Association between Ambient Air Pollution and Low Birth Weight in Southern Nevada

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Abstract

The study assesses whether air pollution is associated with term low birth weight (LBW) among residents of Southern Nevada. Controlling for maternal and fetal covariates and average pollutant measurements in each trimester (trimester exposures assessed simultaneously), exposure to ambient carbon monoxide (CO) during the third trimester was associated with a significantly increased risk for LBW (odds ratio per 1-ppm increment=1.25; 95% CI: 1.06-1.47). Particulate matter with aerodynamic diameter <10 μm (PM_{10}) also exhibited an inverse pattern with birth weight, although mean birth weight reductions associated with PM_{10} were small and only significant for the last trimester exposure. These results suggest that fetuses in the late stages of development are particularly vulnerable to particulate and CO pollution.

Keywords: air pollution, birth weight, CO, PM_{10}, exposure assessment

Introduction

Ambient air pollution is associated with increased morbidity and mortality for multiple health indicators including lung cancer, acute respiratory infections, asthmatic attacks, chronic respiratory and heart diseases (Brunekreef & Holgate, 2002; Newby et al., 2015; Seaton, MacNee, Donaldson, & Godden, 1995; Yang & Omaye, 2009). There are also indications that the adverse health effects of air pollution are higher for vulnerable subgroups such as the elderly population, children and fetuses (Liao, Creason, Shy, Williams, Watts, & Zweidinger, 1999; Morris, Naumova, & Munasinghe, 1995; Šrám, Binkova, Dejmek, & Bobak, 2005).

Indeed, there is now emerging evidence that air pollution is associated with adverse birth outcomes. In a study conducted in Los Angeles in the early 1970s, Williams et al. found that infants born to mothers who lived in the more polluted areas of the city weighed an average of 314 g less than those born to women living in the less polluted areas (Williams, Spence, & Tideman, 1977). More recently, Wang et al. assessed the effects of exposures to sulfur dioxide (SO_2) and total suspended particles (TSP) among Chinese women living in Beijing, and reported an increase in risk for delivery of low-weight (<2,500 g) full-term neonates (Wang, Ding, Ryan, & Xu, 1997). Bobak and Leon (1999) conducted another study in the Czech Republic, and examined the relation between low birth weight (LBW) and maternal exposures to TSP, SO_2, and nitrogen oxides (NO_x). A small increase in risk was observed in administrative districts with increased exposures to SO_2, but not to other contaminants. As well, Chen et al. reported a positive association between birth weight reduction of newborns and maternal exposure to particulate matter (PM) in Northern Nevada (Chen, Yang, Jennison, Goodrich, & Omaye, 2002). No clear relationship was detected between ambient levels of ozone (O_3) or carbon monoxide (CO) and LBW in the same study. In another study by Rogers et al., the association between the risk of very low birth weight (VLBW; <1,500 g) and maternal exposures to ambient SO_2 and TSP was examined for mothers living in Georgia, United States, using the combined average concentrations of SO_2 and TSP as the exposure measure (Rogers, Thompson, Addy, McKeown, Cowen, & Decouflé, 2000). An increased risk of VLBW and maternal exposures above the 95th percentile of the exposure distribution was reported for the combined measure.

Other evidence is less convincing. In a Swedish study by Landgren (1996) which looked at the independent effects of SO_2 and NO_x, no increase in risk for low birth weight was reported for these pollutants. In another study by Alderman et al. which examined the relation between LBW and maternal CO exposure in Denver, Colorado, no association was found between higher CO exposure and higher odds of LBW, after adjustment for the confounding effects of maternal race and education (Alderman, Baron, & Savitz, 1987).

Therefore the epidemiologic evidence for the relation between air pollution and LBW is not consistent. The etiologic mechanism by which these contaminants cause adverse pregnancy outcomes has not been fully understood either. Previous studies on maternal smoking habits and adverse reproductive outcomes suggest that increases in maternal carboxyhemoglobin levels may explain the relation between CO exposure and LBW (Lieberman, Gremy, Lang, & Cohen, 1994; Misra & Nguyen, 1999). There is also molecular evidence that transplacental exposure to biologically active compounds in respirable particles (e.g. polycyclic aromatic

hydrocarbons) may induce DNA damage and compromise fetal development (Šrám, 1999).

In the absence of definitive biological mechanisms for the potential associations between ambient air pollutants and fetal growth restriction, it is important to determine the consistency of the putative effects of specific pollutants by exploring the relation in different populations and sites. The objective of this study is to assess whether air pollution is associated with term LBW among residents of Southern Nevada, and to provide empirical evidence that might help evaluate plausible biological explanations.

