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Air pollution and cardiovascular events at labor and delivery: a case-crossover analysis

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Abstract

Purpose—In this case-crossover study, we investigated the odds of having a labor/delivery with cardiovascular event (i.e., ischemic heart disease, stroke, heart failure, cardiac arrest/failure, and other or unspecified cardiovascular events) associated with acute exposure to common air pollutants.

Methods—We selected 680 women with singleton pregnancy and cardiovascular events at labor/delivery from 12 U.S. clinical sites (2002–2008). Exposures to six criteria air pollutants, six particulate constituents, and 26 air toxics were obtained using modified Community Multiscale Air Quality models. Conditional logistic regression models calculated the odds ratio (OR) and 95% confidence intervals (CI) comparing exposures during the day of delivery, the week before delivery, and each of the days of the week before delivery to two control periods before and after.

Results—An interquartile range increase in particulate matter (PM)_{2.5} microns and nitric oxide exposures during the week before delivery was associated with an 11% (OR 1.11, 95% CI: 1.01–1.23) and 21% (OR 1.21, 95% CI: 1.04–1.42) increased cardiovascular events odds, respectively. These pollutants, sulfur dioxide, carbon monoxide, PM₁₀ microns, and some PM constituents showed associations with event odds for days 0, 1, 5, and 6 before delivery. Inverse associations were observed for O₃ and some PM constituents as well as air toxics.

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Conclusions—Cardiovascular events at labor/delivery merit more attention in relation to air pollution.

Keywords

air pollution; cardiovascular events; labor and delivery; pregnancy

Introduction

Cardiovascular disease is the second leading cause of maternal mortality¹ and among the leading causes of severe maternal morbidity in the U.S.² Pregnant women are potentially susceptible to adverse cardiovascular effects of air pollution due to increased cardiovascular demands associated with pregnancy.³ Many studies have linked exposure to ambient air pollution and risk of various cardiovascular outcomes in the general population.^{4–7} However, the potential effects of air pollution on cardiovascular events among pregnant women receive little attention. We recently published the first study estimating the odds of cardiovascular events at labor/delivery associated with air pollution exposure during the week preceding delivery in a multi-site U.S. obstetric cohort.⁸ Although our study population consisted of mainly young and healthy pregnant women, we were concerned about residual chronic confounding, particularly due to genetic susceptibility, underlying health status (especially concerning the cardiovascular system), and other pregnancy-related conditions with potential acute-on-chronic exacerbations, which may have potentially affected our results.⁹ To account for these non-time varying confounding factors, in the present study we examined the associations between acute and recent exposures to air pollutant exposures and odds of having a labor/delivery with cardiovascular events including ischemic heart disease, stroke, heart failure, cardiac arrest/failure, and other or unspecified cardiovascular events, using a case-crossover study design. We hypothesize that higher recent exposure to air pollutants is associated with increased risk of having a labor/delivery affected by cardiovascular events.

Material and Methods

Study design

The case-crossover design assesses the odds of having a labor/delivery with a cardiovascular event during a short “hazard period” after exposure to potential triggers (i.e., air pollution).¹⁰ An important feature of this design is that each woman serves as her own control. The self-matching feature allows complete control for risk factors that are stable over time within a woman but often differ among them. This way, we can hold all time invariant characteristics about a woman and her delivery/event constant to assess the impact of varying air pollution exposure. Thus, any difference in risk detected after controlling for other varying environmental exposures can be reasonably attributed to a specific air pollutant.

Participants and data

Our participants were from the Consortium on Safe Labor (2002–2008), an observational cohort of 228,438 deliveries at 23 weeks gestation from 12 clinical centers (15 hospital referral regions) across the U.S. with clinical data collected from the electronic medical records¹¹. The study was approved by the institutional review boards of all participating

centers. Informed consent was not required because data were anonymous. Initially eligible for the current study were 686 (0.3%) singleton pregnancies that were complicated by cardiovascular events at labor/delivery. After excluding six pregnancies (0.87%) among women who had a repeated event in a second pregnancy, the final study population consisted of 680 singleton pregnancies with labor/delivery affected by cardiovascular events including ischemic heart disease, stroke, heart failure, cardiac arrest/failure, and other or unspecified cardiovascular events.

