1977). O_2 delivery to fetal tissues is further compromised. The resultant tissue hypoxia has the potential to reduce fetal growth (Bosley et al., 1981; Gabrielli et al., 1995; Ritz and Yu, 1999; Salam et al., 2005). Another possible toxic mechanism of CO is that it can also affect leukocytes, platelets, and the endothelium, inducing a cascade of effects resulting in oxidative injury that contributes to the toxicity of other air pollutants (Ha et al., 2001).

Gaseous pollutants such as SO_2 and NO_2 lead to pulmonary inflammation with a systemic release of cytokines (Walters et al., 2001; Nemmar et al., 2002) and increase blood viscosity (Peters et al., 1997; Prescott et al., 2000). Prenatal exposure to SO_2 can lead to developmental and functional toxicities (Singh, 1989). NO_2 suppresses antioxidant defense systems of the human body (Tabacova et al., 1998). Exposure of experimental animal models to NO_2 during pregnancy induces lipid peroxidation in the placenta and disturbs postnatal development (Tabacova et al., 1985). Exposure to any gas pollutants leads to inflammatory reactions in the lung, leading to systemic release of cytokines that may trigger PTB (Walters et al., 2001). NO_2 may also have direct toxic effects on the fetus (Maroziene and Grazuleviciene, 2002). Particle and NO_2 were correlated strongly with each other and exerted an effect on LBW within similar periods. But considering many published data, the evidence for the association between NO_2 and LBW is inconclusive. Exposure to ozone may have negative effects on birth weight (BW) and neurodevelopment (Dell'Omo et al., 1995), although the mechanism through which ozone can affect pregnancy outcomes is unclear.

Several hypotheses have been postulated to explain the mechanism of triggering PTB. One hypothesis suggests causality between uterine inflammation and PTB. The direct evidence

that infection provokes preterm labor was first shown in an animal study. When Group B streptococci were injected into the amnionic fluid in preterm rhesus monkeys, amnionic fluid cytokine concentrations increased, followed by production of the prostaglandins E_2 and $F_{2\alpha}$ and, finally, uterine contractions (Gravett et al., 1994). Similarly, in humans, preterm labor due to infection is thought to be initiated by cytokines, including interleukin-1 (IL-1), tumor necrosis factor, and interleukin-6, produced by macrophages (Cram et al., 2002; Narahara and Johnston 1993: Mitreski and Radeka 2002).

Additionally, entry of PM into the body by this method may lead to oxidative inflammation in lungs and other organs, including the placenta, thereby increasing the susceptibility of the mother to begin preterm labor (Liu et al., 2003).

Because IL-1β is not present in the membranes of term–laboring patients, it may be the unique mediator by which intrauterine infection induces preterm labor (Cunningham and William, 1997). Antenatal infection can trigger intrauterine inflammation which then promotes preterm labor. In addition, periodontal disease may be an independent risk factor for preterm labor: postulated mechanisms include translocation of periodontal pathogens to the fetoplacental unit and action of a periodontal reservoir of lipopolysaccharides or inflammatory mediators (McGaw, 2002). Our inability to determine the periodontal status of the mother is a potential confounding factor. Cyclooxygenase-2 inhibitor, developed as an anti-inflammatory drug, also has tocolytic effects (Sakai et al., 2001). A similar inflammatory mechanism has been suggested for the effect of smoking on IUGR, PTB, and perinatal mortality (Klesges et al., 2001). There are reports of increased blood viscosity and plasma fibrinogen during air pollution (Peters et al., 1997). It has been speculated that chronic exposure to high pollution levels may influence placental function (Petruzzelli et al., 1998). The placental dysfunction may lead to IUGR. The effects of air pollution on pregnancy outcomes may differ according to the timing of exposure, with early exposures likely to be important for pregnancy end points such as spontaneous abortion, IUGR and birth defects (Antipenko and Kogut 1993; Dejmek et al., 1999; Dejmek et al., 2000; Hansteen et al., 1987). Intrauterine infection during pregnancy could also lead to brain damage of the developing fetus (Huleihel et al., 2004).