Methods

Population

The frequency of LBW was assessed from singletons born alive in Clark County during the period 1995-2008. De-identified birth certificates provided by the Nevada Department of Health and Human Services were used to ascertain birth weight and most covariates included in the analyses. For each birth, the exposure window comprising the first, second and third trimesters was determined using gestational age (based on clinical/obstetric estimates) and date of birth. In addition to excluding multiple births, the analyses also excluded those weighing below 1,000 or above 5,500 g at birth, those born before 37 or after 42 weeks of gestation, and those whose mothers suffered from hypertension, diabetes, or uterine bleeding prior to delivery. The exclusions of multiple, preterm and postterm births, those born at the extreme ends of the birth weight spectrum, and pregnancies presenting certain maternal complications were based on the assumption that any effect of ambient air pollution on such pregnancies would be far outweighed by the influence of the maternal risks or complications and/or the treatments for maternal conditions.

Exposure assessment

Infants with maternal residence in Clark County (as registered on the birth certificate) were used in exposure window-based linkage with air pollution data. Hourly monitor readings of CO, NO_2 and O_3 for each day, 24-hour monitor readings of PM_{10} for every 6^{th} day, and those of $PM_{2.5}$ for every 3^{rd} day were obtained from the U.S. Environmental Protection Agency to estimate average countywide concentrations of pollutants for which routine sampling was conducted during the study period (measurements of $PM_{2.5}$ prior to 1999 and those of NO_2 prior to 2000 were not available due to lack of routine sampling). Levels of SO_2 were negligible, owing to the absence of SO_2-emitting industries in Clark County. Average exposure to ambient air pollutants was derived using available measurements during the potential exposure window for each study subject individually. For each birth therefore, average pollution concentrations were retrospectively calculated for the first, second, and third trimesters of pregnancy.

Statistical analysis

Logistic regression models were constructed to analyze the outcome of term LBW in relation to average exposures to air pollution constituents throughout the trimesters of pregnancy, as well as maternal and fetal covariates including gestational age (linear and quadratic terms), type of delivery, gender, birth cohort (period of 4 years) and season of birth, maternal age, education, race, marital status, parity, adequacy of prenatal care (adequate, intermediate/inadequate, no care), and maternal tobacco and alcohol use (yes, no). Individual models were constructed for each contaminant, with dose-response relationships assessed on the basis of 1-ppm increase in CO average trimester concentrations, 10-ppb increase in NO_2 and O_3 average trimester concentrations, and 10-$\mu g/m^3$ increase in PM_{10} and $PM_{2.5}$ average trimester concentrations. Birth weight was also analyzed as a continuous variable to estimate the reduction of birth weight associated with changes in mean exposure to air pollution during each trimester of pregnancy, controlling for factors related to LBW. Model assessment tools such as the Hosmer and Lemeshow Test and regression diagnostics were examined for model fit and validity.

Results

There were 214,076 singleton infants whose birth certificates provided complete data on maternal and fetal covariates included in the analyses, after excluding multiple, preterm and postterm births, very LBW and very heavy babies, as well as pregnancies for which it was noted on the birth certificate that the mother had suffered from uterine bleeding, hypertension or diabetes prior to delivery. Of these live term births, 4,710 (2.2%) were low in birth weight (<2,500 g). The prevalence of LBW tended to be higher among female than male infants, and among infants whose mothers were younger than 20 years of age or older than 35 years, African American or Asian, unmarried, primiparous, had a lower level of education, had no or inadequate prenatal care, and consumed alcohol or smoked during the pregnancy (Appendix A).

Table 1 outlines sample characteristics of study pollutants pertaining to sampling days, percentile and extreme values in the study period.

Concentrations of the study pollutants were well below the established standards (U.S. EPA, 2011). Table 2 presents the Pearson correlation coefficients among pollutant concentrations. CO, NO_2 and $PM_{2.5}$ levels were positively correlated, due partly to the same vehicular sources. On the other hand, O_3 was negatively correlated with CO, NO_2 and $PM_{2.5}$, a reflection of the seasonal pattern of summer highs for O_3 and winter highs for the others (Figure 1).

Table 1. Summary statistics for daily average concentrations of selected air pollutants in Clark County, Nevada, 1994-2008*

Pollutant	*Sampling days(period)*	*Mean*	*5th*	*25th*	*50th*	*75th*	*95th*	*Highest value (date)*	*2nd highest (date)*	*3rd highest (date)*
CO(ppm)	5,416 (94-08)	0.7	0.1	0.3	0.6	1.0	1.9	5.5 (01/21/94)	5.4 (01/04/94)	5.3 (01/19/94)
NO_2(ppb)	3,196 (00-08)	11.0	3.2	7.1	10.5	14.2	20.5	35.0 (01/03/08)	32.5 (12/12/08)	31.1 (12/11/08)
O_3(ppb)	5,479 (94-08)	30.9	10.0	21.1	31.5	40.6	51.3	81.6 (07/11/94)	73.8 (07/13/94)	72.0 (07/12/94)
PM_{10}(μg/m^3)	5,121 (94-08)	30.9	12.3	21.2	28.6	37.3	55.4	297.2 (04/15/02)	268.3 (07/26/96)	223.3 (01/16/96)
$PM_{2.5}$(μg/m^3)	3,065 (99-08)	9.2	3.1	5.7	7.8	10.8	20.6	84.6 (07/04/03)	56.1 (12/26/01)	46.2 (10/29/03)

