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Exposures to Air Pollution and Risk of Acute-Onset Placental Abruptio: A Case-Crossover Study

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Abstract

Background—Despite abruptio's elusive etiology, knowledge of triggers that precede it by just a few days prior to delivery may help to understand the underpinnings of this acute obstetrical complication. We examine whether air pollution exposures immediately preceding delivery are associated with acute-onset abruptions.

Methods—We applied a bi-directional, time-stratified, case–crossover design to births with an abruptio diagnosis in New York City, 2008–2014. We measured ambient fine particles (PM_{2.5}), and nitrogen dioxide (NO₂). We fit distributed lag nonlinear models based on conditional logistic regression to evaluate individual exposure and cumulative exposures over lags 0–7 days before abruptio, adjusted for temperature and relative humidity (similar lags to the main exposures).

Results—We identified 1,190 abruptio cases. We observed increased odds of abruptio for exposure to PM_{2.5} (per 10 µg/m³) on lag day 3 (odds ratio [OR] 1.19, 95% confidence interval [CI] 0.98–1.43), lag day 4 (OR 1.21, 95% CI 1.01–1.46), and lag day 5 (OR 1.17, 95% CI

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Availability of data

Since data for the project were obtained from the New York City Department of Health and Mental Hygiene (NYCDHMH) with patient identifiers use of the data is governed by a signed data use agreement between NYCDHMH and Columbia University, NY. The agreement precludes sharing or release of data.

1.03-1.33). Similarly, the odds of abruption increased with exposure to NO₂ (per 5 ppb) on lag day 3 (OR 1.16, 95% CI 0.98-1.37), lag day 4 (OR 1.19, 95% CI 1.02-1.39), and lag day 5 (OR 1.16, 95% CI 1.05-1.27). Exposures to PM_{2.5}, and NO₂ at other lags, or cumulative exposures, were not associated with abruption of acute onset.

Conclusions—This case–crossover study showed evidence of an association between short-term ambient air pollution exposures and increased abruption risk of acute onset.

Keywords

Placental abruption; Particulate matter; Nitrogen dioxide; Case-crossover design; Distributed lag models; Nonlinear models

Introduction

Placental abruption, the premature separation of the placenta prior to delivery, is a life-threatening condition to the fetus. Abruption complicates about 1 in 100 to 120 deliveries, is frequently implicated in serious maternal and perinatal complications,¹ and is associated with maternal and infant premature cardiovascular morbidity and mortality later in life.²⁻⁴ Pregnancies diagnosed with abruption end, on average, 3-4 weeks earlier than other uncomplicated pregnancies,⁵ with over half of abruption births resulting in preterm deliveries.⁶⁻⁸ Perinatal mortality rates are 10-fold higher among pregnancies complicated by abruption.⁸ Research on abruption has yet to uncover the etiology of this serious obstetric complication.

Traditionally regarded as an obstetric complication with acute etiology, placental abruption may be characterized as occurring on two distinct pathways:⁹ (i) an acute process stemming from an “excessive or premature placental detachment” pathway (abruption with an “acute onset”), implicated in up to a fourth of all abruption cases;¹⁰⁻¹² and (ii) a chronic process as the consequence of “inadequate placental attachment” pathway (chronic abruption). Virtually all studies have examined risk factors for abruption as a chronic process, but risk factors for acute abruption remain unknown.

Exposures to fine particulate matter (PM_{2.5}; particles with aerodynamic diameter ≤ 2.5 μm), some of its constituents (nickel, zinc, iron, and black carbon), and other gaseous pollutants, including nitrogen dioxide (NO₂), and ozone (O₃), have been linked with preeclampsia,¹³⁻¹⁵ small for gestational age (SGA) birth, gestational diabetes, and preterm delivery.¹⁶⁻¹⁸ Since exposure to air pollutants are linked with increased inflammation, oxidative stress, and hemostasis – etiologies implicated with abruption^{19,20} — it is plausible that air pollution may be associated with increased risk of abruption. However, the extent to which these air pollutants are associated with abruption that has an acute underpinning remain poorly characterized.