Exposure assessment

Daily concentrations of air pollutants were estimated using modified Community Multiscale Air Quality (CMAQ) models, which estimated air pollution levels based on inputs from several sources: local emissions obtained from the National Emission Inventories, local weather obtained from the Weather Research and Forecasting model, and photochemical properties of pollutants.¹² Criteria air pollutant concentrations were fused with observed levels at local air monitors to correct for measurement errors using inverse distance weighting, and weighted by population density to improve accuracy.¹² Due to the lack of routine measurements at monitoring stations, air toxics concentrations were not fused and raw data estimated from CMAQ were used. Model evaluation showed improved accuracy for all pollutants and has been previously published.¹² Average exposures were calculated for the 15 hospital referral regions after weighting for population density as a surrogate for residence and local mobility of the participants. Daily exposures were estimated for six criteria air pollutants including carbon monoxide (CO), ozone (O₃), nitric oxides (NO_x), particulate matter with an aerodynamic diameter 2.5 and 10 microns (PM_{2.5} and PM₁₀), sulfur dioxide (SO₂); six PM_{2.5} constituents including elemental carbon, organic compounds, ammonium ions, sulfate particles, nitrate particles, and dust particles; and 26 air toxics including 12 polycyclic aromatic hydrocarbons (PAHs) and 14 volatile organic compounds (VOCs).

Average daily concentrations of pollutants were obtained for the hazard period: the week preceding delivery (lag07), day of delivery (lag 0), and each of the seven days before delivery (lag1-lag7). The week before delivery and the day of delivery were chosen as the hazard period given existing evidence on the potential acute effects of air pollution on cardiovascular risk among the non-pregnant population.^{13,14}

Using CMAQ outputs, we also obtained average pollution concentrations for two control periods: the second week after delivery and the week two full gestational weeks before delivery. Post-event control period may seem counterintuitive because the person is no longer at risk. However, studies have shown that the bidirectional control selection method we use is preferred over the unidirectional method (i.e., selecting control periods only before the event), which is sensitive to time trend bias.^{15,16} In our case, the control periods were chosen relatively close to delivery, so that the pollutant levels were unlikely to be affected by the seasonal variation.

Outcome assessment

Our primary outcome of interest was any labor/delivery with cardiovascular event consisting of ischemic heart disease, stroke, heart failure, cardiac arrest/failure, and other or unspecified cardiovascular events. These outcomes were identified from the labor/delivery discharge summary using the International Classification of Disease, 9th version (ICD-9) codes (Supplemental Table 1).

Statistical analysis

The “event” under study was the joint occurrence of labor/delivery with a cardiovascular event such that all non-time varying factors are held constant. The analysis for a case-crossover design follows standard procedures for stratified data analysis where each woman represents a stratum. For each woman, we compared a hazard period (lag0 – lag7 and the week preceding delivery) to two alternative control periods before and after the event. We tested whether the women who had a labor/delivery with a cardiovascular event had higher exposure to air pollutants during the case (hazard) periods compared to the control periods while holding everything else about their delivery and time-invariant characteristics constant. While control time after the event may seem counterintuitive since subjects only deliver once and are not at risk for labor/delivery with a cardiovascular event after the event occurred (a “fatal” event), this strategy reduces selection bias¹⁷ and is similar to the approach in other analyses where the event in question is “fatal” such as preterm birth.^{18,19} We estimated the odds ratio (OR) and 95% confidence intervals for an interquartile range (IQR) increase in exposure to criteria air pollutants and PM_{2.5} constituents using conditional logistic regression. Since the air toxics are estimated at very low levels and there are no routine monitor data available to correct for potential measurement error, we dichotomized the exposure to estimate the risk associated with high exposure (75th percentile) compared to low exposure (<75th percentile) rather than assuming a linear model. For the analyses of criteria air pollutants and fine particulate constituents, we also stratified by specific types of cardiovascular event. Lastly, to account for multiple comparisons, *post hoc* adjustment for *P* values were performed using the Benjamini–Hochberg false discovery rate (FDR) controlling method²⁰, which was designed to control the expected proportion of falsely rejected hypotheses, and has better power than other methods.