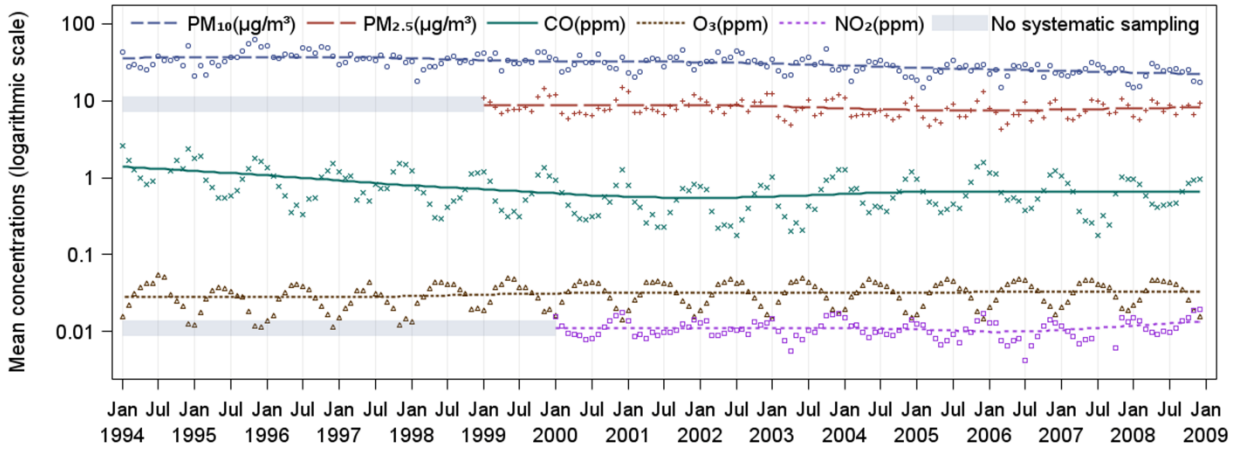
*Routine sampling of $PM_{2.5}$ was implemented in 1999 in Clark County following the promulgation of the National Ambient Air Quality Standard for $PM_{2.5}$ in 1997. There was no systematic sampling of NO_2 in Clark County prior to 2000.

Table 2. Pearson correlation coefficients among daily average concentrations of study pollutants, Clark County, Nevada, 1994-2008

Pollutant	CO	NO_2	O_3	PM_{10}	$PM_{2.5}$
CO	1				
NO_2	0.78*	1			
O_3	-0.71*	-0.64*	1		
PM_{10}	0.22	0.13	-0.02	1	
$PM_{2.5}$	0.66*	0.59*	-0.44*	0.4*	1

*p-value <0.0001.

Figure 1. Variations in monthly mean concentrations of selected air pollutants in Clark County, Nevada, 1994-2008.



Simultaneous adjustment for exposures to pollutants in the first, second and third trimesters as well as cohort effects and seasonal confounding showed that the odds for term LBW increased significantly with the following risk factors: younger or older maternal age (<20 or ≥35 years), maternal race (non-white), education (<12 years), and marital status (unmarried), primiparity, cesarean or operative delivery, no prenatal care, and female gender. After adjustment for maternal and fetal covariates, exposure to ambient CO during the third trimester was associated with a significantly elevate odds ratio of 1.25 for LBW (95% CI: 1.06 to 1.47). Although the risks for LBW were also elevated from first and second trimester exposures to CO, they did not reach statistical significance (Figure 2). There was no indication of a robust association between term LBW and prenatal exposures to other criteria pollutants during the study period (Table 3).

Figure 2. Covariates-adjusted odds ratios and 95% confidence intervals for term LBW (CO-fitted model).