We hypothesize that exposure to air pollution prior to and at the time of labor and delivery is associated with placental abruption of acute onset. We tested this hypothesis in a case–crossover study of pregnancies diagnosed with abruption in New York City. If an association

between air pollution and abruption is present, it would provide important clues as to how premature placental separation is triggered.

Methods

We employed a bi-directional, time-stratified, case–crossover design²¹ to examine the associations between exposure to PM_{2.5} and NO₂ and the risk of abruptions of acute onset. We utilized linked birth records and maternal and newborn hospitalization data in New York City (NYC) from December 2008 to December 2014. Data on NYC births were linked to corresponding maternal and newborn hospitalizations and hospital discharge data files. This linkage was provided by the New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS).²² We obtained ethics approval from the Institutional Review Board of Columbia University Medical Center, as well as approvals from the NYC vital statistics data and SPARCS systems.

Air pollution and exposure assessment

We developed spatio-temporal air pollution exposure models using two sources of air pollution: the New York City Community Air Survey (NYCCAS) data provided directly from New York City Department of Health and Mental Hygiene staff and regulatory data from the Environmental Protection Agency's Air Quality System (AQS) (https://aqsdrl.epa.gov/aqsweb/aqstmp/airdata/download_files.html, accessed 2 Nov 2015). NYCCAS data were collected at 60–150 locations. The number of locations varied depending on the year and at each site 2-week integrated average samples were collected for each of the four seasons. The 2-week averages were converted to daily measurements by repeating the 2-week value for each day. In order to capture true daily air quality variation in the models, we also included daily data from Department of Environmental Conservation's regulatory monitors which collect data on an every-day or every-third-day schedule. Detailed temporal patterns were captured using data from the Environmental Protection Agency (EPA) regulatory monitors, which collect data on an every-day or every-third-day schedule. Depending on the year, there were between 16–23 regulatory monitors for PM_{2.5}, and three to four monitors for NO₂. Exposure assignment was based on model predictions at maternal residences at the time of delivery.

We computed the amount/density of candidate spatial predictors such as traffic and land use-related variables (derived from the New York City Department of City Planning's taxlot database) within 4 different buffer areas around each monitor site: 100, 300, 500 and 1000 meters.²³ We also included several temporal predictors and computed daily city-wide averages. These include temperature, relative humidity, and wind speed. In addition, we computed the mixing depth and air-mass trajectory for each day.

We split the data into training and testing data sets with an 80%–20% split. We used 10-fold cross validation in model building on the training set and resulting root mean square error (RMSE) and R² values to identify the strongest model. We found that gradient boosting machine models were the best fitting models for both PM_{2.5} and NO₂. For PM_{2.5}, the cross validation R² was 79% (RMSE 2.24 µg/m³). The most influential temporal variables were the day of the study period, day of the year and maximum temperature. The most influential

spatial variables were the amount tree canopy, boiler British thermal unit (BTU) capacity, and building area. When the model was applied to the testing dataset, the overall R^2 was 74% (RMSE 2.38 $\mu\text{g}/\text{m}^3$). For NO_2 , the cross-validation R^2 was 78% (RMSE 4.53 ppb). The most predictive spatial variables were building area, number of natural gas permits, and truck traffic. The strongest temporal variables were day of the study period, day of the year, and minimum temperature. When the model was applied to the testing dataset the overall R^2 was 69% (RMSE 4.51 ppb).

Placental abruption

We relied on two sources to identify women diagnosed with abruption. The first was from the birth certificate data, which is based on a diagnosis of the complication by the attendant at delivery. The second was the maternal and newborn hospital delivery and discharge records, where conditions are coded based on the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) discharge diagnoses. We used the ICD-9-CM code of 641.2 to identify cases of abruption. The sensitivity and positive predictive values for abruption are 63% and 82%, respectively, in the combined birth records and hospital discharge data validated against obstetrical charts.²⁴ To avoid the inclusion of false-positive abruption cases, we defined abruption with a listed diagnosis on both of the sources.