Recent studies suggest that antenatal infection and inflammation can increase the preterm infant's susceptibility to develop chronic lung disease. It may be that exposure of the fetal lung to high concentrations of pro-inflammatory cytokines is the cause of this increased susceptibility (Miralles et al., 2002). Photochemically produced gaseous products influence the toxic responses of cells, such as the production of cytokine, in the absence of particles (Sexton et al., 2004). PM_{10} is responsible for the production and release of inflammatory cytokines by the respiratory tract epithelium, as well as for activation of the transcription factor NfkappaB (Baeza-Sqiban et al., 1999; Bonvallot et al., 2001). Although fetal exposures to air pollution are probably much lower than exposure to the constituents of cigarette smoke, the biological mechanism of PTB could be through increased prostaglandin levels that are triggered by inflammatory mediators during exposure periods.

The pathophysiology of carbon monoxide may be more complex, involving hypoxic stress on the basis of interference with oxygen transport to the cells and possibly impairment of electron transport. Carbon monoxide can also affect leukocytes, platelets and the endothelium, inducing a cascade of effects resulting in oxidative injury (Hardy and Thom 1994). Carbon monoxide may interfere with metabolic and transport function of the placenta and, after crossing the placental barrier, concentrate more in the fetus than in the

mother (Hardy and Thom, 1994). These placenta insufficiency may be associated with preterm birth.
The causality between air pollution and risk of IUGR, LBW, short birth length, and small head circumference has been suggested through molecular epidemiologic studies where levels of DNA adducts are positively correlated with these outcomes (Sram et al., 2005). With the same biologic mechanism of the DNA damage, high levels of DNA adducts may be a cause of PTB.

3.3 Window periods

The possible biological mechanisms involved in the reduction of birth weight associated with maternal exposure to air pollution vary according to the timing of this exposure. The implantation of the fetus and the formation of the placenta occur during the first trimester while weight gain occurs predominantly during the third trimester. Therefore, exposure during both periods presents the possibility of interference with the final birth weight. In the first trimester, genetic mutations are considered to be the most important element in placental abnormalities, and in the second and third trimesters extremely complex vascular alterations are considered the main cause of placental abnormalities and consequent IUGR. Pollutants are recognized as being able to have an effect on both dimensions (Gouveia et al., 2004).
The possible biological mechanisms of air pollution on birth weight might vary according the time of pregnancy, such as the implantation of the fetus and the formation of placenta during the first trimester, as well as important weight gain during the third trimester. Placental abnormalities, DNA damage, disruption of the endocrine system and change of blood coagulability are those potential biological mechanisms, which have been reported (Dejmek et al., 2000; Maisonet et al., 2004; Perera et al., 1999, 2002; Whyatt et al., 1998).
The finding of a significant effect of PM exposure on LBW during the first trimester is consistent. Its effect is striking at window periods during the first trimester.
The highest ambient air pollution concentrations during the first trimester were significantly associated with elevated relative risks of PTB. These results are generally consistent with the findings from China, South Korea, the United States, Canada, and the Czech Republic (Bobak 2000; Liu et al., 2003; Mohorovic 2004; Ritz et al., 2000; Tsai et al., 2003; Woodruff et al., 2003; Xu et al., 1995; Yang et al., 2002a; Yang et al., 2002b, Yang et al., 2003; Yang et al., 2004; Leem et al., 2006). These studies reported significant associations between air pollution and PTB during early pregnancy (i.e., first or second month, first trimester) (Mohorovic 2004; Ritz et al., 2000), late pregnancy (i.e., last month, last trimester, 7 days or 6 weeks before birth) (Liu et al., 2003; Xu et al., 1995), or during both early and late pregnancies (Bobak 2000).

3.4 Disease burden from air pollution and smoking

Population-attributable risk (PAR) is used to determine by what percentage the incidence of a disease in a population would be reduced if exposure were eliminated. PAR measures the potential impact of control measures on a population, and is relevant to decisions on public health. PAR is a very important concept in guiding policy decisions regarding the preventive approaches to APO, such as LBW, and PTB (Seo et al., 2010).
PAR measures the potential impact of control measures on a population, and is relevant to decisions on public health. PAR is a very important concept in guiding policy decisions regarding the preventive approaches to many diseases, such as cancer, hypertension, diabetes mellitus, and stroke.