Results

Of the 680 women with labor/delivery affected by cardiovascular events, 64 (9.4%) had ischemic heart disease, 70 (10.3%) had stroke, 88 (12.9%) had heart failure, 319 (46.9%) had cardiac arrest/failure, and 143 (21.0%) had unspecified events during labor/delivery (Table 1). Women with events were 29 years old on average and more than half of them were married (Table 1). Distribution of air pollutants during the week preceding labor/delivery and their Spearman correlation coefficients are described in Supplemental Tables 2 and 3, respectively.

Odds of having a labor/delivery affected by any cardiovascular event were associated with an IQR increase in exposures to PM_{2.5} (OR: 1.11, 95% CI: 1.01–1.23) and NO_x (OR: 1.21, 95% CI: 1.14–1.42) during the week preceding labor/delivery (Table 2). Elemental carbon

exposure appeared to be inversely associated with cardiovascular event odds (OR: 0.84, 95% CI: 0.71–0.99). When studying the acute effects of pollutants in the days preceding labor/delivery, exposure to PM₁₀, PM_{2.5}, CO and NO_x were associated with events with exposure at days 0, 1, 5 and 6 before labor/delivery (Table 2). Additionally, exposure to SO₂, sulfate particles, dust particles, and ammonium ions were associated with events at some studied lag points). O₃, elemental carbon and organic compound exposures were associated with inverse odds of events at some studied lags (Table 2). When stratified by specific types of cardiovascular event, some inverse associations were driven by specific outcomes. For example, while having an overall inverse association, O₃ appeared to have strong positive associations with ischemic heart disease and stroke at lags 2–4 days after FDR adjustment (Table 2). Organic compounds were also associated with ischemic heart disease at lag 4 days. Furthermore, the overall inverse associations with elemental carbon were largely driven by inverse associations with unspecified events and cardiac arrest while heart failure risk increased with elemental carbon exposure at lags 0 and 6 days (Table 2).

Air toxic analyses also suggested positive associations between daily exposure to indeno[1,2,3-cd]pyrene and xylenes and cardiovascular events at all lags (Supplemental Table 4). However, inverse associations between cardiovascular risk and exposures to 1,3-butadiene, cyclohexane, fluorene, and phenanthrene in the week prior to labor/delivery were observed (Supplemental Table 4), as were inverse odds with other pollutants when studying the effects of daily exposures to air toxics on cardiovascular events.

Discussion

Increased exposures to ambient air pollution are associated with elevated cardiovascular risks in the general and pregnant population,^{8,21} but studies that do not control for non-time-varying factors may be biased by residual chronic confounding and our studies are the first to examine these effects in pregnant women. This is the first report examining the odds of cardiovascular events during labor/delivery using a case-crossover analysis. Controlling for individual-level factors by design, we find positive associations between exposures to NO_x and some air toxics in the present analysis that are consistent with our previous findings in the full cohort analysis.⁸ In addition, we detected novel associations with exposure to PM₁₀, PM_{2.5}, CO, SO₂, some PM_{2.5} constituents and some air toxics using the case-crossover design. The harmful effects of PM₁₀ and PM_{2.5} were not evident in our previous analysis,⁸ but are consistent with the literature.²¹

The exact biological mechanisms between ambient air pollution and cardiovascular risk remain unclear. Air pollution exposures have been associated with many adverse cardiovascular changes.²² These changes may put pregnant women at higher risk for cardiovascular events at delivery, as they already experience higher cardiovascular burden associated with pregnancy itself.³ The acute associations found in our study might be due to changes in heart rate variability and autonomic tone, which could occur as early as two hours post-exposure,²³ or related to increased blood viscosity, oxidative stress, and/or inflammation which might be reflected by lags of several days.¹⁴ Some inverse associations with O₃, elemental carbon, organic compounds, and a number of air toxics were also observed. It is not likely that these effects are biologically plausible, since there is no reason

