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Individual Exposure to Nitrogen Dioxide and Preterm Birth Risk in Kaunas

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Several epidemiological studies have found relationships between exposures to air pollution and adverse birth outcomes, particularly for traffic-related air pollutants, suggesting that the exposure may increase risk of preterm birth. Nitrogen dioxide (NO_2) is the main traffic-related urban air pollutant associated with health effects. The purpose of this study was to assess individual maternal exposure to NO_2 during pregnancy and to study links between the exposure and preterm birth risk in Kaunas, Lithuania. Prospective cohort study comprised all singleton newborns, born to Kaunas citizens in 2008-2009. Case group consisted of 187 preterm births (< 37 weeks), while controls were 3100 term (≥ 37 weeks) singleton newborns. Individual exposure to NO_2 was assigned to each subject during each trimester pregnancy as well as throughout the entire pregnancy by using a dispersion air quality modelling system AIRVIRO. To assess the association between preterm birth and exposure to NO_2 logistic regression analysis was used and odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated. Pregnant women exposed to NO_2 have a slightly increased risk of preterm birth. That risk was shown to be higher when women were exposed to NO_2 levels 24.0–53.2 μg m^{-3} during the first and second trimesters, OR 1.21, 95% CI 0.84–1.75 and 1.22, 95% CI 0.84–1.76, respectively. The study results indicate that residential air pollution might contribute to preterm birth risk.

Keywords: *Nitrogen dioxide, exposure, modelling, preterm birth.*

1. Introduction

Environmental pollutants have been studied for their potential to increase the risk of adverse birth outcomes. Several adverse birth outcomes have been found to be associated with exposures to air pollutants during pregnancy, including effects on growth, development and duration of pregnancy, although effects were not always consistent between the studies (Dugandzic et al. 2006; Maisonet et al. 2001; Maroziene and Grazuleviciene 2002; Sram et al. 2005).

In addition, a number of epidemiological studies have found various level relationships between exposures to traffic-related air pollution and birth outcomes, particularly for nitrogen dioxide (NO_2) and particulate matter, suggesting that exposure to these air pollutants may increase a woman's risk for preterm birth (Maroziene and Grazuleviciene 2002; Gehring et al. 2011; Llop et al. 2010; Bobak 2000; Leem et al. 2006). Preterm births cause a large public-health burden because of its high prevalence, associated mortality and morbidity (Tucker and McGuire 2004; Colvin et al. 2004; Fraser et al. 2004; Murphy et al. 2004).

A few potential biological mechanisms have been described through which air pollution could influence pregnancy outcomes, such as the induction inflammation of placenta, respiratory system and cardiovascular mechanisms of oxidative stress, coagulation, endothelial function, and hemodynamic responses (Kannan et al. 2006).

The principal source of air pollution in Kaunas city is road traffic, and NO_2 is the main traffic-related air pollutant associated with health effects (Belander et al. 2001). The European Union limit value of the annual mean NO_2 concentration is 40 μg m^{-3} (World Health Organization 2003). NO_2 is considered as a marker for air pollution from traffic (Rijnders et al. 2001).

NO_2 pollution is higher along busy roads, in city centres and districts near highways, and is related to traffic density of the highways, and the distance to the highway (Bogo et al. 2001; Carslaw 2005; Beckerman et al. 2008).

The epidemiological studies on preterm birth risk relied on different methods of assessing exposure, measurement of health effects and control of confounding variables. This presented difficulties in making comparisons between investigations and generalizing results. Further research on this subject is thus necessary. A crucial aspect of the study of prenatal exposure to air pollutants is the identification of vulnerable periods to the detrimental effects of the exposure during pregnancy (Hackley et al. 2007; Woodruff et al. 2009). Results of the studies published indicate that the first and third trimesters are the most vulnerable periods for low birth weight and preterm births.

The present study reports the association of NO_2 exposure during pregnancy and preterm birth in an epidemiological study of pregnant women with a detailed assessment of traffic related NO_2 pollution at the subjects' current residential addresses using a geographic information system (GIS). In GIS geographic data can be combined with pollutants concentration measurements to estimate exposures for individual members of large study populations (Bellander et al. 2001; Brauer et al. 2003).

We performed NO_2 dispersion calculations during three pregnancy trimesters and the entire pregnancy using the Gaussian model in the AIRVIRO system (Airviro Users Documentation 1997).