Study population

Of a total of 720,743 live births to residents in NYC between December 2008 and December 2014, we sequentially excluded the following: multiple births ($n=22,379$), non-abruption pregnancies ($n=692,394$), abruption cases with missing data on air pollution exposures ($n=3$), and abruption cases with either a hospital discharge or birth records diagnosis but not both ($n=4,776$). After exclusions, 1,190 pregnancies with an abruption diagnosis remained.

Statistical analysis

We employed a case–crossover design, where each case acts as their own control, thus eliminating time-invariant confounding by any personal characteristics (e.g., maternal age, parity) that are stable over short follow-up periods.²¹ The association between the exposure and the outcome is then assessed by comparing the distribution of exposures on the days when the case occurred versus the days when the subject did not experience the outcome (control days). The control days were chosen bi-directionally and matched on the same day of the week for all non-case weeks in the same month and year as the case day. We chose control days bi-directionally (i.e., from both before and after each case's occurrence date), matching on the same year, month, and day of week (time stratified approach).²⁵ In doing so, we avoided confounding due to day-to-day correlation of the environmental exposures,²⁶ and limited confounding by seasonality, long-term trends, and any potential confounding by day of week.²⁷

Since the exact time of abruption is unknown, and it is likely that the initiation of premature placental separation process may take several hours prior to delivery, we defined a case day as one day before delivery, as previously defined.²⁸ We fit conditional logistic regression models, with the case and control days for each event as the matched sets, and adjusted for temperature (lags 0-7) and relative humidity (lags 0-7) using natural cubic splines with three

knots. We assessed associations for the case day (lag 0) and for lags 1-7 to explore the effects of lag response.

Associations between air pollution and abortion were assessed using distributed lag nonlinear models (DLNM).²⁹ The DLNM framework allows examination of the effect at each lag from 0-7 days with adjustment for exposures at the other lags, assuming that it varies smoothly as a function of time before the event. We modeled this smooth function using natural splines with 4 degrees of freedom (df).²⁹ From these DLNMs, we extracted the estimated individual lag effect estimates (i.e., lag 0, lag 1, lag 2, etc.), and the cumulative effect estimates of air pollutant exposures at lags 0-1, lags 0-2, lags 0-3, ..., lag 0-7. The lag-specific effect estimates can be interpreted as the contribution of exposure experiences at times prior to the event (i.e., the different lags) to the risk of event. The overall cumulative association can be interpreted as the risk associated with the entire exposure history experienced within the considered lag period. Lagged temperature and relative humidity (similar to PM_{2.5} and NO₂ analysis; described above) were also adjusted in the models to account for potential residual confounding by weather, using natural cubic splines with 4-df for temperature and a linear function for relative humidity. For a particular lag time in a given analysis, that same lag time was applied to exposure status, temperature, and relative humidity. We assessed the assumption of a linear exposure-response curve including natural splines in the model. We used the Akaike Information Criterion to select the best fitting model, i.e., linear versus nonlinear. Since temperature and ambient fine particle concentrations differed by season,³⁰ we ran stratified analyses by season: warm season (April to September) and cold season (October to March).

Finally, we also explored two-pollutant models using regular conditional logistic regression, including both PM_{2.5} and NO₂, to account for potential co-pollutant confounding and to obtain independent traffic- and non-traffic-related effect associations with acute abortions. These models were also adjusted for temperature and relative humidity as described above.

Sensitivity analysis

Since the intent of this analysis was to examine if air pollution was associated with abortions of acute onset, we excluded pregnancies with a diagnosis of obstetrical complications suggestive of long-standing pathology (i.e., chronic complications) or exposure to smoking during pregnancy. To accomplish this, women diagnosed with preeclampsia, smokers, or those that delivered an SGA infant were excluded.

