Outdoor Air Pollution, Low Birth Weight, and Prematurity

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This study tested the hypothesis, suggested by several recent reports, that air pollution may increase the risk of adverse birth outcomes. This study analyzed all singleton live births registered by the Czech national birth register in 1991 in 67 districts where at least one pollutant was monitored in 1990–1991 (n = 108,173). Maternal exposures to sulfur dioxide (SO_2), total suspended particles (TSP), and nitrous oxides (NO_x) in each trimester of pregnancy were estimated as the arithmetic means of all daily measurements taken by all monitors in the district of birth of each infant. Odds ratios of low birth weight (< 2,500 g), prematurity (< 37 weeks of gestation), and intrauterine growth retardation (IUGR; < 10th percentile of birth weight for gestational age and sex) were estimated by robust logistic regression. The median (and 25th and 75th percentile) trimester exposures were 32 (18, 56) µg/m^3 for SO_2; 72 (55, 87) µg/m^3 for TSP; and 38 (23, 59) µg/m^3 for NO_x. Low birth weight (prevalence 5.2%) and prematurity (prevalence 4.8%) were associated with SO_2 and somewhat less strongly with TSP. IUGR was not associated with any pollutant. The effects on low birth weight and prematurity were marginally stronger for exposures in the first trimester, and were not attenuated at all by adjustment for socioeconomic factors or the month of birth. Adjusted odds ratios of low birth weight were 1.20 [95% confidence interval (CI), 1.11–1.30] and 1.15 (CI, 1.07–1.24) for a 50 µg/m^3 increase in SO_2 and TSP, respectively, in the first trimester; adjusted odds ratios of prematurity were 1.27 (CI, 1.16–1.39) and 1.18 (CI, 1.05–1.31) for a 50 µg/m^3 increase in SO_2 and TSP, respectively, in the first trimester. Low gestational age accounted for the association between SO_2 and low birth weight. These findings provide further support for the hypothesis that air pollution can affect the outcome of pregnancy. *Key words*: air pollution, birth, epidemiology, low birth weight, pregnancy, premature birth. *Environ Health Perspect* 108:173–176 (2000). [Online 10 January 2000]
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The adverse effects of air pollution on mortality and respiratory symptoms have been studied extensively (*1,2*). More recently, several studies reported an association between air pollution and birth outcomes, such as birth weight (*3–5*), premature births (*6*), or intrauterine growth retardation (IUGR) (*7*).

The literature on this subject is surprisingly sparse. An early U.S. study found that dustfall, a measure of air pollution, was related to neonatal deaths with signs of prematurity (*8*). A more recent British study, although not specifically designed to study birth weight, did not find an excess in the frequency of low birth weight in a polluted area as compared to a control area (*9*). With < 6,000 births, however, the study had only a modest statistical power. A study in four residential areas of Beijing, China, reported a significant dose–response relationship between maternal exposures to sulfur dioxide (SO_2) and total suspended particles (TSP) during the last trimester and the risk of low birth weight (*3*) and premature birth (*6*). A study of birth outcomes in Teplice, Czech Republic (*7*), found that the risk of IUGR was increased in term births when mothers were exposed to high levels of outdoor particulate matter ≤ 10 µm in aerodynamic diameter (PM_{10}) in the first month of pregnancy, after controlling for maternal characteristics. A study of births in southern California (*5*) found an association between ambient concentrations of carbon monoxide and increased risk of low birth weight. Finally, our ecologic analysis of data on live births in the Czech Republic in 1986–1988 also found an association between SO_2 and low birth weight; because individual data were not available, possible confounding by socioeconomic status could not be excluded (*4*).

Birth outcomes is a previously unexplored area in air pollution epidemiology, and it is not known whether the findings described above can be replicated in different populations or datasets. To address this question, I analyzed data from the Czech national birth register linked with the air pollution data.