The AIRVIRO dispersion models use meteorological data and emission distributions as an input to the simulations. The modelling of pollutant dispersion in AIRVIRO is performed via a Gaussian model. Among the advantages of the model are the following points: it produces results that agree with experimental data just as well as any other model; it is fairly easy to perform mathematical operations on this equation; it is appealing conceptually; it is consistent with the random nature of turbulence. The limitations of the Gauss model are that it performs simulations on a larger scale; a low wind speed may influence the dispersion; the dispersion model simulates the steady states of pollution concentrations.

The purpose of this study was to assess individual maternal exposure to NO_2 during pregnancy and to analyze the links between the exposure and preterm birth controlling for an influence of potential confounding variables.

2. Methods

Study design and population characteristic

We conducted a prospective cohort study of pregnant women in Kaunas city, the second largest city in Lithuania, which covers approximately 157.2 km^2. On their first visit to a general practitioner, all pregnant women living in Kaunas city in the period of. 2008 and 2009 were invited to join the cohort. The women were enrolled in the study only if they consented to participate in the cohort. The study ethics complied with the Declaration of Helsinki. The research protocol was approved by the Lithuanian Bioethics Committee and an oral informed consent was obtained from all subjects.

In total 5,405 women were approached; 79 % of them agreed to participate in the study. The first interview was completed during the first pregnancy trimester. The interview queried women regarding demographics, residence and job characteristics, chronic diseases, reproductive history, including date of the last menstrual period, previous preterm birth. We also asked the women to report their age (younger than 20 years, 20–29 years, 30 years, and more), educational level (primary, secondary, university), marital status (married, not married), smoking during pregnancy (non-smoker, smoker <5 cigarettes per day, and smoker ≥5 cigarettes per day), alcohol consumption (0 drinks per week, at least one drink per week), blood pressure (<140/80 mm Hg^{-1}, ≥140 or ≥ 90 mm Hg^{-1}), body mass index (<25 kg m^{-2}, 25–30 kg m^{-2}, >30 kg m^{-2}), and other potential risk factors for preterm birth. Adjustment for those variables was made for the studies of associations between NO_2 exposures and preterm birth. The outcome of interest was singleton preterm birth (<37 weeks of gestation) and term (>37 weeks of gestation) newborn. We restricted our analyses to infants born with a birth weight below 4.500 g to mothers with estimated residential exposure at least one year, leaving data for 3287 women in the final analysis.

NO_2 exposure assessment

Exposure to ambient NO_2 pollution estimates at each cohort number home address was assigned using GIS and an AIRVIRO dispersion model, developed by the Swedish Meteorological and Hydrological Institute (Airviro User Documentation 1997).

Kaunas streets NO_2 emission data were used to create emission database within the AIRVIRO Air Quality Management System. Gaussian plume dispersion simulations were run for a model domain encompassing the entire city area on a course grid resolution.

Geographic data for the Kaunas city streets, their type were measured by combining GIS and manual measurements. Total traffic counts and its composition (calculated as cars/day time's km street length) were measured based on the 2008 Municipal traffic-count data for Kaunas. If no counts were available for a specific street, the numbers were estimated by a person with local information about the traffic conditions based on comparison with the roads on which data were available. Traffic count data were available for 80% of the streets nearest to cohort addresses.

In order to validate the Gaussian model within AIRVIRO, annual averaged ambient NO_2 concentrations predicted by this model were compared to NO_2 concentrations from Ogawa passive samplers at 41 sites in Kaunas city.

To attribute the NO_2 exposure to each study subject, the health data base and the environmental NO_2 pollution data base were joined. Each subject's full street address and residential NO_2 pollution level measurement data, and the current residence history data were combined to assess the individual NO_2 pollution exposure. A GIS assigning the NO_2 pollution level was used for each woman by applying different GIS functions and possibilities. First, the study subjects data were converted to a database file structure for use in the GIS software (ArcInfo version 9.3, ESRI). Geocoding was performed to obtain latitude and longitude coordinates for each patient's home address. Initially, 63 % records were matched and 37 % were left unmatched. All unmatched records were reviewed and corrected, leading to another 37 % matched addresses (total of 3287). Then, a spatial join was performed that allowed the GIS user to append the attributes of one data layer (patient address points) to the attributes of another layer (nitrogen dioxide) assessed with AIRVIRO.