Missing data

Missing data was uncommon. In the abortion case and control days, data on relative humidity was missing for 1 (0.08%) and 15 (0.4%) pregnancies, respectively. Owing to the very small number of missing data, we undertook a complete case analysis.

We used Pearson's correlation coefficients to evaluate the correlation between air pollutants and weather conditions (temperature and relative humidity) at the same day as well as the correlation of same air pollutant at different lag days. For statistical analyses, we used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and R Studio, version 3.4.2 (Foundation for Statistical Computing, Vienna, Austria) with "dlm" package (version 2.1.3).³¹

Results

We identified 1,190 abruption cases. Of these, 25% of women were aged 35 or older; 33% were African-Americans, 26% were Caucasians, 28% were Hispanics, and 13% were of other race/ethnicity; 4.5% smoked during pregnancy; and 60% were Medicaid enrollees, while 5% were diagnosed with chronic hypertension. Almost two-thirds (63%) of women with a diagnosis of abruption were delivered by cesarean, 12% had preeclampsia, and 16.9% of births were SGA (birthweight <10 percentile for gestational age). The mean (standard deviation) gestational age at delivery was 34.8 (4.4) weeks. The stillbirth rate was 32 per 1000 births. We also compared maternal and infant characteristics across three abruption diagnosis groups: abruption cases identified from either birth certificates or hospital discharges (n=5,966), cases identified from both birth certificates and hospital discharges (n=1,190), and cases excluded from the study (n=4,776). While these analyses show that the distribution of maternal and infant characteristics was fairly similar between women included and excluded from the analysis for most variables, the proportion of Medicaid enrollees were higher in the excluded versus the analyzed sample (56.6% and 61.6%, respectively) and cesarean delivery were higher in the included than in the excluded sample (72.3% and 60.2%, respectively; eTable 1).

The distribution of air pollution at lag 0 day for abruption case-days and matched control-days are shown in Table 1. The Pearson's correlation coefficients amongst these exposures (at lag 0) are shown in Table 2. We observed a positive correlation between PM_{2.5} and NO₂ (r=0.48), and a negative correlation between NO₂ and average daily temperature (r=-0.52). Some of these correlations were different between warm and cold seasons (eTable 2). For instance, the correlation between PM_{2.5} and NO₂ was stronger in cold (r=0.63) than warm seasons (r=0.30). Further, the correlation between PM_{2.5} and average daily temperature was positive in the warm season (r=0.49) but not in the cold season (r=-0.37). The correlation matrix for both PM_{2.5} and NO₂ across lag days 0-7 is shown in eTable 3.

We fit models adjusted for temperature and relative humidity to examine the association between exposure to air pollution at each lag and abruption. We found no evidence for non-linearity based on the Akaike Information Criterion and likelihood ratio tests, and thus we retained the linear terms for PM_{2.5}, NO₂, and relative humidity in the final models, while the daily mean temperature was fit with a natural cubic spline with 4 degrees of freedom. Increased odds of abruption were evident among women exposed to higher levels of PM_{2.5} (per 10 µg/m³) on lag day 3 (OR 1.19, 95% CI 0.98-1.43), lag day 4 (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.01-1.46), and lag day 5 (OR 1.17, 95% CI 1.03-1.33) (Figure 1), with the associations seen in the cold season. Similarly, we observed increased odds of abruption for women exposed to NO₂ (per 5 ppb) on lag day 3 (OR 1.16, 95% CI 0.98-1.37), lag days 4 (OR 1.19, 95% CI 1.02-1.39), and lag day 5 (OR 1.16, 95% CI 1.05-1.27) (Figure 2); again, these associations were observed only in the cold season, although the confidence intervals overlapped between the warm and cold seasons. In contrast, NO₂ exposure (per 5 ppb) on lag day 0 was associated with reduced odds of abruption (OR 0.74, 95% CI 0.54-1.02). We did not observe associations between cumulative exposures to PM_{2.5}, and NO₂ and abruption (Table 3).