to suggest exposure would be protective. In particular, many previous studies suggest that elemental carbon, a large component of fine particulate matter, is associated with health risks including cardiorespiratory outcomes.^{24,25} While some inverse findings may be due to chance, many survived FDR adjustment suggesting that there may be other reasons. Inverse associations for some pollutants may be due to the high correlations among some co-occurring pollutants (see Supplemental Table 3). For example, O₃ and NO_x tend to be negatively correlated because of their compensatory role in atmospheric chemistry, and in models such as CMAQ that account for atmospheric chemistry, such inverse associations may be observed. The inverse associations observed for air toxics may potentially be due to their low concentrations, and still need further investigation. The case-crossover analysis allows us to estimate air pollution exposure effects accounting for non-time-varying individual level confounders by design. This builds on our prior finding and suggests that the effects of ambient air on cardiovascular events at labor and delivery are not a result of any unmeasured individual level factors such as genetics or an underlying cardiovascular susceptibility unrelated to exposure.

Although cardiovascular events at labor/delivery are rare, they are becoming an increasingly common cause of maternal mortality in the U.S.²⁶ If our findings are replicated, the association between these events and common air pollutants including NO_x and PM_{2.5} may pose a significant public health concern given their ubiquitous nature. Our findings also suggest that this could be even more important for pregnant women in countries where air pollution levels are much higher than in the U.S.

This study has several limitations. First, we did not have residential address and assessed exposure based on hospital referral region, which may be associated with misclassification but it also allows us to account for short-range local mobility among pregnant women.²⁷ The use of hospital referral region as a proxy for residential exposure likely decreased exposure variability and biased our results towards the null. Second, we lack data on exact time of event, which could potentially lead to error in determining case and control windows. Most cardiovascular events occur around labor/delivery or shortly postpartum.²⁸ Since most cardiovascular events in our study (80%) could be identified from the medical record as occurring during delivery or shortly after, as a complication of surgical delivery for example,⁸ the error in outcome and exposure lag timing using day and week intervals were not likely to profoundly affect our results. In addition, the use of a broader weekly average exposure ought to minimize this concern. While we anticipate that medical records were likely to capture these serious and potentially life-threatening complications, misspecification of the outcome is possible. However, we expect those potential reporting errors will be small and unrelated to ambient air pollution exposure. Lastly, we modelled the outcome as a joint occurrence of labor/delivery with cardiovascular events so the independent effect of air pollution on cardiovascular risk was not assessed here but is addressed in our earlier paper.⁸ Specifically, in our earlier paper, we compared air pollution exposure among cases (deliveries with cardiovascular events), with the controls (deliveries without cardiovascular events). This approach allowed us to study cardiovascular event risk independent of delivery, but may have been subject to unobserved individual-level confounders. The present case-crossover study removes some unobserved confounding, but answers a slightly different question on risk of a labor/delivery with cardiovascular event.

The study also has some notable strengths. First, the case-crossover design allowed us to adjust for measured and unmeasured time-invariant confounders (e.g., genetic and other underlying comorbidities such as pregnancy complications that would increase cardiovascular event risks). Second, our method of exposure assessment accounted for population density, spatial and temporal variation of air pollution, meteorological factors, as well as photochemical properties of pollutants. These considerations ensured improved spatial and temporal accuracy. Finally, we note that in our case-crossover model, women with events serve as their own controls, essentially testing if exposure is the reason why the event occurred at one time and not another while our prior cohort models⁸ ask whether air pollution helps to explain why some women had cardiovascular events and not others. Both sets of analyses reach a similar conclusion – air pollutant exposure is associated with increased risk for cardiovascular events at labor/delivery.