Methods

Individual data on all singleton live births registered by the Czech national birth register in 1991 (n = 126,752) were linked with area based indicators of air pollution. The birth registration forms are completed at birth by the doctor or nurse attending the delivery. The forms contain the following information: date of birth; birth weight; gestational age (estimated by the last menstruation period method); parity; birth order; maternal age, education, and marital status; and the nationality of the mother and father. The quality of the birth register has not been formally validated but the register is considered reliable (*10*).

The air pollution monitoring system in the Czech Republic is overseen by the Hydrometeorological Institute in Prague, where data are compiled and their quality is checked. Data from monitoring stations operated by the Hydrometeorological Institute and the Czech Public Health Service were considered the most reliable in the early 1990s, and they were used in the present analyses. All stations used an old fashioned but uniform monitoring technology: gravimetric method for TSP and colorimetric method for SO_2 and nitrous oxides (NO_x).

Maternal exposures in each trimester of pregnancy were calculated for outdoor SO_2, TSP, and NO_x. These were estimated as the arithmetic means of all 24-hr measurements by all monitors in the district of birth of each infant. In 1990–1991, at least one pollutant was monitored in 67 of the total 85 districts (covering > 85% of all births). The geographic distribution of monitors was influenced by financial possibilities and by pollution levels (more polluted districts were monitored more extensively), but the monitored districts were similar to the remaining 18 districts in terms of both pregnancy outcomes and socioeconomic factors. All three pollutants were not measured in each district; therefore, the numbers of births with data on exposure were different for individual pollutants. Most of the infants had data on SO_2, followed by TSP, then NO_x (Table 1).

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Table 1. Numbers of births with data on pollutants, and 25th, 50th, and 75th percentile of mean trimester exposures to SO_2, TSP, and NO_x.

Pollutant	Births with data (*n*)	Percentile of exposure (μg/m³) 25th	50th	75th
SO_2	108,173	17.5	32.0	55.5
TSP	78,148	54.8	71.5	86.9
NO_x	69,935	23.0	37.7	58.5

Table 2. Correlation matrix of mean pollutant concentrations in pregnancy trimesters.

Pollutant, trimester	SO_2 1	SO_2 2	SO_2 3	TSP 1	TSP 2	TSP 3	NO_x 1	NO_x 2
SO_2, 2	0.25	–	–	–	–	–	–	–
SO_2, 3	-0.45	0.16	–	–	–	–	–	–
TSP, 1	0.71	0.09	-0.22	–	–	–	–	–
TSP, 2	0.17	0.68	0.13	0.39	–	–	–	–
TSP, 3	-0.39	0.16	0.73	0.07	0.45	–	–	–
NO_x, 1	0.53	0.33	0.04	0.52	0.36	0.06	–	–
NO_x, 2	0.19	0.62	0.30	0.20	0.60	0.30	0.79	–
NO_x, 3	-0.05	0.26	0.63	0.09	0.24	0.50	0.67	0.76

Odds ratios (ORs) of low birth weight (< 2,500 g), prematurity (< 37 weeks of gestation), and IUGR (< 10th percentile of birth weight for gestational age and sex) were calculated by robust logistic regression using the Huber formula [subcommand "cluster(district)" in STATA statistical software (*11*)]. This procedure takes into account the fact that the exposures were area based, and that individuals may be more similar to each other within districts than between districts. Several models were constructed. First, crude effects were estimated. Second, crude effects were adjusted for maternal age group, education, marital status and nationality, parity, and month of the birth. All maternal factors were related to birth outcomes in bivariate analyses. Finally, in the analyses of low birth weight, the effects of air pollutants were also adjusted for gestational age. I also examined models where trimester-specific exposures to all three pollutants were adjusted for each other, and models where all three trimesters were entered simultaneously. In the initial analyses the associations between quintiles of pollutant levels and outcomes were approximately linear. The pollutants were therefore modeled as continuous variables, and the effects were reported as ORs for a 50-μg/m³ increase in mean pollutant concentration during a given trimester.