Results from the analyses of co-pollutant models (Table 4) indicated that after adjusting for NO₂, there was no association between exposure to PM_{2.5} and the odds of abruption. However, after accounting for PM_{2.5}, NO₂ exposure at lag day 4 (OR 1.30, 95% CI 1.01-1.67), lag day 6 (OR 1.32, 95% CI 1.03-1.70), and lag day 7 (OR 1.28, 95% CI 1.01-1.65) was associated with abruption.

Sensitivity analysis

We undertook a sensitivity analysis after excluding women diagnosed with preeclampsia, those who delivered an SGA infant, or women who smoked during pregnancy. This analysis showed that exposure to PM_{2.5} and NO₂ were associated with higher odds of abruption at lag days 4-5 for the individual pollutant models, and these associations were restricted to the cold season (eTable 4). No associations were seen in the cumulative exposure models (eTable 5). In the co-pollutant models (eTable 6), there was a trend toward higher odds of abruption for NO₂ exposure (adjusted for PM_{2.5}) on lag days 4-6 in the cold season.

Discussion

The ubiquity of air pollution exposures, their potential harmful effects on humans, in general, and their associations with an array of adverse maternal and perinatal outcomes, in particular, makes the study of these exposures in relation to abruption important. We hypothesized that exposures to PM_{2.5} and NO₂ around critical exposure windows during labor and delivery may be associated with increased risk of abruptions of acute onset. This hypothesis rests on the notion that abruption is an obstetrical complication with an acute etiology.³² This bi-directional, time-stratified case–crossover study supports our hypothesis, and shows that exposures to PM_{2.5}, and NO₂ 4-6 days (lag days 3-5) prior to delivery were associated with increased odds of abruption of acute onset. These associations persisted after excluding pregnancies diagnosed with preeclampsia, SGA, and maternal smoking. However, we did not observe any effect measure modification of the associations by season.

In a case–crossover analysis of 726 abruption cases, Michikawa and colleagues²⁸ reported a temperature-adjusted odds ratio of 1.4 (95% CI 1.1-1.8) for a 2-day lag in NO₂ exposure. They argued that premature rupture of membranes, a condition indicative of acute inflammation, was associated with abruption, and increased risk of such abruption was observed after 24 hours of membrane rupture.²⁸ We found increased odds of abruption among women exposed to NO₂ at exposure lags 3-5 days. The median NO₂ exposure in the Japanese study was 9.0 ppb (interquartile range [IQR] 4.8-15.0). This exposure level is much lower than that of NO₂ in NYC (median 21.9 ppb, IQR 17.4-25.6). We also found increased odds of abruption among women exposed to PM_{2.5} on lag days 3-5 during the cold season. This latter finding is in sharp contrast to those of the Japanese data that reported no association between PM_{2.5} and abruption risk; it is likely that the composition of PM in Japan is very different from that in NYC.²⁸ In addition, in a model including both NO₂ and PM_{2.5}, only the estimates for NO₂ remained associated with abruption. We interpret NO₂ in these analyses as a tracer of traffic emissions; these results indicate that traffic-related air pollution seems to be especially toxic for risk of abruption of acute onset.

We examined whether season might be an effect modifier of the associations between air pollution and abruption, given that the air pollution mixture composition is known to vary across seasons,^{33,34} as was also apparent in the observed correlations across pollutants in the warm versus the cold season in NYC during the study period. Nonetheless, there was no evidence that season modified the association between PM_{2.5} or NO₂ and abruption.

