Maternal exposure to low level air pollution and pregnancy outcomes: population-based study

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Abstract

Background

Recent reports showed that air pollution might increase the risk of adverse birth outcomes. We evaluated the relation between ambient air pollution and the occurrence of low birth weight and preterm delivery.

Methods

Epidemiological study comprised all singleton newborns (N=3,997), born in 1998 to women, residing in Kaunas city. Among them, 140 (3.5%) were low birth weight (<2,500 g) and 203 (5.1%) were premature births (<37 weeks of gestation). Birth data and information on maternal characteristics was obtained from Lithuanian National Birth Register. We used measurements of ambient nitrogen dioxide (NO_2) and formaldehyde, collected at 12 monitoring posts to estimate residential exposure for the period of 1997-1998. Multivariate logistic regression was used to estimate the effect of each pollutant on risk of LBW and premature birth, controlling for potential confounders.

Results

Adjusted odds ratios (OR) for low birth weight increased in an exposure-response pattern with increasing formaldehyde exposure ($OR_{2nd\ quartile}$=1.89, 95% CI 0.81-4.47; $OR_{3rd\ quartile}$=2.13, 95% CI 0.86-5.29; $OR_{4th\ quartile}$=2.96, 95% CI 1.25-7.00). For each interquartile increase for formaldehyde, OR was 1.35, 95% CI 1.06-1.72. Similarly, low birth weight risk increased by 9% (adjusted OR=1.09, 95% CI 0.86-1.38) per interquartile increase in NO_2 concentrations. Adjusted odds ratios of preterm birth were 1.14, 95% CI = 0.99-1.31 for NO_2, and 1.06, 95% CI = 0.92-1.22 for formaldehyde also per interquartile increase in concentrations.

Conclusion

Our findings suggested that there might be a relation between maternal exposure to ambient NO_2 and formaldehyde and the risk of LBW or preterm delivery in Kaunas.

Keywords

air pollution, low birth weight, preterm delivery

Background

Growing evidence of adverse air pollution effect on human health raises the question at what extent it affects fetus and newborns, which are likely to be more vulnerable than adults to environmental toxicants.

Recent epidemiological studies, conducted in different countries, found an association between elevated levels of air pollution and birth outcomes, such as low birth weight (LBW), prematurity, intrauterine growth retardation (IUGR), neonatal and postneonatal mortality. Few studies produced negative findings [1,2,3].

The first study, that reported association between high air pollution and lower mean birth weight in infants of nonsmoking women, was conducted in Los Angeles, California in early 1970s [4]. A small increase in LBW risk was observed among Denver residents, who were exposed to ambient carbon monoxide (CO) levels, exceeding 3 ppm [5]. The study of births in southern California indicated that exposure to high concentrations of CO during the last trimester of pregnancy may increase the risk of LBW and that exposure to CO and particulate matter (PM) either shortly after conception or before birth may trigger preterm birth [6,7]. Chinese study reported a significant dose-response relation between maternal exposures to high concentrations of sulphur dioxide (SO_2) and total suspended particles (TSP) during the last trimester and the risk of LBW [8] and premature birth [9]. An ecological study found a small increase in prevalence of LBW in Czech districts with high levels of SO_2 [10]. Later study, with individual data on newborns and area based indicators of air pollution, confirmed relation between maternal exposures to SO_2 and TSP in each trimester of pregnancy and increased risks for LBW and prematurity [11]. It was reported that exposure to PM_{10}, $PM_{2.5}$ [12] and carcinogenic fraction of polycyclic aromatic hydrocarbons [13] during the first month of pregnancy was associated with IUGR. Rogers et al found an increased risk of very low birth weight newborns among women exposed to high levels of SO_2 and TSP [14]. The study of six northeastern cities of USA provided evidence of an increased risk between term LBW and ambient levels of CO and SO_2, but no evidence of an association of term LBW with ambient levels of PM_{10} [15].

Recently published data have shown that ambient nitrogen dioxide (NO_2), SO_2, CO and TSP concentrations during the first trimester of pregnancy were associated with risk of term LBW after adjusting for a number of covariates [16]. Norwegian study observed a significantly lower mean birth weight for newborns in the industrial residential area, compared with the urban and rural areas [17]. A population-based study, conducted in Kaunas in 1994, reported an increased LBW risk among women, exposed to outdoor formaldehyde and TSP [18].

The biological mechanisms by which air pollutants may interfere with processes of prenatal development are still not clear. Several potential mechanisms have been hypothesized, including maternal susceptibility to infectious, oxidative stress [19], hematological factors (e.g., blood viscosity) [20,21] and direct effect of specific pollutants on fetal development or on DNA and its transcription [22,23].