Results

Table 1 shows the numbers of births with data on exposure to individual pollutants, the median, and the 25th and 75th percentiles of the mean trimester exposures. The exposures were high by Western standards, and the variation was largest for SO_2 and NO_x. Pollutant concentrations in different trimesters were mutually correlated (Table 2). The strong inverse association between the first and third trimester means of SO_2 and TSP was due to the strong seasonal variation in these pollutants.

Table 3 shows characteristics of the infants and the mothers on which data on at least one pollutant were available. The prevalence of low birth weight was 5.2%, and 4.8% of births occurred before the 37th week of gestation. Socioeconomic confounding is a major threat to studies of outcomes such as low birth weight or prematurity, which are strongly related to socioeconomic status. Therefore, I examined the relationship between maternal education, nationality, and marital status to pollutant concentrations. To be potentially confounding, socioeconomic factors would need to be related to exposure, i.e., pollution. The differences in mean exposures by maternal education, marital status, or nationality were negligible, and no association was significant (data not shown). The only correlation coefficients stronger than ± 0.1 were positive (and not statistically significant) between maternal education and NO_x.

Low birth weight (< 2,500 g) was significantly associated with SO_2, somewhat less strongly with TSP, and not with NO_x (Table 4). The crude associations were not attenuated by adjustment for socioeconomic factors and the month of birth. ORs of low birth weight, adjusted for sex of the infant, education, parity, age and marital status of the mother, and the month of birth appeared marginally stronger for exposures in the first trimester. The adjusted ORs were 1.20 [95% confidence interval (CI), 1.11–1.30] and 1.15 (CI, 1.07–1.24) for a 50-μg/m³ increase in mean SO_2 and TSP concentrations, respectively, in the first trimester. The associations were approximately linear; for example, the ORs for the second to fifth quintiles of SO_2 in the first trimester were 1.06 (CI, 0.96–1.16); 1.05 (CI, 0.96–1.16); 1.22 (CI, 1.10–1.36); and 1.26 (CI, 1.11–1.43), respectively, as compared to the first quintile (p for trend < 0.001). Further adjustment for gestational age eliminated the effects of SO_2 but not those of TSP (Table 3, last column). The effects were substantially weaker in analyses restricted to term births, as consistent with the strong influence of gestational age. In these analyses, the ORs were 1.10 (CI, 0.96–1.26) for SO_2 and 1.01 (CI, 0.88–1.15) for TSP in the first trimester, after controlling for sex of the infant, education, parity, age and marital status of the mother, and the month of birth (data not shown). In analyses of birth weight as a continuous variable, an increase in SO_2 and TSP by 50 μg/m³ in the first trimester was associated with a reduction in the mean birth weight by 11.4 g (CI, 5.9–16.9) and 10.8 g (CI, 3.1–18.4), respectively.

The two components of low birth weight, prematurity and IUGR, were then analyzed separately. Prematurity (gestational age < 37 weeks) was also significantly associated with air pollution (Table 5). The adjusted ORs per 50-μg/m³ increase in mean concentrations during the first trimester were 1.27 (CI, 1.16–1.39) for SO_2; 1.18 (CI, 1.05–1.31) for TSP; and 1.10 (CI, 1.00–1.21) for NO_x. For each pollutant in each trimester, the effects on prematurity were stronger than those on low birth weight. Restriction of the analyses to premature birth without IUGR did not change these estimates; adjusted ORs were 1.26 (CI, 1.14–1.40) for SO_2 and 1.16 (CI, 1.02–1.31) for TSP in the first trimester (data not shown). Effects on gestational age as a continuous variable were small; a 50-μg/m³ increase in the mean concentrations of SO_2 and TSP during the first trimester reduced the gestation by 0.056 weeks (CI, 0.037–0.075) and 0.075 weeks (CI, 0.049–0.101), respectively.

There were no significant associations between pollutant concentrations and IUGR. For example, the adjusted OR was 0.91 (CI, 0.80–1.04) and 0.89 (CI, 0.75–1.06) for a 50-μg/m³ increase in SO_2 and TSP in the first trimester, respectively; all p-values were > 0.10 (data not shown). Restriction of the analyses to term babies with IUGR did not change the pattern, and the ORs were virtually identical to those in the full dataset (data not shown).