Some studies have reported the PAR levels for LBW attributable to environmental factors, such as smoking (Levi F, 1999; Matsubara et al., 2000; Suzuki et al., 2008) and indoor pollution (Boy et al., 2002). Cigarette smoking during pregnancy is a strong dose-dependent risk factor for LBW (Chiolero et al. 2005; Windham et al. 2000). Women exposed to prenatal secondhand smoke were more at risk for preterm birth (odds ratio [OR]=2.3; 95% Confidence Interval [CI] [.96, 5.96]), and their infants were more likely to have immediate newborn complications (OR=2.4; 95% CI [1.09, 5.33]) than non-exposed women. Infants of passive smoking mothers were at increased risk for respiratory distress syndrome (OR=4.9; 95% CI [1.45, 10.5]) and admission to a Neonatal Intensive Care Unit ((OR=6,5; 95% CI[1.29, 9.7]) when compared to infants of smoking mothers (OR=3.9; 95% CI [1.61, 14.9]; OR=3.5; 95% CI [2.09, 20.4], respectively). Passive smokers and/or women with hair nicotine levels greater than .35 ng/ml were more likely to deliver earlier (1 week), give birth to infants weighing less (decrease of 200-300 g), and deliver shorter infants (decrease of 1.1-1.7 cm) (Ashford et al., 2010). Environmental tobacco smoke (ETS) and traffic-related air pollution share a few characteristics. They are widespread exposures in both developed and developing countries, and they have several chemical components in common. Mothers who smoke during pregnancy are twice as likely to give birth to a LBW newborn. In high-income countries, the mean PAR for tobacco smoking in both genders combined is estimated to be 25-30% of the total cancer mortality. Some studies reported PAR for LBW attributable to environmental factors, such as smoking (Chiolero et al., 2005; Windham et al., 2000; Matsubara et al., 2000; Suzuki et al., 2008) and indoor pollution (Boy et al., 2002). Chiolero et al., (2005) reported that maternal smoking during pregnancy was closely associated with LBW, small-for-gestational age (SGA), and pre-term birth. Comparing smokers to non-smokers, the adjusted odds ratios (AOR) were 2.7 (2.1-3.5) for LBW, 2.1 (1.7-2.5) for SGA, and 1.4 (1.1-1.9) for preterm birth. Past smoking was not associated with the outcomes. In that study, maternal smoking during pregnancy accounted for 22% (15-29%) of all LBW babies in the population, 14% (10-18%) of SGA babies, and 7% (1-12%) of preterm babies. Ojima et al. (2004) reported on the population-attributable proportion of active and passive smoking for LBW. These results showed the population-attributable proportion of smoking among mothers without preeclampsia during pregnancy was 7.0% for active smoking and 15.6% for passive smoking. Leonardi-Bee et al. (2008) reported that exposure of non-smoking pregnant women to ETS reduces mean birth weight by 33 g or more, and increases the risk of birth weight below 2500 g by 22%, but has no clear effect on gestation or SGA risk.

Misra and Nguyen (1999) suggested that there is consistent evidence to relate maternal ETS exposure to an increased APO risk and that this association may be generalized to the work environment. In studies with positive findings, infants exposed to ETS antenatally were 1.5-4 times more likely to be born with LBW, but few studies examined LBW. Most studies looked at measures of IUGR. ETS was associated with reductions in birth weight (adjusted for gestational age) ranging from 25 to 90 g. Infants born to women exposed to ETS were generally 2-4 times more likely to be born SGA. ETS exposure in the workplace can and should be minimized to protect pregnant women from its adverse effects.

Such research is urgently needed so as to calculate the etiologic fractions of the PAR that contribute directly to PTB. This will enable preventive strategies to be established to protect fetuses against air pollutants.

Most studies have reported an association between exposure to air pollution and PTB, with risk ratios from 1.03-1.36. Especially, PM_{10} air pollution was found to be significantly associated with PTB.

Some studies reported PAR for PTB attributable to environmental factors, such as smoking, outdoor air pollution, and indoor pollution. Maternal smoking during pregnancy was closely associated with LBW, SGA, and PTB. In a study of seven Korean cities, air pollution accounted for 7~18% of all LBW babies (Seo et al., 2010).

PAR to PM_{10} pollution for LBW was comparable to the figure derived from maternal smoking for PTB. Because air pollution is an important risk factor for PTB, a large proportion of PTB could be prevented if air pollution is reduced.

PAR depends on the strength of the relative risk, but also on the prevalence of the risk factor. Causes for APO may include metals, inhalational of anesthetics, organic solvents, air pollution, radiation, stress, and physical stress. Common risk factors carry larger PARs than do rare risk factors. The PAR attributable to PM_{10} pollution for LBW was similar to that regarding smoking for LBW because every pregnant woman was exposed to air pollution. Though those who smoke are in the minority, the relative risk due to smoking is greater than air pollution.

Air pollution is an important risk factor for LBW and PTB because every pregnant woman is exposed to air pollution. Thus, a large proportion of LBW and PTB pregnancies could be prevented if air pollution were reduced.