The purpose of this study was to investigate the association between low-level maternal exposures to outdoor air pollutants and risk of having LBW or preterm newborn.

Methods

We studied associations between air pollution and birth outcomes. The study was conducted in Kaunas, the second largest city of Lithuania, which covers approximately 157.2 km^2. The city, with approximately 400,000 inhabitants and 4,000 births per year, is situated in the valley and plain. Air pollution in Kaunas, as well as in whole Lithuania, has essentially decreased during transformational economy decrease. During the last decade, the concentrations of SO_2 decreased almost ten times, NO_2 and TSP – twice, while no essential change was noted for formaldehyde levels [24]. The major air pollution source in the city is automobile exhaust emissions, which account for over 70% of the total emissions.

We conducted a population-based study. Data on pregnancy outcomes were obtained from Lithuanian National Birth Register. Birth registration records include information, obtained through maternal interviews during first prenatal visit and at delivery. The following information was available: home address, date of birth, sex, birth weight, gestational age (estimated by the last menstruation period method), parity, maternal age, education, marital status, employment status, diseases, history of previous pregnancies, maternal and paternal smoking status.

The study included all singleton births in Kaunas city from January 1st, 1998 through December 31st, 1998. The outcomes of interest were low birth weight (defined as birth weight of <2500 g), and premature birth (defined as birth at <37 weeks of gestation), codes P07.0-3, International Classification of Diseases, 10th revision. Out of 4,067 births registered in Kaunas in 1998, 161 (4.0%) was low birth weight and 226 (5.6%)

were premature births. We excluded 70 (1.7%) twins, leaving us with 3,997 eligible study subjects, among them 140 (3.5%) were LBW and 203 (5.1%) premature births.

To assess exposure to ambient air pollution, we used Kaunas municipal ecological monitoring data. Information on pollutants concentrations from 3 governmental fixed-site monitoring stations was used for the reference. The measurements were taken from 12 municipal monitoring sites, one in each residential district. Monitors were located inside of residential quarters, mostly near schools and kindergartens. We used all available daily measurements of NO_2 (colorimetric method) and formaldehyde (colorimetric method) to assess mean residential exposure of each mother over the period of 1997-1998. Two years (the year of delivery and the preceding year) were chosen as the exposure period to avoid exposure classification errors for births, which occurred at the beginning of a year.

We examined contingency tables for several independent variables because of their established relation with risk of LBW and preterm birth [25]. Maternal age was divided into four age groups, ≤19, 20-29, 30-34, ≥35 years, with age of 20-29 years old as the referent group. We classified marital status as married (referent group), single, and divorced. We dichotomized education as secondary or lower (≤12 years of education) and college or university (>12 years of education), with the latter as referent group. Maternal and paternal smoking were categorized as yes versus no. The other variables were employment status (unemployed vs. employed), infant sex, parity, threatened abortion, previous pregnancy loss, and previous premature birth.

The effect of ambient air pollution on birth outcomes was estimated by logistic regression. We calculated crude odds ratios (OR) and their 95% confidence intervals (CI) of low birth weight and prematurity across exposure categories for each pollutant. Then, in the analyses of low birth weight, crude effects of air pollution were adjusted for gestational age. In the final model we adjusted for potential confounding factors (in categories described above), identified in literature and univariate analysis: gestational age (low birth weight model only), infant sex, maternal age, marital status, education, employment status, previous premature birth, threatened abortion, maternal and paternal smoking.

We ranked pollutants' concentrations into four categories and applied exposure variable in both categorical and continuous forms. For formaldehyde the range of values for exposure categories were ≤1.29 μg/m^3, 1.30-2.12 μg/m^3, 2.13-3.26 μg/m^3, and >3.26 μg/m^3. NO_2 cutoffs were ≤6.0 μg/m^3, 6.1-10.0 μg/m^3, 10.1-12.0 μg/m^3, and >12 μg/m^3. These cutoffs were roughly equal to quartiles for both pollutants. We used exposure to levels below the 1st quartile as the reference category for each pollutant and conducted the analysis of continuous exposure parameters on the basis of interquartile increase in concentrations of formaldehyde and NO_2.

We used SPSS version 10.0 for statistical analysis.

Results

The distribution of demographic factors and potential risk factors for LBW and premature birth is presented in table 1. Both pregnancy outcomes were associated with maternal age, marital status (single or divorced), unemployment, lower maternal education, threatened abortion, previous premature birth, maternal and paternal smoking.