Exposures to PM_{2.5} and other air pollutants have been linked to inflammation, and oxidative stress in the vascular and hemostatic systems, potentially leading to increased risks of stillbirth,^{35,36} preterm delivery,³⁷ and intrauterine growth restriction.³⁸ However, the associations of air pollution with preeclampsia and gestational hypertension remain equivocal.^{13,15} Along with preeclampsia and SGA births, abruption has been classified as one of three clinical manifestations in the syndrome of “ischemic placental disease”.^{39,40} Inadequate trophoblast invasion of the spiral arteries, endothelial cell dysfunction, and oxidative stress at the maternal–fetal interface are the chief pathophysiologic mechanisms that result in inflammation and uteroplacental ischemia leading to abruption.³² In addition, maternal distance to major road has been associated with changes in DNA methylation in the placenta.⁴¹ PM_{2.5} has also been associated with changes in placental expression of imprinted genes.⁴² Given the seemingly similar pathophysiologic mechanisms through which air pollution may be associated with increased risks of cardiovascular disease, and other adverse pregnancy outcomes, it is plausible that these pollutants may trigger hypoxic-ischemic injury to the placenta,³⁶ leading to an abruption.

Despite abruption being classically regarded as an “acute event”, histologic lesions in the placenta, cord and membranes is implicated in a fourth of abruption cases.¹¹ We designed this bi-directional case–crossover analysis to examine air pollution exposures within a week of delivery in an attempt to evaluate the extent to which such exposures may result in abruptions of acute onset. Even after excluding pregnancies with a diagnosis of preeclampsia, SGA, and women that smoked – all associated with chronic abruptions – the overall associations still persisted. However, it is difficult, if not impossible, to separate abruptions with a true acute onset versus those that bear a chronic underpinning. We therefore urge caution that these findings should not be interpreted as providing clues to abruption etiology.

Limitations of the data

Important limitations must be considered when interpreting these findings. Exposure measurement error is possible given that exposure assignment was based on model predictions at residences at the time of delivery, and no information was available on daily activity patterns and time spent in and away from residence. However, any measurement error would likely be non-differential. There is also no reason to believe that there will be more (or less) exposure measurement error during control versus case days. Any resulting bias, therefore, would likely attenuate the associations toward the null.⁴³ Second, although the predictive ability of the models was very high, some of the input variables were only available as 2-week averages or one every 3 days. This may have induced some further bias toward the null. Third, the proportion of women that were Medicaid enrollees and cesarean

delivery rates were different between the included and excluded abruption cases, which may have resulted in some bias.

Strengths of the study

The study has several strengths. First, linking birth records data with corresponding hospital discharges substantially reduces misclassification of abruption. For a rare outcome such as abruption, it remains important to minimize false-positive diagnosis in the setting of a case–crossover design. Second, residential mobility is not an issue in this study since it is highly unlikely that women moved in the week prior to their delivery. Third, if 75% of the abruptions were of chronic origin,^{10–12} which would not be associated with acute exposure, that would be expected to attenuate the association with air pollutants. Fourth, exposure predictions were based on state-of-the-art modeling methods with characterization of air pollution modeled through non-parametric smoothing methods with high spatial resolution and strong predictive ability. Fifth, women who deliver in New York City are very diverse, and the study affords generalizability of findings.

Conclusions

In this bi-directional, time-stratified, case–crossover study of abruption of acute onset in New York City, we found associations between PM_{2.5} and NO₂ exposures and abruption risk on lag days 4–5. Corroboration of these findings in larger, geographically diverse populations with well-characterized air pollution exposures and refined diagnosis of abruption may be worthy of future investigations. In addition, efforts to understand the source and patterns of pollutants, and policies designed to curb such exposures will have beneficial and lasting impact on human health globally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Association between $PM_{2.5}$ at lags 0-7 days with case-day defined as the day prior to delivery and placental abruption of acute onset from distributed lag nonlinear models: Case-crossover analysis of singleton live births in New York City, 2008-2014. CI indicates confidence interval.

Figure 2.