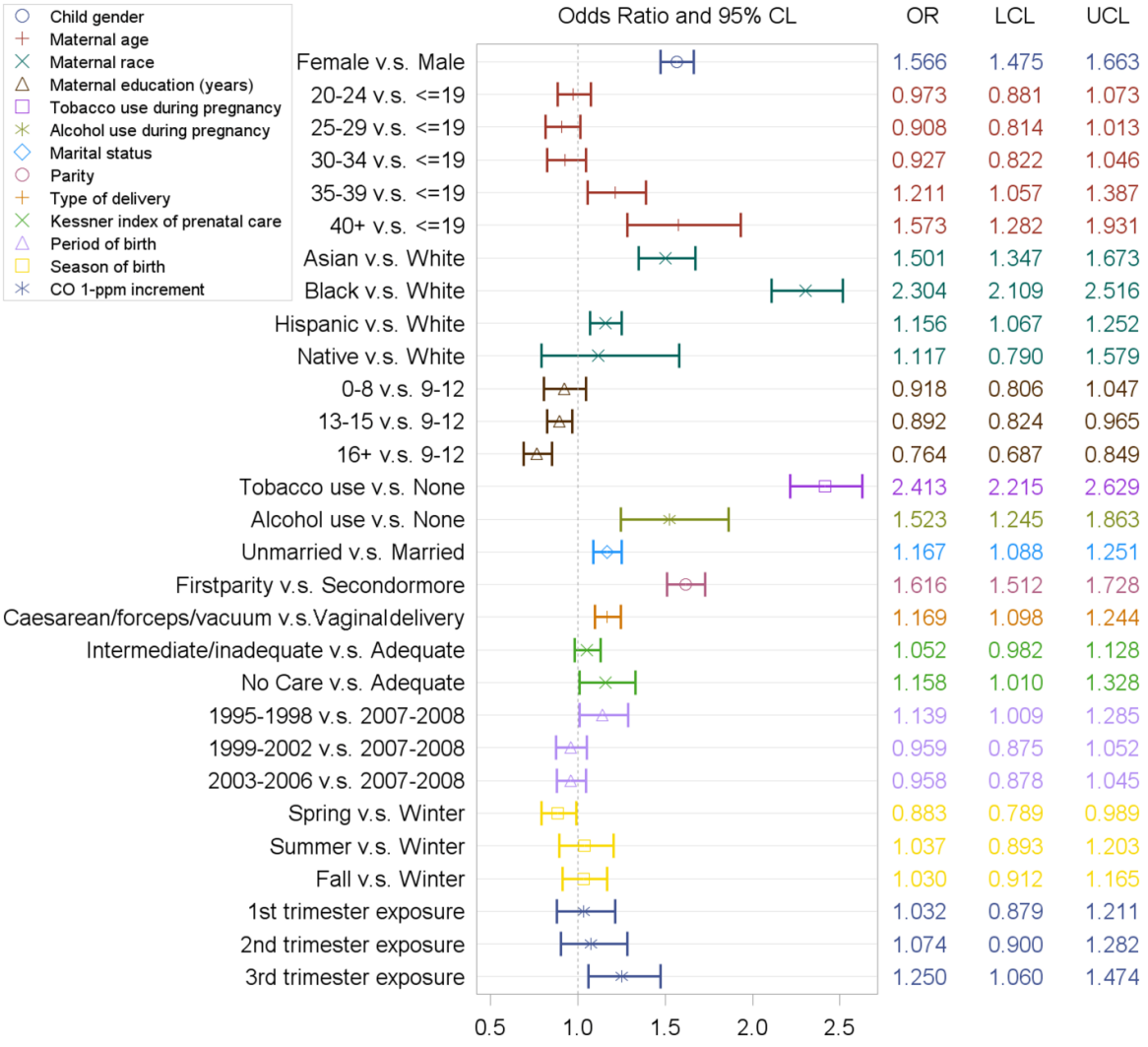


Table 3. Covariates-adjusted odds ratios and 95% confidence intervals for term LBW at each trimester of pregnancy (trimester exposures included together; each pollutant separately fitted)

	Period of pregnancy		
Pollutant (increment)	*1st trimester*	*2nd trimester*	*3rd trimester*
CO (1-ppm)	1.03 (0.88 to 1.21)	1.07 (0.90 to 1.28)	**1.25 (1.06 to 1.47)**
NO_2 (10-ppb)	0.97 (0.95 to 0.99)	1.00 (0.97 to 1.02)	1.00 (0.98 to 1.02)
O_3 (10-ppb)	1.01 (0.99 to 1.02)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.01)
PM_{10} (10-μg/m^3)	1.00 (1.00 to 1.01)	1.00 (0.99 to 1.01)	1.01 (1.00 to 1.01)
$PM_{2.5}$ (10-μg/m^3)	1.00 (0.97 to 1.02)	0.99 (0.97 to 1.02)	1.01 (0.99 to 1.04)

Table 4 shows the coefficients obtained in linear regression models for changes in mean birth weight according to increments in air pollutant levels in each trimester of pregnancy. Inverse relations between CO levels and birth weight were statistically significant for first and third trimester exposures: a 1-ppm increase in first and third trimester exposures was associated with mean reductions in birth weight of 14.5 g (95% CI: -24.2 to -4.9) and 20.9 g (95% CI: -30.9 to -10.9) respectively. PM_{10} also exhibited an inverse pattern with birth weight, although mean birth weight reductions associated with PM_{10} were small and only significant for third trimester exposure.