Conclusions

Cardiovascular event risk was increased at labor/delivery in association with higher exposures to PM₁₀, PM_{2.5}, CO, SO₂, and NO_x, some particulate constituents, and some air toxics in the days prior to delivery in this case-crossover study. Our results suggest that individual factors such as genetics or underlying cardiovascular susceptibilities unrelated to air pollution cannot explain the risks we observed and they are more likely to be due to the exposures under study. Given the increased cardiovascular burden among pregnant women, these findings merit further investigation of event risk at labor and delivery as well as throughout pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

CI confidence intervals

CMAQ	Community Multiscale Air Quality
CO	carbon monoxide
ICD-9	International Classification of Disease, 9 th version
IQR	interquartile range
NO_x	nitric oxides
PAH	polycyclic aromatic hydrocarbons
O₃	ozone
OR	odds ratio
PM_{2.5}	particulate matter with aerodynamic diameter 2.5 microns
PM₁₀	particulate matter with aerodynamic diameter 10 microns
VOC	volatile organic compounds

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Highlights

- Acute exposure to air pollution may increase risk of CVD events at labor/delivery.
- $PM_{2.5}$, PM_{10} , CO, SO₂, NO_x, and some $PM_{2.5}$ constituents were associated with risks.
- Exposures during 0, 1, 5 and 6 days preceding labor/delivery had higher risks.
- Case-crossover analyses accounted for individual-level time-invariant confounders.

Table 1

Characteristics of singleton pregnancies with cardiovascular events in the Consortium on Safe Labor (n=680).

Characteristics	Mean or n	SD or %
Age	29.0	6.8
Race/ethnicity		
Non-Hispanic White	297	43.7
Non-Hispanic Black	204	30.0
Hispanic	122	17.9
Asian/Pacific Islanders	23	3.4
Others/Unknown	34	5.0
Marital status		
Not Married	281	41.3
Married	367	54.0
Unknown	32	4.7
Pre-pregnancy body mass index		
<18.5	23	3.4
18.5–24.9	197	29.0
25–29.9	104	15.3
30	132	19.4
Unknown	224	32.9
Insurance type		
Private	314	46.2
Public	308	45.3
Other	9	1.3
Unknown	49	7.2
Nulliparous	285	41.9
Gestational diabetes	46	6.8
Hypertensive disorders of pregnancy	105	15.4
Smoked during pregnancy	52	7.7
Used alcohol during pregnancy	22	3.2
Cardiovascular events ^a		
Ischemic heart disease	64	9.4
Stroke	70	10.3
Heart failure	88	12.9
Cardiac arrest/failure	319	46.9
Unspecified events	143	21.0

^aTotal number of events is greater than any event due to multiple events among some cases.

Table 2

Associations of criteria air pollutants and fine particulate constituents with labor/delivery with specific cardiovascular events