Statistical analysis

We established the individual outdoor NO_2 exposure during three trimesters and entire pregnancy for each subject at the geocoded residential address. We grouped the pollutant concentrations into three categories (tertiles) and applied the exposure variable as both categorical and continuous parameters. We used exposure levels in the 1st tertile as the reference category (low exposure) and then also conducted an analysis of continuous exposure parameters on the basis of an increase of 10 μg m^{-3} in NO_2 concentrations. The effect of ambient NO_2 exposure on preterm birth was estimated by logistic regression. We calculated crude odds ratios (OR) and their 95 % confidence intervals (CIs) of preterm birth exposure categories. We adjusted crude effects of NO_2 for potential confounding factors: maternal education, family status, renal diseases, diabetes, cardiovascular disease, stress, body mass index, smoking, alcohol consumption, parity, previous preterm birth, and infant birth year. Statistical analyses were performed with the SPSS software for Windows version 13.

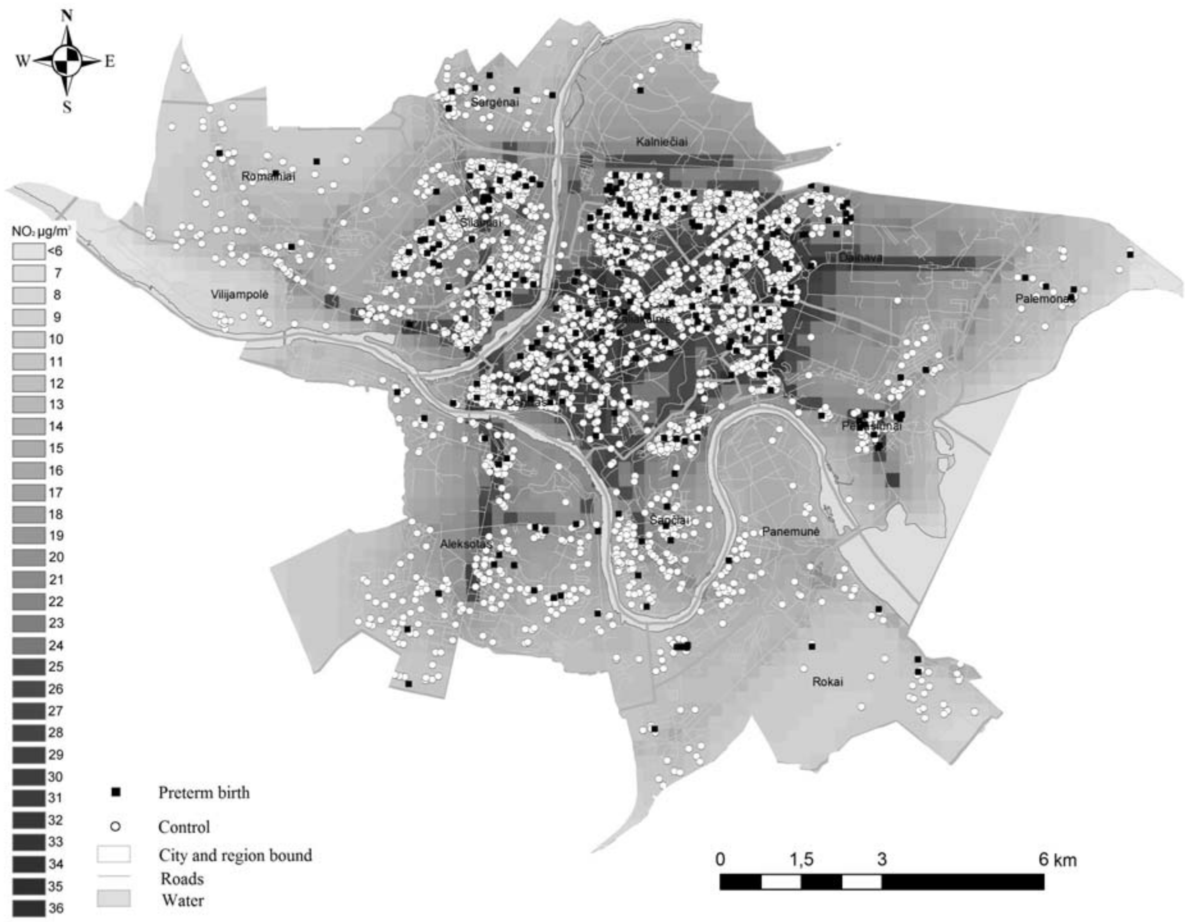

Fig.1. Modelled annual NO_2 concentration and geocoded birth outcomes

3. Results

Among 3287 singleton births 187 (5.7 %) preterm birth cases were registered. Distribution of pregnancy outcomes and NO_2 pollution levels are presented in Figure 1. Higher level of NO_2 was in streets with heavy traffic density. In Karaliaus Mindaugo Avenue, Vytauto Avenue, Savanorių Avenue, Pramonės Avenue and Taikos Avenue the annual mean NO_2 concentration exceeded 30 μg m^{-3}.