Examining Pearson correlation coefficients (r) of air pollutants averages for two years period, we found that formaldehyde and NO_2 correlated with each other ($r=0.45$, $p<0.01$). This correlation may reflect the fact that both pollutants are produced by the same vehicular sources.

Table 2 shows the number of eligible births and cases of LBW and premature births by quartile of exposure to formaldehyde and NO_2. LBW prevalence increased with increasing pollutant level, from 2.7% in the low formaldehyde exposure category to 4.4% in the high category, and from 3.1% to 4.0% for NO_2 exposure categories. For both pollutants, the prevalence of premature births only in the highest exposure category (4^{th} quartile) was higher than mean prevalence in 1^{st} to 3^{rd} quartiles.

We estimated the risk of LBW for mothers exposed to different levels of formaldehyde and NO_2. The crude odds ratios for LBW increased with each quartile of formaldehyde exposure (table 3). After adjustment for gestational age the risk of LBW was significantly increased for those newborns whose mothers had high levels of exposure to formaldehyde (3^{th} and 4^{th} quartiles), OR=2.54, 95%CI 1.06-6.07 and OR=3.08, 95%CI 1.36-7.00, respectively. These estimates were not substantially changed by further adjustment for known LBW risk factors: infant sex, maternal age, marital status, employment status, education, previous premature birth, threatened abortion, and parental smoking. The results suggested an exposure-response relation between exposure to formaldehyde and low birth weight; therefore an analysis of continuous data was examined. Using a continuous exposure variable, we estimated that the risk of LBW increased by 35% (fully adjusted OR=1.35; 95% CI 1.06-1.72) for each interquartile increase in formaldehyde concentrations.

Similar patterns were also observed for NO_2, although the estimates were somewhat weaker and lacked statistical significance. Crude OR for the 2^{nd} to 4^{th} quartile of NO_2 were 1.00, 1.17, and 1.33, respectively, compared to the first quartile. Adjustment for gestational age and other covariates had minor effect on crude estimates. The analysis of continuous data revealed that the risk of LBW tended to increase by 9% (fully adjusted OR=1.09, 95% CI 0.86-1.38) for quartile change in NO_2 concentrations.

The effects of exposure to pollutants on prematurity were weaker than those on LBW. A dose-response pattern was observed for NO_2, adjusted OR for the 2nd to 4th quartile were 0.96, 1.04, and 1.43, respectively. A modest increase in risk was observed only at highest formaldehyde level (4th quartile), adjusted OR=1.13, 95% CI 0.73-1.75. Using a continuos measure, we estimated that the risk of preterm birth increased by 14% (fully adjusted OR=1.14, 95% CI 0.99-1.31) per interquartile increase in NO_2 concentrations and by 6% (fully adjusted OR1.06, 95% CI = 0.92-1.22) per interquartile increase in formaldehyde concentrations.

Discussion

Our findings suggested that there existed association between formaldehyde and NO_2 exposure during pregnancy and the likelihood of having LBW newborn. This pattern was less evident for premature births. The increased risk of LBW remained after adjusting for gestational age, infant sex, maternal age, marital status, employment status, education, previous premature birth, threatened abortion, and parental smoking. Risk of premature birth was only weakly related to highest level of formaldehyde exposure, whereas for NO_2 we observed a modest exposure-response pattern.

How do our results compare with those of others? It is not known whether the associations between air pollution and pregnancy outcomes found in some populations can be replicated in others, as the studies varied in terms of examined pollutants, exposure levels and timing, confounding factors as well as outcomes of interest, and the magnitude of observed effects.

In this study we confirmed our previous findings of an association between LBW risk and formaldehyde exposure (adjusted OR 1.37, 95%CI 0.90-2.09) [18] although exposure levels in the earlier study were higher (annual mean for formaldehyde was 3.14 μg/m^3). To our knowledge, no other epidemiological study has examined exposure to outdoor formaldehyde as a risk factor for adverse pregnancy outcomes.

Our results on an increased risk for LBW and preterm delivery in relation to increasing levels of NO_2 during pregnancy were consistent with findings in previous studies. Ha et al reported the increased relative risk of LBW (RR 1.07; 95% CI 1.03-1.11) for each interquartile increase for NO_2 concentrations during the first trimester of pregnancy after adjusting for time trends, gestational age, maternal age, parental education level, parity, infant's birth order and gender [16]. Another study showed that elevated exposure to oxidized nitrogen, including nitrogen oxides (NO_x), has been associated with low birth weight [19]. Czech study reported relation between maternal exposure to NO_x and slightly increased risk of premature birth (adjusted OR 1.10; 95% CI 1.00-1.21 per 50 μg/m^3 increase in NO_x), but no association with LBW risk [11]. In California no consistent effects was found on preterm birth for NO_2 over any of pregnancy periods [7]. Increased ambient concentrations of NO_2 were associated with intrauterine mortality in Brazil. The effect size increased when an index of the combined concentration of three pollutants (NO_2, CO, and SO_2) was used [26].