Table 4. Changes in birth weight (g) and 95% confidence intervals per increment in exposure to air pollutants at each trimester of pregnancy adjusted for covariates (trimester exposures included together; each pollutant separately fitted)

	Period of pregnancy		
Pollutant (increment)	*1st trimester*	*2nd trimester*	*3rd trimester*
CO (1-ppm)	**-14.53 (-24.16 to -4.89)**	-4.58 (-15.06 to 5.90)	**-20.93 (-30.93 to -10.93)**
NO_2 (10-ppb)	13.71 (-0.02 to 27.44)	9.88 (-4.92 to 24.68)	-1.77 (-14.12 to 10.59)
O_3 (10-ppb)	-2.42 (-8.75 to 3.90)	-0.52 (-4.59 to 3.54)	0.78 (-5.69 to 7.26)
PM_{10} (10-μg/m^3)	-0.55 (-4.17 to 3.06)	-1.14 (-5.38 to 3.11)	**-7.63 (-11.43 to -3.82)**
$PM_{2.5}$ (10-μg/m^3)	9.23 (-4.84 to 23.30)	10.81 (-5.65 to 27.27)	-13.24 (-26.96 to 0.47)

Discussion

The study of singleton term infants in Southern Nevada provided evidence of an increased risk for LBW and birth weight reduction in relation to maternal exposures to ambient CO and PM pollutants, especially during the third trimester of pregnancy. Further, results of this population-based study suggest that ambient concentrations of CO confer risk of LBW even in the lower range of exposure. Exposures to NO_2 and O_3 were not associated with risks for LBW or birth weight reduction based on the analyses.

The elevated effect estimates for CO and particle pollution are consistent with findings from several studies on air pollution and adverse pregnancy outcomes. Ritz & Yu (1999) reported a significantly increased risk for LBW from last trimester exposure to higher levels of ambient CO (>5.5 ppm) among women living in the Los Angeles area, while Ha et al. found significant associations between LBW and exposures to CO and TSP during the first trimester in Seoul, South Korea (Ha, Hong, Lee, Woo, Schwartz, & Christiani, 2001). In another study conducted in six northeastern cities of the United States, Maisonet et al. found an increased risk for LBW in relation to increasing levels of CO >1.46 ppm during the third trimester (Maisonet, Bush, Correa, & Jaakkola, 2001). The investigation found no indication of a positive association between prenatal exposures to PM_{10} and LBW.

While results from this study support a relation between CO and particle concentrations and birth weight, with CO presenting a more consistent effect, some methodological aspects of this study need to be discussed. First, as with previous epidemiological investigations (Chen et al., 2002; Ha et al., 2001; Lieberman et al., 1994; Maisonet et al., 2001; Ritz & Yu, 1999; Wang et al., 1997), this study assessed birth weight at term to evaluate the impact of air pollution on fetal growth. The restriction to

term births in fetal growth evaluation was based on weeks of gestation is indicative of intrauterine growth restriction (IUGR). This restriction was important because the pathophysiological mechanisms responsible for preterm birth, a prognostic of LBW, are quite different than those causing IUGR (Lang, Lieberman, & Cohen, 1996; Villar, Khoury, Finucane, & Delgado, 1986). However, excluding preterm births from the assessment of IUGR may impact the study findings if pollutant exposures exerted an effect on fetal growth in these births. Also, even with the exclusion of preterm births, term LBW is still a heterogeneous entity, and may include incorrectly classified preterm births. Nevertheless, measurement error regarding gestational age was likely nondifferential, and any bias introduced would probably attenuate effect estimates towards null.

Second, the study defined maternal exposure according to countywide levels of air pollution during each trimester of pregnancy. Limitations of this exposure estimation approach should be recognized. For example, while most studies that assessed pregnancy outcomes in relation to air pollution used trimester exposures, it could be argued that a smaller time window-based pollution indicator than trimester averages may better represent maternal exposure. At present, few studies took into account the variability of air pollution levels during each trimester. A study in the Czech Republic found an increased risk of IUGR with exposures in the first month of pregnancy (Dejmek, Selevan, Benes, Solanský, & Srám, 1999), while another reported a relation between birth defects and second-month exposures to outdoor air pollution in Southern California (Ritz, Yu, Fruin, Guadalupe, Shaw, & Harris, 2002). The reporting of adverse birth outcomes associated with exposures early in pregnancy suggests a more chronic-type effect for air pollution. In contrast, this study reported results that are more consistent with the hypothesis that exposures in the third trimester or at the late stages of pregnancy are more likely to interfere with fetal growth (Maisonet et al., 2001; Ritz & Yu, 1999; Wang et al., 1997). As such, critical time windows of exposure merit further investigation, and exposure measurements that differentiate cumulative effects from late effects are warranted to help elucidate potential mechanisms involved in the effects of air pollution on growth restriction.