In these streets there was registered a higher proportion of preterm birth to compare to the streets of lower NO_2 concentration. The mean levels of NO_2 to which the women were exposed outside their homes throughout their pregnancies ranged from 5.3 to 53.2 µg m^{-3}.

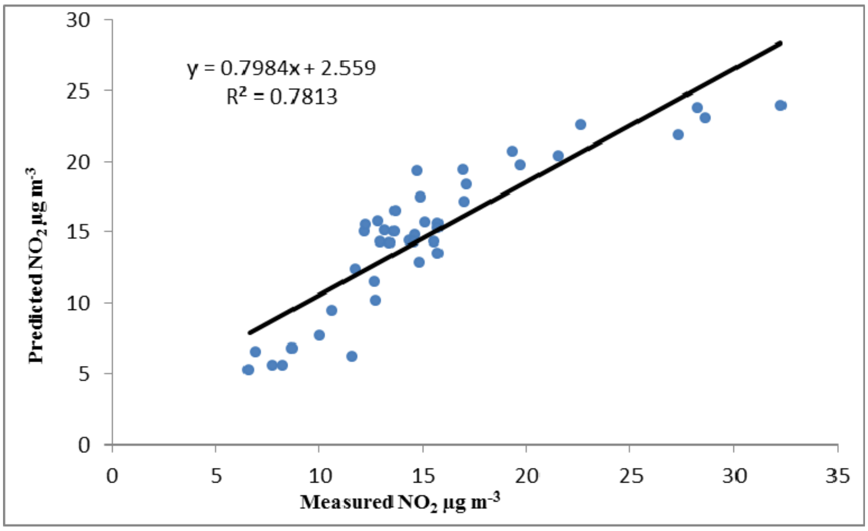

Fig. 2. *Relationship between ambient concentrations of NO_2 predicted using the Gaussian model in AIRVIRO and measured by Ogawa passive samplers*

Table 1. *Crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI) for preterm birth by trimester specific and entire pregnancy NO_2 exposure*

NO_2 exposure tertiles	Preterm birth (<37 weeks)		Control (>37 weeks)		Crude odds ratio OR (95 % CI)	Adjusted* odds ratio OR (95 % CI)
	N	%	N	%		
Entire pregnancy						
1st tertile (6.4-18.7 µg m^{-3})	62	5.5	1061	94.5	1	1
2nd tertile (18.7-23.7 µg m^{-3})	57	5.3	1026	94.7	0.95 (0.66-1.38)	0.95 (0.66-1.39)
3rd tertile (23.7-44.3 µg m^{-3})	68	6.3	1018	93.7	1.14 (0.80-1.63)	1.16 (0.81-1.66)
Continuous variable (per 10 µg m^{-3} increase in concentration)	-	-	-	-	1.06 (0.83-1.34)	1.06 (0.84-1.35)
First trimester						
1st tertile (5.3-16.7 µg m^{-3})	63	5.5	1081	94.5	1	1
2nd tertile (16.7-24.0 µg m^{-3})	56	5.2	1020	94.8	0.94 (0.65-1.36)	0.95 (0.65-1.38)
3rd tertile (24.0-53.2 µg m^{-3})	68	6.3	1004	93.7	1.16 (0.82-1.66)	1.21 (0.84-1.75)
Continuous variable (per 10 µg m^{-3} increase in concentration)	-	-	-	-	1.03 (0.86-1.23)	1.04 (0.87-1.26)
Second trimester						
1st tertile (5.3-16.7 µg m^{-3})	58	5.2	1051	94.8	1	1
2nd tertile (16.7-24.5 µg m^{-3})	63	5.7	1052	94.3	1.09 (0.75-1.57)	1.10 (0.70-1.60)
3rd tertile (24.5-53.2 µg m^{-3})	66	6.2	1002	93.8	1.19 (0.83-1.72)	1.22 (0.84-1.76)
Continuous variable (per 10 µg m^{-3} increase in concentration)	-	-	-	-	1.07 (0.89-1.26)	1.07 (0.89-1.27)
Third trimester						
1st tertile (5.3-16.7 µg m^{-3})	66	5.8	1068	94.2	1	1
2nd tertile (16.7-24.2 µg m^{-3})	64	5.8	1041	94.2	1.00 (0.70-1.42)	1.01 (0.70-1.44)
3rd tertile (24.2-51.9 µg m^{-3})	57	5.4	996	94.6	0.93 (0.64-1.20)	0.92 (0.63-1.33)
Continuous variable (per 10 µg m^{-3} increase in concentration)	-	-	-	-	1.01 (0.85-1.20)	1.00 (0.84-1.20)