Our study had several strengths. The study population was homogeneous with respect to ethnic culture, unified prenatal care, and the health care system. The another strength of this study was the ability to adjust for a number of potential confounding factors for LBW and premature birth, including gestational age, infant sex, maternal age, marital status, education, employment status, previous premature birth, threatened abortion, maternal and paternal smoking.

We did not have information on some known LBW risk factors, such as maternal nutrition, prepregnancy weight, and occupational exposures. However, the risk factors for which we had no information were likely to vary independently of the average ambient pollutant levels and so should not confound the relations we observed. Misclassification of LBW cases as noncases and vice versa was not likely, as birth weight data, recorded in birth register, are generally considered reliable. The estimation of gestational age, based on the date of mother's last menstrual period, was of less reliability, therefore some misclassification of preterm birth cases might have occurred. However, the assignment of cases was independent from exposure assessment, therefore such classification errors were nondifferential and might have tended to underestimate air pollution effects.

The most important source of bias in our study, as was in most studies in which exposure was based on place of residence, was misclassification of exposure. We estimated maternal exposure to pollutants basing on average measures for entire residential district. True personal exposure depends upon a number of exposure pathways, for example time spent indoors versus time outdoors, time spent at specific locations such as work or home, and migration into or out of a study area. Nevertheless, factors expected to contribute to differences between area-wide and individual exposures were most likely to be independent from exposure assessment and to underestimate the effects of air pollution. Evidence was provided, that when area-wide measures of exposure to air pollution were used as proxies for personal exposures, estimates of pollutant effects were generally smaller than those based on exposure levels determined by personal sampling [27].

A wide range of agents, including passive smoking [28] and occupational exposures [29] were found to increase the risk of adverse pregnancy outcomes, and insufficient control of other environmental risk factors could have influenced the observed associations.

Conclusions

Although the effects of unmeasured risk factors could not be excluded with certainty, our findings suggested that there might be a relation between maternal exposure to outdoor NO_2 and formaldehyde and the likelihood of having LBW or premature newborn.

List of abbreviations

NO_2 Nitrogen dioxide
OR Odds ratio
LBW Low birth weight
IUGR Intrauterine growth retardation
CO Carbon monoxide
PM Particulate matter
SO_2 Sulphur dioxide
TSP Total suspended particles

Competing interests

None.

Authors' contributions

Grazuleviciene R. conceived and designed the study, Maroziene L. coordinated the study, performed statistical analysis and drafted the manuscript.

Both authors read and approved the final manuscript.

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Tables

Table 1 - Demographic characteristics and potential risk factors for low birth weight and premature birth

Characteristics	Total no. of births		Low birth weight				Premature births			
	N	%	N	%	OR	95%CI	N	%	OR	95%CI
Maternal age group (years)										
≤19	229	5.7	8	5.7	1.17	0.51-2.54	18	8.9	2.00	1.15-3.44
20-29 (referent)	2591	64.8	78	55.7			106	52.2		
30-34	761	19.0	28	20.0	1.23	0.77-1.95	47	23.2	1.54	1.07-2.23
≥35	416	10.4	26	18.6	2.15	1.33-3.46	32	15.8	1.95	1.27-2.99
Marital status										
Married (referent)	3480	87.1	111	79.3			151	74.4		
Single	467	11.7	26	18.6	1.79	1.13-2.83	47	23.2	2.47	1.73-3.52
Divorced	50	1.3	3	2.1	1.94	0.47-6.59	5	2.5	2.45	0.85-6.56
Employment status										
Employed	3068	76.8	85	60.7			120	59.1		
Unemployed	929	23.2	55	39.3	2.21	1.56-3.13	83	40.9	2.41	1.80-3.22
Education (years)										
>12	1998	50.0	56	40.0			82	40.4		
≤12	1997	50.0	84	60.0	1.52	1.08-2.15	121	59.6	1.51	1.13-2.01
Infant sex										
Male	2140	53.5	64	45.7			117	57.6		
Female	1857	46.5	76	54.3	1.38	0.99-1.94	86	42.4	0.84	0.63-1.12
Parity										
Nuliparous	2028	50.7	79	56.4	1.08	0.76-1.54	112	55.2	1.19	0.89-1.60
Multiparous	1969	49.3	61	43.6			91	44.8		
Threatened abortion										
No	2883	72.1	86	61.4			116	57.1		
Yes	1114	27.9	54	38.6	1.66	1.17-2.34	87	42.9	2.02	1.52-2.69
Previous pregnancy loss										
No	3514	87.9	126	90.0			176	86.7		
Yes	483	12.1	14	10.0	0.80	0.46-1.41	27	13.3	1.12	0.74-1.70
Previous premature birth										
No	3923	98.1	130	92.9			188	92.6		
Yes	74	1.9	10	7.1	4.56	2.29-9.08	15	7.4	5.05	2.81-9.07
Maternal smoking										
No	3859	96.5	121	86.4			183	90.1		
Yes	138	3.5	19	13.6	4.93	2.94-8.27	20	9.9	3.40	2.07-5.59
Paternal smoking										
No	2485	62.2	69	49.3			95	46.8		
Yes	1512	37.8	71	50.7	1.72	1.23-2.42	108	53.2	1.94	1.46-2.57