Another limitation concerns the extrapolation from microenvironmental measurements to individual exposures, where daily air quality measures were averaged across available monitoring sites to obtain countywide means (across gestational trimesters), which do not necessarily represent exposures at the individual level. Indeed, the assumption that failure to reach 2,500 g after 37 evidence suggests that while PM levels are more homogeneously distributed across different areas of a city (Burton, Suh, & Koutrakis, 1996), and correlate well over time with individual monitoring data (Janssen, Hoek, Harssema, & Brunekreef, 1999), CO concentrations can vary considerably over a region (Alm, Jantunen, & Vartiainen, 1999; Ritz et al., 2002). The presence of larger spatial variations in CO when compared to PM suggests that the effects of CO assessed by this study were more obscured by nondifferential exposure misclassification than those of PM. To reduce ecological bias, Ritz et al. in their studies in the Los Angeles area assigned maternal exposure according to the closest monitoring station to maternal residence (Ritz & Yu, 1999; Ritz et al., 2002). However, considering that pregnant women may spend substantial amounts of time outside the perimeter of a monitoring station for reasons such as working or shopping, it is not clear that their exposure is well represented by ambient air observed in one station. In fact, any approach that uses air quality registered at fixed sites to approximate personal exposures will be subject to measurement error, although this error is likely random and the impact would be to attenuate the effect estimates. As well, residential mobility presents another problem in exposure assessment. According to previous studies in Maryland and California, about 20% of pregnant women changed residence during pregnancy (Khoury, Stewart, Weinstein, Panny, Lindsay, & Eisenberg, 1988; Shaw & Malcoe, 1992). Data were not available to assess the rate of residential mobility among the study subjects or the extent to which it may affect the results. Notwithstanding, the main consequence of such residential mobility would be nondifferential errors in exposure classification and decreased estimates for the effects of the air pollutants studied.

Finally, although the analyses controlled for a number of risk factors for LBW at the individual level, the records available to this study did not have information on socioeconomic status (maternal education adopted as a proxy indicator), maternal nutrition, occupational exposures, indoor sources of pollution, or behavioral risk factors (e.g. drug abuse). Therefore incomplete adjustment for potential confounders may have resulted in an overestimation of the magnitude of the LBW risks due to air pollution, if these uncontrolled variables covary with ambient pollutant levels.

Several biological mechanisms for the adverse effects of air pollutants on the fetus have been suggested. CO toxicity may occur through hypoxic stress as CO competes with oxygen for hemoglobin binding sites, blocking oxygen transport

to body tissues and possibly impairing electron combine with fetal hemoglobin after crossing the placenta, and concentrate more in the fetus than in the mother, as its elimination is slower in fetal blood than in maternal circulation (Hardy & Thom, 1994; Koren et al., 1991). As placental CO diffusing capacity increases with gestational age (Longo & Ching, 1977), the possibility of greater fetal vulnerability later in pregnancy with higher placental CO exchange cannot be excluded. In addition, oxidative stress pathways are possibly relevant for CO-mediated effects on fetal growth, since CO can affect leukocytes, platelets and the endothelium, inducing a cascade of effects resulting in oxidative injury (Hardy & Thom, 1994).

With respect to the embryotoxic effects of PM, transplacental exposure to carcinogenic polycyclic aromatic hydrocarbons (PAHs) absorbed to respirable particles has been suggested as a potential mechanism (Perera et al., 1998). This hypothesis is consistent with the finding that infants with higher PAH-DNA adduct levels from umbilical cord leukocytes had decreased birth weight, length and head circumference compared to those with lower PAH-DNA adducts (Perera et al., 1998). Although the role of PAHs in fetal growth modulation is not well understood, disruptions to the endocrine system and DNA damages with resulting activation of apoptotic pathways are some possibilities (Perera, Jedrychowski, Rauh, & Whyatt, 1999; Šrám et al., 2005). Another toxic mechanism of PM involves the hematologic effects of inhaled particles. It has been shown that PM can induce a broad polyclonal expression of proinflammatory mediators capable of changing blood viscosity and artery vasoconstriction (Brunekreef & Holgate, 2002; Seaton et al., 1995). As such, the PM-mediated inflammatory processes contribute to enhanced blood coagulation and impaired efficiency of maternal circulation and placental functions including oxygen and nutrients exchange, thereby restricting fetal growth. As well, given the heterogeneous chemical and physical nature of PM, there may be a plausible set of biological mechanisms through which particulate pollution interferes with fetal growth and development.