***** *maternal smoking, education, family status, renal diseases, diabetes, parity, previous preterm birth, stress, and birth year*

Correlation between ambient NO_2 concentrations predicted by using the Gaussian model in AIRVIRO and Ogawa diffusion tubes was high, r = 0.884 (Figure 2). Linear regression analysis on the relationship between the two concentrations revealed that 78 % of variance was accounted for. Differences between predicted and measured NO_2 concentrations ranged between 0.4 and 46 % with an average difference of 14 % calculated from all 41 monitoring sites. Discrepancies between predicted and measured concentrations were more pronounced when ambient NO_2 concentrations were higher.

In crude and adjusted analyses, we found statistically non-significant positive associations between preterm birth and NO_2 levels during the entire pregnancy and during the three trimesters of pregnancy (Table 1). Fully adjusted models by trimesters revealed that none of those associations reached statistical significance. After adjustment for confounding variables (maternal smoking, education, family status, renal diseases, diabetes, parity, previous preterm birth, stress, and birth year) the strongest relation was in the first and in the second trimesters of pregnancy. The OR for preterm birth among women exposed to third tertile NO_2 during the first trimester was 1.21 (95 % CI 0.84–1.75) and 1.22 (95 % CI 0.84–1.76) for the second trimester, respectively, to compare to the first NO_2 exposure tertile. During the third pregnancy trimester the second NO_2 exposure tertile was associated with OR 1.01 (95 % CI 0.70–1.44) and the third NO_2 tertile OR was 0.92 (95 % CI 0.63–1.33), compared to the lowest NO_2 exposure.

Using a continuous measure, we estimated that the risk of preterm birth for entire pregnancy tended to increase by 6 % (adjusted OR = 1.06; 95% CI 0.84–1.35) per 10 µg m^{-3} increase in NO_2 concentrations. There was no statistically significant association between preterm birth and exposure. An analysis of specific exposures by trimester also revealed a slightly increased risk of preterm birth associated with NO_2 exposure in the second trimester (adjusted OR = 1.07; 95 % CI 0.89–1.27). We found no such effect for any other trimester of gestation.

4. Discussion

The results of the study have shown that the dispersion air quality modelling system AIRVIRO is a useful tool to establish individual NO_2 exposure to a large population sample. Ambient NO_2 concentrations predicted by AIRVIRO well correlated with the outdoor levels established by Ogawa diffusion tubes (r = 0.7813) and are good predictors of individual exposure.

Our findings provide little support to the hypothesis of an adverse effect of maternal exposure to NO_2 during pregnancy on preterm birth. NO_2 exposure during the entire pregnancy and during the three trimesters of pregnancy tended to be associated with an increase in risk of preterm birth after adjustment for the main possible confounders: maternal smoking, education, family status, renal diseases, diabetes, parity, previous preterm birth, stress, and birth year. In this study we were able to estimate individual exposure during pregnancy trimesters. We also have possibility to control for effect of change residence during pregnancy. Adjusted odds ratios for second trimester was found to be 1.22, 95 % CI 0.84–1.76. The risk of preterm birth increased by 7% (adjusted OR = 1.07, 95% CI 0.89–1.27) per 10 µg m^{-3} increase in NO_2 concentrations.

A limited statistical power of the study may be associated with a low prevalence of preterm birth in our cohort (5.7 %) and also be a consequence of the low NO_2 exposure level, since only a low percentage of pregnant women were exposed to the levels exceeding the established limit value of the annual mean NO_2 concentration (40 µg m^{-3}).

Results of the study confirm the data of epidemiological studies performed in other countries. The reported NO_2 effect on preterm birth was small with odds ratios in the range 1.1–1.2 per 10 µg m^{-3} increase in NO_2 levels or no effect was found (Gehring et al. 2011; Liu et al. 2003; Hansen et al. 2006; Jalaludin et al. 2007; Ritz et al. 2007). Association of NO_2 exposure and increased risk of preterm birth was reported during first trimester (Lee et al. 2003), first and second trimesters (Jalaludin et al. 2007), first and third trimesters (Bobak 2000). A study in Valencia, Spain, says that the highest association between NO_2 levels during pregnancy and preterm birth was found in second trimester (1.11, 95 % CI 1.03–1.21) (Llop et al. 2010).