Table 2 - Number of all births, cases of low birth weight and premature birth by quartile of pollutant

	Births	Low birth weight	Premature birth
Quartile of formaldehyde exposure (μg/m^3)			
1 (≤1,29)	673	18(2.7%)	40(5.9%)
2 (1,30-2,12)	1535	50(3.3%)	69(4.5%)
3 (2,13-3,26)	865	31(3.6%)	39(4.5%)
4 (>3,26)	924	41(4.4%)	55(6.0%)
Quartile of nitrogen dioxide exposure (μg/m^3)			
1 (≤6.0)	716	22(3.1%)	34(4.7%)
2 (6.1-10.0)	876	27(3.1%)	39(4.5%)
3 (10.1-12,0)	1341	48(3.6%)	64(4.8%)
4 (>12.0)	1064	43(4.0%)	66(6.2%)
Total	3997	140(3.5%)	203(5.1%)

Table 3 - Crude and adjusted odds ratios (OR) for low birth weight by pollution exposure

Exposure	Crude odds ratio		Adjusted* odds ratio		Adjusted† odds ratio	
	OR	95%CI	OR	95%CI	OR	95%CI
Formaldehyde						
Categorical variable (quartiles)						
1 (referent)						
2	1.22	0.71-2.12	1.78	0.79-4.04	1.89	0.81-4.47
3	1.35	0.75-2.44	2.54	1.06-6.07	2.13	0.86-5.29
4	1.69	0.96-2.97	3.08	1.36-7.00	2.96	1.25-7.00
Continuous interquartile change						
	1.18	1.00-1.39	1.40	1.14-1.77	1.35	1.06-1.72
Nitrogen dioxide						
Categorical variable (quartiles)						
1 (referent)						
2	1.00	0.57-1.78	1.09	0.48-2.44	1.25	0.55-2.87
3	1.17	0.70-1.96	1.21	0.58-2.54	1.25	0.58-2.69
4	1.33	0.79-2.24	1.35	0.64-2.81	1.36	0.64-2.92
Continuous interquartile change						
	1.11	0.94-1.31	1.11	0.88-1.39	1.09	0.86-1.38

*Adjusted for gestational age

†Adjusted for gestational age, infant sex, maternal age (≤19, 20-29, 30-34, ≥35), marital status, employment status, education, previous premature birth, threatened abortion, maternal and paternal smoking.

Table 4 - Crude and adjusted odds ratios (OR) for premature birth by pollution exposure

Exposure	Crude odds ratio		Adjusted* odds ratio	
	95%CI	95%CI	OR	95%CI
Formaldehyde				
Categorical variable (quartiles)				
1 (referent)				
2	0.74	0.49-1.11	0.77	0.51-1.17
3	0.75	0.48-1.18	0.73	0.46-1.16
4	1.00	0.66-1.52	1.13	0.73-1.75
Continuous interquartile change				
	1.03	0.90-1.18	1.06	0.92-1.22
Nitrogen dioxide				
Categorical variable (quartiles)				
1 (referent)				
2	0.94	0.58-1.50	0.96	0.59-1.56
3	1.01	0.66-1.54	1.04	0.67-1.62
4	1.33	0.87-2.03	1.43	0.92-2.22
Continuous interquartile change				
	1.12	0.97-1.27	1.14	0.99-1.31

*Adjusted for infant sex, maternal age (≤19, 20-29, 30-34, ≥35), marital status, employment status, education, previous premature birth, threatened abortion, maternal and paternal smoking.