In conclusion, the present study provides evidence that ambient air pollution is associated with a modestly increased risk for LBW among women in Southern Nevada. The results suggest that fetuses in the late stages of development are particularly vulnerable to particulate and CO pollution. Further studies are necessary to validate fetal susceptibility to air pollutants in terms of critical exposure windows, magnitude of effects, and relevant toxic components. Further investigation is also needed to advance our transport (Hardy & Thom, 1994). CO can also understanding of the biologic mechanisms likely to explain the adverse effects of air pollutants on pregnancy and fetal outcomes.

References:

Alderman, B.W., Baron, A.E., & Savitz, D.A. (1987). Maternal exposure to neighborhood carbon monoxide and risk of low infant birth weight. *Public Health Report*, 102, 410–414.

Alm, S., Jantunen, & M.J., Vartiainen, M. (1999). Urban commuter exposure to particle matter and carbon monoxide in an automobile. *Journal of Exposure Analysis and Environmental Epidemiology*, 9, 237–244.

Bobak, M., Leon, & D.A. (1999). Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986-8. *Occupational and Environmental Medicine*, 56, 539–543.

Brunekreef, B, Holgate, & S.T. (2002). Air pollution and health. *Lancet*, 360, 1233–1242.

Burton, R.M., Suh, H.H., Koutrakis, P. (1996). Spatial variation in particulate concentrations within metropolitan Philadelphia. *Environmental Science & Technology*, 30, 400–407.

Chen, L., Yang, W., Jennison, B.L., Goodrich, A., & Omaye, S.T. (2002). Air pollution and birth weight in northern Nevada, 1991–1999. *Inhalation Toxicology*, 14(2), 141–157.

Dejmek, J., Selevan, S.G., Benes, I., Solanský, I., & Srám, R.J. (1999). Fetal growth and maternal exposure to particulate matter during pregnancy. *Environmental Health Perspective*, 107, 475–480.

Ha, E.H., Hong, Y.C., Lee, B.E., Woo, B.H., Schwartz, J., & Christiani, D.C. (2001). Is air pollution a risk factor for low birth weight in Seoul? *Epidemiology*, 12, 643–648.

Hardy, K.R., & Thom, S.R. (1994). Pathophysiology and treatment of carbon monoxide poisoning. *Journal of Toxicology. Clinical toxicology*, 32(6), 613–629.

Janssen, N.A., Hoek, G., Harssema, H., & Brunekreef, B. (1999). Personal exposure to fine particles in children correlates closely with ambient fine particles. *Archives of Environmental Health*, 54, 95–100.

Khoury, M.J., Stewart, W., Weinstein, A., Panny, S., Lindsay, P., & Eisenberg, M. (1988). Residential mobility during pregnancy: implications for environmental teratogenesis. *Journal of Clinical Epidemiology*, 41:15–20.

Koren, G., Sharav, T., Pastuszak, A., Garrettson, L.K., Hill, K., Samson, I.,… Dolgin, J.E. (1991). A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. *Reproductive Toxicology*, 5, 397–403.

Landgren, O. (1996). Environmental pollution and delivery outcome in Southern Sweden: a study with central registries. *Acta Paediatrica*, 85, 1361–1364.

Lang, J.M., Lieberman, E., & Cohen, A. (1996). A comparison of risk factors for preterm labor and term small-for-gestational-age birth. *Epidemiology*, 7, 369–376.

Liao, D., Creason, J., Shy, C., Williams, R., Watts, R., & Zweidinger, R. (1999). Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environmental Health Perspective*, 107, 521–525.

Lieberman, E., Gremy, I., Lang, J.M., & Cohen, A.P. (1994). Low birthweight at term and the timing of fetal exposure to maternal smoking. *American Journal of Public Health*, 84, 1127–1131.

Longo, L.D., & Ching, K.S. (1977). Placental diffusing capacity for carbon monoxide and oxygen in unanesthetized sheep. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, 43(5), 885–893.

Maisonet, M., Bush, T.J., Correa, A., & Jaakkola, J.J. (2001). Relation between ambient air pollution and low birth weight in the Northeastern United States. *Environmental Health Perspective*, 109(suppl 3), 351–356.

Misra, D., & Nguyen, R.H.N. (1999). Environmental tobacco smoke and low birth weight: a hazard in the workplace? *Environmental Health Perspectiv*, 107, 897–904.

Morris, R.D., Naumova, E.N., & Munasinghe, R.L. (1995). Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. *American Journal of Public Health*, 85(10), 1361–1365.

Newby, D.E., Mannucci, P.M., Tell, G.S., Baccarelli, A.A., Brook, R.D., Donaldson, K.,… Storey, R.F. (2015). Expert position paper on air pollution and cardiovascular disease. *European Heart Journal*, 36, 83–93.

Perera, F.P., Whyatt, R.M., Jedrychowski, W., Rauh, V., Manchester, D., Santella, R.M., & Ottman, R. (1998). Recent developments in molecular epidemiology: a study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. *American Journal of Epidemiology*, 147, 309–314.