3.5 Gender as effect modifier

Does the effect of air pollution on pregnancy outcomes differ by gender? Gender is known to influence pregnancy outcomes. Recent studies have reported an association between air pollution exposure and APO, but gender differences have not been considered. In order to assess the current evidence of the interactive effects between gender and air pollution on pregnancy outcomes, Ghosh R et al.(2007) undertook a systematic literature review. In total 11 studies were included. Of the 11 studies, four evaluated LBW, one each evaluated very LBW and fetal growth and six examined PTB. Females were at higher LBW risk: AOR ranged from 1.07 to 1.62. Males were at higher risk for PTB: AORs ranged from 1.11 to 1.20. In addition, there was some evidence to suggest that the effect of air pollution on LBW is gender dependent; however, the evidence was available only from four studies.

3.6 Socioeconomic status(SES): health disparity

People with low socioeconomic status (SES) are more vulnerable to air pollution than others. They are exposed to infection, nutritionally deficient, and often lived in more polluted area.

Infection in pregnancy is a predictor of premature births (Gibbs RS et al., 1992), and it could be speculated that repeated infections, possibly related to pollution, might play a part. Increased blood viscosity, found during air pollution episodes (Peters A et al., 1997) may be related to impaired placental function (Zondervan HA et al., 1987). Increased concentrations of DNA adducts have been found in the blood (Perera FP et al., 1992; Petruzzelli S et al., 1998) and placentas (Topinka J et al., 1997) of subjects living in polluted areas, and were also found to be related to birthweight (Perera FP et al., 1998). Maternal nutrition status can be acting as a effect modifier between exposures to airborne particulate matter and adverse perinatal outcomes (Kannan et al, 2006). Maternal pulmonary function has been linked to altered placental vascular function and growth retardation in asthmatic pregnancies (Bracken et al. 2003; Clifton et al. 2001; Schatz et al. 1990). Mothers with lowered pulmonary function are more likely to have increased risks of LBW and PTB. Other theories about these associations include a) altered cardiac function from changes in heart rate variability; b)

inhalation by the mother of PAHs that then relate to placental exposure, potentially disrupting endocrine and nervous systems; c) changes in blood viscosity due to alveolar inflammation from PM, which in turn affects placental function; and d) binding of CO to hemoglobin binding sites, preventing the binding of oxygen and subsequent function (Glinianaia et al. 2004; Maisonet et al. 2004; Sˇrám et al. 2005).

Despite advances in medical care, preterm birth and its associated racial/ethnic disparities remain major public health issues. Environmental exposures may contribute to racial disparities in preterm birth (Burris HH et al., 2011). Interestingly, a study in South Korea recently demonstrated that SES modifies the association between air pollution and preterm birth (Yi O et al., 2010).

Hispanic, African-American, and Asian/Pacific Islander mothers experienced higher mean levels of air pollution and were more than twice as likely to live in the most polluted counties compared with white mothers after controlling for maternal risk factors, region, and educational status [Hispanic mothers: AOR = 4.66; 95% confidence interval (95% CI), 1.92-11.32; African-American mothers: AOR = 2.58; 95% CI, 1.00-6.62; Asian/Pacific Islander mothers: AOR = 2.82; 95% CI, 1.07-7.39](Woodruff et al. 2003).

PTB increased from 8.3% in counties with low income inequality to 10.0% in counties with high inequality. The Gini Index remained modestly associated with PTB after adjusting for individual level variables and mean county-level per capita income within the total population (AOR: 1.06; 95% CI 1.03-1.09) as well as within most of the racial/ethnic groups. PNM(post-natal mortality) increased from 1.15 deaths per 1000 live births in low inequality counties to 1.32 in high-inequality counties. However, after adjustment, income inequality was only associated with PNM within the non-Hispanic black population (AOR: 1.20; 95% CI 1.03-1.39). These findings may provide some support for the association between income inequality and PTB. Further research is required to elucidate the biological mechanisms of income inequality (Huynh M et al., 2005).

4. Conclusion

The association between air pollution, such PM and SO_2, and APO has been clearly shown in the literature although the mechanisms have not been elucidated. More work is required to fully elucidate the physiologic mechanisms by which air pollution may affect fetal growth and development and to determine if the mechanisms are pollutant specific.