Association between NO₂ at lags 0-7 days with case-day defined as the day prior to delivery and placental abruption of acute onset from distributed lag nonlinear models: Case–crossover analysis of singleton live births in New York City, 2008-2014. CI indicates confidence interval.

Table 1

Distribution of air pollutants and weather conditions among placental abruption on lag day 0 (with case-day defined as the day prior to delivery): Case-crossover analysis of singleton live births in New York City, 2008-2014

	Number of births	Mean (standard deviation)	Percentile distributions						
			5	10	25	50	75	90	95
Abrupton case days									
PM _{2.5} (µg/m ³)	1,190	10.1 (2.8)	6.5	7.1	8.1	9.6	11.6	14.3	15.5
NO ₂ (ppb)	1,190	21.5 (5.9)	11.8	13.8	17.2	22	25.4	29	31.2
Average temperature (°C)	1,190	13.3 (9.4)	-2.3	0.8	5.9	14	21.3	25.1	27.3
Relative humidity (%)	1,189	67.2 (15.8)	42.0	47.1	54.9	66.7	79.6	89.3	93.1
Control days									
PM _{2.5} (µg/m ³)	4,064	10.2 (2.9)	6.6	7.1	8.2	9.7	11.8	14.2	15.8
NO ₂ (ppb)	4,064	21.5 (5.9)	11.8	13.7	17.2	21.8	25.4	28.8	31.1
Average temperature (°C)	4,064	13.5 (9.5)	-2.7	0.6	5.9	14.1	21.7	25.5	27.5
Relative humidity (%)	4,049	67.2 (15.6)	42.8	47.5	55	66.7	79.6	88.5	92.9

Table 2

Pearson's correlation between air pollution and weather conditions among placental abruption of acute onset on lag day 0 (with case-day defined as the day prior to delivery): Case–crossover analysis of singleton live births in New York City, 2008-2014

Exposures	PM _{2.5} (µg/m ³)	NO ₂ (ppb)	Average temp (°C)	Relative humidity (%)
PM _{2.5} (µg/m ³)	1.00	0.48	−0.09	0.01
NO ₂ (ppb)		1.00	−0.52	−0.02
Average temperature (°C)			1.00	0.18
Relative humidity (%)				1.00

Correlations were based on 1,190 abruption case-days and 4,064 control days

Table 3

Adjusted odds ratio of placental abruption of acute onset associated with cumulative lag days with case-day defined as the day prior to delivery for PM_{2.5} and NO₂ based on constrained distributed lag nonlinear models: Case–crossover analysis of singleton live births in New York City, 2008–2014

Cumulative lag-days	Adjusted odds ratio (95% confidence interval) of abruption		
	Overall (1,190 abruption cases)	Season of delivery	
		Warm season (593 abruption cases)	Cold season (597 abruption cases)
Odds ratios per 10 µg/m ³ change in PM _{2.5}			
0	0.77 (0.55, 1.08)	0.93 (0.54, 1.61)	0.67 (0.43, 1.04)
0-1	0.71 (0.44, 1.16)	0.90 (0.40, 2.04)	0.59 (0.30, 1.11)
0-1-2	0.77 (0.46, 1.29)	0.90 (0.38, 2.19)	0.64 (0.33, 1.27)
0-1-2-3	0.91 (0.54, 1.54)	0.92 (0.37, 2.28)	0.82 (0.42, 1.62)
0-1-2-3-4	1.11 (0.64, 1.93)	0.92 (0.35, 2.21)	1.12 (0.55, 2.27)
0-1-2-3-4-5	1.29 (0.73, 2.30)	0.87 (0.31, 2.40)	1.47 (0.70, 3.07)
0-1-2-3-4-5-6	1.40 (0.80, 2.46)	0.77 (0.27, 2.15)	1.78 (0.87, 3.61)
0-1-2-3-4-5-6-7	1.37 (0.75, 2.29)	0.63 (0.20, 1.98)	1.93 (0.93, 4.00)
Odds ratios per 5 ppb change in NO ₂			
0	0.75 (0.58, 0.98)	0.83 (0.51, 1.34)	0.74 (0.54, 1.02)
0-1	0.68 (0.48, 0.97)	0.77 (0.39, 1.52)	0.67 (0.43, 1.03)
0-1-2	0.71 (0.50, 1.01)	0.79 (0.39, 1.56)	0.70 (0.46, 1.06)
0-1-2-3	0.83 (0.60, 1.15)	0.85 (0.43, 1.69)	0.83 (0.57, 1.21)
0-1-2-3-4	0.98 (0.69, 1.40)	0.94 (0.46, 1.94)	1.01 (0.67, 1.52)
0-1-2-3-4-5	1.14 (0.79, 1.65)	1.01 (0.49, 2.12)	1.19 (0.77, 1.84)
0-1-2-3-4-5-6	1.23 (0.90, 1.69)	1.04 (0.54, 2.00)	1.32 (0.91, 1.91)
0-1-2-3-4-5-6-7	1.22 (0.91, 1.62)	1.01 (0.55, 1.86)	1.33 (0.95, 1.86)