Perera, F.P., Jedrychowski, W., Rauh, V., & Whyatt, R.M. (1999). Molecular epidemiologic research on the effects of environmental pollutants on the fetus. *Environmental Health Perspective*, 107, 451–460.

Ritz, B., & Yu, F. (1999). The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. *Environmental Health Perspective*, 107, 17–25.

Ritz, B., Yu, F., Fruin, S., Guadalupe, C., Shaw, G.M., & Harris, J.A. (2002). Ambient air pollution and risk of birth defects in Southern California. *American Journal of Epidemiology*, 155, 17–25.

Rogers, J.F., Thompson, S.J., Addy, C.L., McKeown, R.E., Cowen, D.J., & Decouflé, P. (2000). Association of very low birth weight with exposures to environmental sulfur dioxide and total suspended particulates. *American Journal of Epidemiology*, 151, 602–613.

Shaw, G.M., & Malcoe, L. (1992). Residential mobility during pregnancy for mothers of infants with or without congenital cardiac anomalies: a reprint. *Archives of Environmental Health*, 47, 236–238.

Seaton, A., MacNee, W., Donaldson, K., & Godden, D. (1995). Particulate air pollution and acute health effects. *Lancet*, 345, 176–178.

Šrám, R.J. (1999). Impact of air pollution on reproductive health. *Environmental Health Perspective*, 107, A542–543.

Šrám, R.J., Binkova, B., Dejmek, J., & Bobak, M. (2005). Ambient air pollution and pregnancy outcomes: a review of the literature. *Environmental Health Perspective*, 113, 375–382.

U.S. Environmental Protection Agency (EPA). (2011). National Ambient Air Quality Standards (NAAQS). Available from http://www.epa.gov/air/criteria.html.

Villar, J., Khoury, M.J., Finucane, F.F., & Delgado, H.L. (1986). Differences in the epidemiology of prematurity and intrauterine growth retardation. *Early Human Development*, 14, 307–320.

Wang, Y., Ding, H., Ryan, L., & Xu, X. (1997). Association between air pollution and low birth weight a community-based study. *Environmental Health Perspective*, 105, 514–520.

Williams, L., Spence, A.M., & Tideman, S.C. (1977). Implications of the observed effect of air pollution on birth weight. *Social Biology*, 24, 1–9.

Yang, W., & Omaye, S.T. (2009) Air pollutants, oxidative stress and human health. *Mutation Research*, 674(1-2), 45–54.

Appendix A

Table. Prevalence* of term LBW according to selected maternal and infant characteristics in Clark County, Nevada, 1995-2008

	No. of live births	*%Col.*	*LBW (%)*
All	214,076	100.0	2.2
Child gender			
Male	108,873	50.9	1.8
Female	105,203	49.1	2.6
Maternal age (years)			
<=19	24,425	11.4	3.0
20-24	57,557	26.9	2.3
25-29	61,156	28.6	1.9
30-34	46,431	21.7	1.8
35-39	20,534	9.6	2.5
40+	3,973	1.9	3.3
Maternal race			
White	99,443	46.5	1.9
Black	20,320	9.5	4.5
Native	1,559	0.7	2.2
Asian	16,201	7.6	2.8
Hispanic	76,553	35.8	1.9
Maternal education (years)			
0-8	15,745	7.4	1.8
9-11	42,398	19.8	2.6
12	69,914	32.7	2.4
13-15	50,455	23.6	2.1
16+	35,564	16.6	1.6
Cigarette smoking during pregnancy			
Yes	18,021	8.4	4.8
No	196,055	91.6	2.0
Alcohol use during pregnancy			
Yes	2,378	1.1	5.0
No	211,698	98.9	2.2
Marital status			
Unmarried	78,363	36.6	2.8
Married	135,713	63.4	1.8

Parity			
First parity	83,291	38.9	2.6
Second or more	130,785	61.1	1.9
Delivery method			
Caesarean or operative delivery	73,062	34.1	2.4
Vaginal delivery	141,014	65.9	2.1
Kessner index of prenatal care			
Adequate	142,505	66.6	2.0
Intermediate/inadequate	62,654	29.3	2.4
No Care	8,917	4.2	2.9
Period of birth			
1995-1998	45,305	21.2	2.4
1999-2002	60,980	28.5	2.0
2003-2006	70,296	32.8	2.2
2007-2008	37,495	17.5	2.3
Season of birth			
Spring	50,790	23.7	2.1
Summer	52,017	24.3	2.3
Fall	57,239	26.7	2.1
Winter	54,030	25.2	2.2

*Among singleton births excluding those weighing below 1,000 or above 5,500 grams at birth, those born before 37 or after 42 weeks of gestation, and those whose mothers suffered from hypertension, diabetes, or uterine bleeding prior to delivery.