Table 3. Descriptive characteristics of infants[a] and mothers[a] included in the analyses.

Variable	Mean ± SD or percentage
Mean (SD) birth weight (g)	3,291 ± 515
Prevalence of low birth weight (< 2,500 g)	5.2%
Mean (SD) gestational age (weeks)	39.5 ± 1.8
Prevalence of prematurity (< 37 weeks)	4.8%
Male sex of the infant	51.5%
Mean (SD) maternal age (years)	24.1 ± 4.8
Single mother	10.2%
Non-Czech mother	5.6%
Maternal education	
Primary	13.5%
Vocational	39.2%
Secondary	38.4%
University	8.9%

[a]On whom data for at least one pollutant was available (n = 108,173).

I also explored the association between birth outcomes and exposures in models with concentrations of a given pollutant in all trimesters, concentrations of all pollutants during a given trimester, and concentrations of all pollutants in all trimesters. In pollutant-specific analyses, the effects of both SO_2 and TSP on both outcomes appeared to be the strongest for exposures in the first trimester. In trimester-specific analyses, SO_2 was the strongest predictor of both low birth weight and prematurity. In the model containing all three pollutants in all three trimesters, SO_2 in the last trimester and TSP in the first trimester appeared to be related to prematurity, and SO_2 in the first and the last trimester appeared to be related to low birth weight. However, because of the collinearity between pollutants and trimesters (Table 2), these analyses produced unstable estimates and are not reported in detail.

Discussion

In this study, low birth weight and prematurity were associated with maternal exposure to air pollution. The association between air pollution and birth weight was to a large extent explained by low gestational age, but was not accounted for by individual maternal characteristics.

The Czech birth register is generally considered complete and reliable (*10*). It is highly unlikely that there would be geographic variation in the register quality that would be related to the geographic distribution of air pollution of sufficient strength to produce a bias that could explain our results. The levels of pollution in the Czech Republic have been declining since the mid-1980s, but were still high in the study period (1990–1991) and agree well with national data (*12*). Maternal exposure to pollution was district based. Although most monitors are, in principle, located where people live, i.e., in the main cities and towns, area-based exposures are only crude approximation of individual exposures. True personal exposures of mothers were inevitably misclassified. However, this misclassification was most likely random, and would tend to underestimate the effects of air pollution. Internal migration has been negligible in the Czech Republic, and should not affect the study results. Another complication of using area-based exposures is that mothers and infants within districts may be more similar to each other than between districts (clustering). For this reason, we used the robust logistic regression equivalent to multilevel modeling. Even with this conservative procedure, the associations were highly significant and are unlikely to be due to chance.

Confounding, or residual confounding, was our initial response to both the hypothesis and these results. The problem is with identifying the factor(s) that could be the confounder(s). Socioeconomic status, the most obvious candidate, is unlikely for two reasons. First, there was no association between socioeconomic factors and pollutants (association with exposure is a necessary requirement for describing a factor as confounding). Second, adjustment for socioeconomic factors, strongly related to birth outcomes in this data (*10,13*), did not attenuate the effect estimates; this does not indicate any possibility for a residual confounding. Maternal smoking is a well-known risk factor for low birth weight, but it is not plausible that it would be related to air pollution independently from maternal socioeconomic status. Moreover, maternal smoking affects fetal growth, and any such confounding would be seen for IUGR. However, we did not observe any association between pollution and IUGR. To avoid seasonal bias, we also controlled for the month of birth. If anything, this produced higher effect estimates for pollution. Although other unmeasured factors may differ between districts and could potentially confound the associations, it appears unlikely that the results are due to bias or confounding.

Most other studies found that low birth weight or IUGR was associated with particles (*3,6,7*). We found the strongest association with SO_2. However, this difference can be related to the measurement. In the Czech Republic at the time of the study, the main source of SO_2 and particles was the industry and, to a lesser extent, home burning of low quality coal with high sulfur content (*14*). Inhalable particles were not monitored. SO_2 may be a good indirect measure of small respirable particles (perhaps better than TSP) that may underlie the observed association. The effects of TSP on low birth weight and prematurity found in this study are compatible with this suggestion.