Our data are consistent with the findings of a cohort study in Vancouver, Canada, where the association between preterm birth and NO_2 concentrations was found during different periods of pregnancy (Liu et al. 2003).

In our previous study we found a moderately increased premature birth risk for NO_2 exposures estimated at the entire residential district level (Maroziene and Grazuleviciene 2002). Adjusted ORs of preterm birth for the medium and high NO_2 tertile exposures were OR = 1.14 (95% CI 0.77–1.68) and OR = 1.68 (95% CI 1.15–2.46), respectively. Using a continuous measure, the risk of preterm birth increased by 25% (adjusted OR = 1.25, 95% CI 1.07–1.46) per 10 µg m^{-3} increase in NO_2 concentrations. An analysis by trimester showed that increased odds ratios were associated with a first-trimester exposure. However, there were no significant relationships in other pregnancy periods between preterm birth and exposure to NO_2.

Some researchers suppose that the highest vulnerability for exposure to air pollution during pregnancy is in the first and in third trimesters, depending on birth outcome (Hansen et al. 2006; Leem et al. 2006; Ritz et al. 2007). Women whose pregnancy started in winter, when air pollution levels are higher, were more likely to have higher exposures in first trimester compared to other seasons. Therefore the exposure assessment should take into account the spatial and temporal variability of air pollution levels.

Although the effects of unmeasured risk factors could not be excluded with certainty, our findings suggest that there may be a relationship between maternal exposure to ambient NO_2 exposure and the risk of preterm birth.

5. Conclusions

1. There was a tendency towards an increased risk of preterm birth with increasing ambient air NO_2 exposure.
2. An analysis of NO_2 exposure by trimesters showed that strongest exposure of NO_2 and preterm birth risk relation was in the first and in the second trimesters of pregnancy.
3. Maternal exposure to NO_2 may adversely affect the risk of preterm birth, even when residential air pollution does not exceed the limit value. The risk of preterm birth tends to increase by 6% (adjusted OR = 1.06, 95 % CI 0.84–1.35) per 10 $\mu g\ m^{-3}$ increase in NO_2 concentrations.

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Individuali ekspozicija azoto dioksidu ir priešlaikinio gimdymo rizika Kaune

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Šiame straipsnyje nagrinėjamas ryšys tarp individualios nėščių moterų ekspozicijos azoto dioksidu (NO_2) ir priešlaikinio gimdymo rizikos. Epidemiologinio tyrimo tikslas – nustatyti ryšį tarp gyvenamosios vietos oro taršos NO_2 ir priešlaikinio gimdymo rizikos. Ryšiui nustatyti atliktas atvejis – kontrolė-tyrimas, kuris apėmė visus 2008–2009 m. Kaune gimusius vienavaisius naujagimius. Atvejų grupę sudarė 187 naujagimiai, gimę iki 37 nėštumo savaitės, o kontrolinę – 3100 laiku gimę vienavaisiai naujagimiai. Informacija apie potencialius priešlaikinio gimdymo rizikos veiksnius surinkta apklausus motinas. Individualiai ekspozicijai NO_2 nustatyti buvo geokoduoti moterų adresai, kurie susieti su sumodeliuota tos vietos NO_2 koncentracija. NO_2 sklaida sumodeliuota naudojant AIRVIRO programą. Naudojant daugiaveiksnę logistinę regresiją, apskaičiuota standartizuota santykinė priešlaikinio gimdymo rizika tarp skirtingos ekspozicijos veikiamų ir neveikiamų motinų viso nėštumo metu ir atskirais trimestrais (galimybių santykis, GS), taip pat 95 % pasikliautinieji intervalai (PI). NO_2 gyvenamojoje aplinkoje didino priešlaikinio gimdymo riziką. Ši rizika buvo didesnė, kai nėščios moterys pirmame ir antrame nėštumo trimestruose gyveno didesnėje – 24,0–53,2 μg m^{-3} – azoto dioksido koncentracijos zonoje, GS 1,21, 95% PI 0,84–1,75 ir 1,22, 95% PI 0,84–1,76, atitinkamai. Remiantis gautų rezultatų duomenimis, priešlaikinio gimdymo riziką gali didinti leistinų higienos normų neviršijanti oro tarša NO_2 gyvenamojoje aplinkoje.

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