Table 4

Adjusted odds ratio of placental abruption of acute onset associated with PM_{2.5} and NO₂ exposures based on co-pollutant analysis from constrained distributed lag nonlinear models with case-day defined as the day prior to delivery: Case–crossover analysis of singleton live births in New York City, 2008-2014

Individual lag-days	Adjusted odds ratio (95% confidence interval) of abruption		
	Overall (1,190 abruption cases)	Season of delivery	
		Warm season (593 abruption cases)	Cold season (597 abruption cases)
Odds ratios per 10 µg/m ³ change in PM _{2.5}			
Lag 0	0.80 (0.51, 1.26)	0.82 (0.41, 1.64)	0.78 (0.43, 1.45)
Lag 1	1.21 (0.78, 1.89)	1.09 (0.54, 2.19)	1.31 (0.73, 2.36)
Lag 2	0.92 (0.60, 1.43)	0.93 (0.48, 1.81)	0.93 (0.51, 1.68)
Lag 3	1.23 (0.81, 1.89)	0.87 (0.45, 1.67)	1.57 (0.88, 2.79)
Lag 4	0.84 (0.55, 1.29)	0.62 (0.31, 1.22)	1.07 (0.61, 1.85)
Lag 5	0.97 (0.62, 1.51)	0.80 (0.41, 1.59)	1.15 (0.63, 2.09)
Lag 6	0.79 (0.51, 1.22)	0.50 (0.25, 0.99)	1.03 (0.58, 1.83)
Lag 7	1.17 (0.76, 1.80)	0.92 (0.47, 1.81)	1.42 (0.79, 2.54)
Odds ratios per 5 ppb change in NO ₂			
Lag 0	0.92 (0.70, 1.19)	0.86 (0.53, 1.39)	0.95 (0.68, 1.31)
Lag 1	0.94 (0.72, 1.22)	0.78 (0.49, 1.27)	0.98 (0.71, 1.35)
Lag 2	1.11 (0.86, 1.42)	0.96 (0.61, 1.52)	1.16 (0.85, 1.59)
Lag 3	1.06 (0.83, 1.36)	0.91 (0.58, 1.44)	1.05 (0.77, 1.44)
Lag 4	1.30 (1.01, 1.67)	1.31 (0.83, 2.05)	1.22 (0.90, 1.66)
Lag 5	1.19 (0.93, 1.54)	1.16 (0.73, 1.84)	1.14 (0.83, 1.56)
Lag 6	1.32 (1.03, 1.70)	1.11 (0.71, 1.72)	1.33 (0.98, 1.82)
Lag 7	1.28 (1.00, 1.65)	1.23 (0.80, 1.91)	1.27 (0.93, 1.75)