These results are consistent with our previous ecologic study where the OR of low birth weight for the 50-μg/m^3 increase in SO_2 was 1.10 (CI, 1.02–1.17) (*4*). At the general level, these results also appear to confirm the recent findings from China (*3*), the United States (*5*), and another Czech study (*7*). Our estimates of the effects on birth weight and gestational age measured as continuous variables were also comparable to the Chinese studies (*3,6*). With a closer look, however, there are differences between the individual reports. In the Chinese study, low birth weight was associated with SO_2 and TSP in the last trimester of pregnancy, with OR 1.11 (CI, 1.06–1.16) and 1.10 (CI, 1.05–1.14) for a 100-μg/m^3 increase in SO_2 and TSP, respectively, after controlling for maternal age, residential area, infant sex, and gestational age (> 37 weeks) (*3*). However, exposures in earlier trimesters were not positively related to birth outcomes. The comparability to our results is limited by the fact that only births after 37 weeks of gestation were included. Xu et al. (*6*) previously found an association between prematurity and short-term variation in SO_2 and TSP, with ORs of 1.21 and 1.10 (per 100 μg/m^3), respectively (*6*), but the extrapolation from short-term to long-term exposures is difficult (*15*).

In the Czech–U.S. Environmental Protection Agency study (*7*), exposure to PM_{10} in the first month of pregnancy was associated with an elevated risk of IUGR; the OR was 2.64 (CI, 1.48–4.71) for comparing high (> 50 μg/m^3) versus low (≤ 40 μg/m^3) IUGR risk, controlling for maternal characteristics. Exposure in the later months of pregnancy was not related to IUGR. However, this study was based on < 2,000

Table 4. ORs (CIs) for low birth weight per 50 μg/m^3 increase in mean concentrations of SO_2, TSP, and NO_x during a given trimester of pregnancy (pollutant-trimester-specific estimates).

Pollutant	Trimester	Crude OR (CI)	Adjusted OR[a] (CI)	Adjusted OR[b] (CI)
SO_2	1	1.12 (1.03–1.23)	1.20 (1.11–1.30)	1.01 (0.88–1.17)
	2	1.10 (1.01–1.19)	1.14 (1.06–1.22)	0.95 (0.82–1.10)
	3	1.12 (1.03–1.21)	1.14 (1.06–1.23)	0.97 (0.85–1.10)
TSP	1	1.13 (1.04–1.22)	1.15 (1.07–1.24)	1.13 (0.93–1.38)
	2	1.11 (1.01–1.22)	1.12 (1.04–1.21)	1.14 (0.92–1.40)
	3	1.10 (1.01–1.22)	1.11 (1.00–1.22)	1.14 (0.93–1.38)
NO_x	1	0.99 (0.84–1.16)	1.05 (0.95–1.16)	0.98 (0.81–1.18)
	2	1.00 (0.83–1.21)	1.06 (0.94–1.19)	0.99 (0.80–1.23)
	3	1.01 (0.86–1.19)	1.05 (0.94–1.15)	0.97 (0.80–1.18)

[a]OR adjusted for sex, parity, maternal age group, education, marital status and nationality, and month of birth. [b]OR adjusted for sex, parity, maternal age group, education, marital status and nationality, month of birth, gestational age.

Table 5. ORs (CIs) for prematurity per 50-μg/m^3 increase in mean concentrations of SO_2, TSP, and NO_x during a given trimester of pregnancy [pollutant-trimester (Tri)-specific estimates].