The findings of prior studies of air pollution effects on adverse birth outcomes are difficult to synthesize due to differences in study design, although a few studies have included meta-analysis. Location-specific analyses of air pollution effects on birth weight need to be conducted using a common protocol and a standardized statistical approach to understand how differences in research methods contribute to variations in findings. Study groups such as The International Collaboration on Air Pollution and Pregnancy Outcome (ICPPO) have been formed to perform these kinds of collaboration study. Variability in PM_{10}-LBW relationships among study locations has remained, despite the use of a common statistical approach by a pilot study (Parker et al., 2011). A more detailed meta-analysis and use of more complex protocols for future analysis may uncover the reasons for heterogeneity across locations.

Many studies demonstrated air pollution levels critical to LBW and PTB in humans. These levels are very important because they may be a good indication on how to protect fetuses

against adverse effects from air pollutants. Annual standards for air quality are certainly too high in some countries and do not prevent APO. Many studies showed that statistically significant effects of LBW and PTB are seen below the air quality standards for PM_{10} and SO_2 and potentially below the standards for CO and NO_2. The adverse effects on pregnancy are increased for smaller particles like $PM_{2.5}$. Several lines of evidence support the plausibility of a negative effect of CO exposure on birth weight. CO reduces oxygen-carrying capacity of maternal hemoglobin, which could adversely affect O2 delivery to fetal circulation. Low-concentration exposure to CO, even below 1ppm, increased PTB risk. The current air quality standard for CO is 9 ppm. The air quality standards for $PM_{2.5}$ should be established, and the air quality standards for CO should be lowered to 1ppm to protect fetuses' health against the hazardous toxicities of $PM_{2.5}$ and CO. Many studies may provide supportive evidence that reduction in the current air quality standards may increase the health of pregnancy outcomes.

We observed that exposure to sulphur dioxide was associated with PTB, and exposure to $PM_{2.5}$ was associated with LBW and PTB. The evidence for N_2O, ozone and carbon monoxide was inconclusive. However, the observed adverse effects were generally small. Possible important factors such as maternal activity pattern, diet, smoking and occupation, which are usually not reported on the birth certificate, might have led to exposure misclassification and confounding and could have hidden moderately increased risks. Additional well-conducted studies that include detailed information on maternal risk factors and use validated models for estimating maternal exposure are needed to establish the extent of the association between air pollution and birth outcomes.

In conclusion, several studies showed that relatively low concentrations of air pollution below current air quality standards during critical gestational periods may contribute to increased risk of LBW and PTB. Fetuses in the early and late stages of development are susceptible to air pollutants. Further studies are needed to validate the fetuses' susceptibility to air pollutants with more detailed information on personal exposures, confounders, and effect modifiers. Many investigators reported reductions in ETS exposure and the risk of LBW and very early preterm birth. Clues about potential mechanisms underlying the disparities in LBW and preterm birth can be gained from exploring differences in environmental exposures. Investigators should include environmental variables when studying birth outcomes. Such efforts should result in targeted interventions to decrease the incidence of LBW, preterm birth and its disparities.

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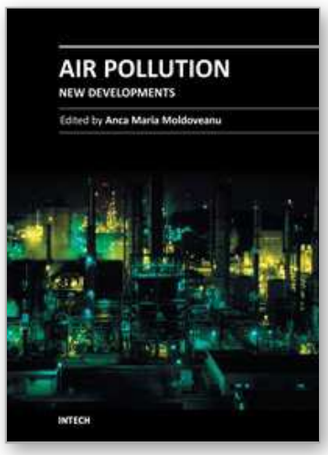

Air Pollution - New Developments

Edited by Prof. Anca Moldoveanu

ISBN 978-953-307-527-3
Hard cover, 324 pages
Publisher InTech
Published online 06, September, 2011
Published in print edition September, 2011

Today, an important issue is environmental pollution, especially air pollution. Due to pollutants present in air, human health as well as animal health and vegetation may suffer. The book can be divided in two parts. The first half presents how the environmental modifications induced by air pollution can have an impact on human health by inducing modifications in different organs and systems and leading to human pathology. This part also presents how environmental modifications induced by air pollution can influence human health during pregnancy. The second half of the book presents the influence of environmental pollution on animal health and vegetation and how this impact can be assessed (the use of the micronucleus tests on TRADESCANTIA to evaluate the genotoxic effects of air pollution, the use of transplanted lichen PSEUDEVERNIA FURFURACEA for biomonitoring the presence of heavy metals, the monitoring of epiphytic lichen biodiversity to detect environmental quality and air pollution, etc). The book is recommended to professionals interested in health and environmental issues.

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