Pollutant	Tri	Crude OR (CI)	Adjusted OR[a] (CI)
SO_2	1	1.10 (1.00–1.21)	1.27 (1.16–1.39)
	2	1.09 (1.02–1.16)	1.25 (1.14–1.38)
	3	1.18 (1.11–1.26)	1.24 (1.13–1.36)
TSP	1	1.11 (1.02–1.22)	1.18 (1.05–1.31)
	2	1.06 (0.96–1.16)	1.11 (0.97–1.26)
	3	1.14 (1.03–1.26)	1.12 (0.97–1.28)
NO_x	1	1.03 (0.93–1.14)	1.10 (1.00–1.21)
	2	1.01 (0.91–1.12)	1.08 (0.98–1.19)
	3	1.09 (0.97–1.23)	1.11 (1.00–1.23)

[a]OR adjusted for sex, parity, maternal age group, education, marital status and nationality, and month of birth.

births (gestational age 37–43 weeks), and did not have the statistical power to discover an effect on low birth weight of the size reported here or in the Chinese study (*3*). In contrast to the Czech study, there was no suggestion of an association between air pollution and IUGR in our data.

In the U.S. study, the risk of low birth weight among singleton infants born between 37 and 44 weeks of gestation was increased among babies of mothers exposed to high levels (> 95th percentile) of carbon monoxide in the last trimester (OR 1.22; CI, 1.03–1.44) (*5*). Little data on other pollutants were available, and their effects were not analyzed. Because carbon monoxide was correlated with NO_x ($r = 0.62$) and PM_{10} ($r = 0.39$), it is possible that birth weight could also be related to other pollutants. There were no effects of carbon monoxide in earlier trimesters.

The results of these studies raise the question of biologic mechanisms. Although a range of social and behavioral determinants of birth weight or preterm birth have been identified, the biologic mechanisms leading to prematurity and the critical period of vulnerability are not well understood (*16,17*). Premature births and IUGR have different determinants (*18,19*), and it is likely that different mechanisms may be involved at different stages of pregnancy. The observation that maternal alcohol consumption and cigarette smoking early in pregnancy affect birth outcomes (*20*) suggests that exposures during the early gestational period are also important for the birth outcome.

In our study, the differences between the effects of trimester-specific exposures were not large, although the effects of both SO_2 and TSP appeared to be largest for maternal exposures in the first trimester. This could partly be due to a larger misclassification of exposure in the last trimester in premature births. Nevertheless, our results indicate that acute effects which provoke premature labor are not the only mechanisms involved. Several other potential mechanisms could be considered. First, the known determinants include intrauterine infection (*16,17*). Although most published reports focus on genitourinary infections (*21*), maternal illness due to respiratory infection in pregnancy may also be involved. Second, the potential mechanisms could be related to hematologic factors. There are reports of increased blood viscosity (*22*) and plasma fibrinogen (related to blood coagulation) (*23*) during air pollution episodes. Rheologic variables, including blood viscosity, influence the blood perfusion of the placenta (*24,25*), and one could speculate that chronic exposure to high pollution levels may influence placental functions.

Third, air pollution may affect DNA or its transcription. DNA adducts are more common in areas with higher levels of pollution (*26–28*). Placental DNA adducts were more common among mothers exposed to higher levels of outdoor air pollution (*29*). There may be a link between DNA adducts and fetal growth: newborns with more adducts had lower birth weight and length (*30*). The effects of air pollution on DNA adducts levels seem similar (although weaker) to the effects of cigarette smoking (*26–29*). There may also be a parallel with maternal smoking, an accepted risk factor for low birth weight (*20*), 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. The clarification of biologic mechanisms is important but, as the example of cigarette smoking illustrates, it is not indispensable to assess environmental hazards.

This is a new area of air pollution epidemiology, and the evidence needs to be interpreted cautiously. There have now been five independent datasets that suggested an association between air pollution and birth outcomes. There are important discrepancies between these reports, and the biologic mechanisms for such associations are not clear. The effects are not large, and even if they are confirmed, outdoor air pollution is not a major determinant of low birth weight or prematurity. On the other hand, the effects are not negligible; they are several times larger than those on adult mortality as estimated from time–series studies and are generally accepted as causal (*1*). The associations of air pollution with birth outcomes do not seem to be due to bias or confounding, and this question deserves serious examination.

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