CVD (n)	Pollutant	Days before delivery								
		Week average	Lag 0	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6	Lag 7
All (680)	Criteria pollutants ^a									
	Ozone	0.89 (0.71–1.12)	1.04 (0.83–1.30)	0.89 (0.70–1.14)	1.02 (0.80–1.32)	1.18 (0.94–1.48)	1.22 (0.96–1.53)	0.67 (0.53–0.85) *	0.56 (0.44–0.72) *	0.76 (0.60–0.97)
	PM ₁₀	1.09 (0.99–1.19)	1.16 (1.02–1.33)	1.15 (1.01–1.31)	1.02 (0.89–1.17)	1.04 (0.92–1.18)	1.05 (0.93–1.18)	1.14 (1.01–1.29)	1.12 (1.00–1.25)	1.11 (0.99–1.23)
	PM _{2.5}	1.11 (1.01–1.23)	1.19 (1.05–1.34) *	1.20 (1.07–1.36) *	1.05 (0.93–1.18)	1.04 (0.93–1.16)	1.04 (0.92–1.17)	1.17 (1.03–1.32)	1.14 (1.00–1.29)	1.04 (0.92–1.17)
	CO	1.17 (0.99–1.38)	1.26 (1.07–1.47) *	1.20 (1.02–1.41)	0.99 (0.83–1.18)	0.99 (0.83–1.17)	1.02 (0.86–1.20)	1.23 (1.05–1.45) *	1.19 (1.01–1.40)	0.95 (0.80–1.14)
	SO ₂	1.04 (0.90–1.22)	1.20 (1.05–1.37) *	0.99 (0.87–1.14)	0.95 (0.82–1.09)	0.89 (0.77–1.04)	0.98 (0.85–1.12)	1.16 (1.01–1.32)	1.05 (0.91–1.20)	1.02 (0.89–1.18)
	NO _x	1.21 (1.04–1.42)	1.19 (1.05–1.35) *	1.20 (1.05–1.37) *	0.99 (0.86–1.13)	0.97 (0.84–1.12)	1.01 (0.89–1.15)	1.23 (1.09–1.39) *	1.32 (1.15 – 1.50) *	1.00 (0.87–1.14)
	PM _{2.5} constituents ^b									
	Elemental carbon	0.76 (0.63–0.91) *	0.89 (0.71–1.11)	0.81 (0.63–1.04)	0.92 (0.73–1.16)	0.72 (0.56–0.92) *	0.70 (0.56–0.88) *	1.04 (0.83–1.30)	1.01 (0.81–1.27)	0.76 (0.61–0.94) *
	Organic compounds	0.81 (0.68–0.98)	0.77 (0.57–1.03)	0.69 (0.53–0.89) *	0.97 (0.74–1.26)	1.05 (0.83–1.32)	0.97 (0.74–1.27)	1.03 (0.81–1.31)	0.94 (0.75–1.18)	0.88 (0.70–1.11)
Cardiac arrest (319)	Ammonium ions	0.84 (0.66–1.05)	1.26 (0.71–2.26)	2.07 (1.14–3.76) *	1.04 (0.59–1.82)	1.05 (0.61–1.81)	1.22 (0.71–2.10)	0.75 (0.44–1.27)	1.07 (0.66–1.74)	1.85 (1.11–3.09) *
	Sulfate particles	0.83 (0.66–1.05)	1.31 (1.02–1.68)	1.20 (0.93–1.56)	1.01 (0.75–1.36)	0.96 (0.73–1.27)	1.01 (0.76–1.34)	0.80 (0.60–1.06)	0.94 (0.73–1.20)	1.07 (0.83–1.38)
	Nitrate particle	0.95 (0.85–1.07)	0.96 (0.84–1.11)	1.07 (0.94–1.23)	0.96 (0.86–1.09)	0.99 (0.89–1.12)	0.98 (0.87–1.11)	1.05 (0.94–1.16)	1.06 (0.96–1.16)	1.01 (0.90–1.13)
	Dust particles	0.93 (0.81–1.06)	0.91 (0.75–1.12)	0.93 (0.77–1.12)	1.08 (0.92–1.27)	1.15 (1.00–1.32)	1.15 (0.96–1.39)	1.04 (0.88–1.22)	0.87 (0.70–1.07)	0.92 (0.77–1.11)
	Criteria pollutants ^a									
	Ozone	0.62 (0.44–0.86) *	0.97 (0.70–1.35)	0.69 (0.49–0.99)	0.66 (0.46–0.96)	0.95 (0.68–1.33)	0.87 (0.61–1.24)	0.38 (0.26–0.55)	0.39 (0.27–0.58) *	0.75 (0.53–1.06)
	PM ₁₀	1.09 (0.97–1.23)	1.25 (1.06–1.48) *	1.24 (1.06–1.45) *	1.06 (0.89–1.26)	1.00 (0.85–1.19)	0.96 (0.81–1.14)	1.13 (0.96–1.32)	1.14 (0.99–1.30)	1.14 (1.00–1.31)
	PM _{2.5}	1.15 (1.02–1.29)	1.31 (1.13–1.53) *	1.34 (1.16–1.55) *	1.13 (0.99–1.30)	1.07 (0.93–1.23)	1.04 (0.89–1.21)	1.16 (1.00–1.35)	1.13 (0.97–1.33)	1.10 (0.95–1.27)
	CO	1.31 (1.04–1.63)	1.38 (1.12–1.70) *	1.35 (1.09–1.68) *	1.23 (1.00–1.53)	1.01 (0.79–1.28)	0.98 (0.78–1.24)	1.28 (1.03–1.59) *	1.38 (1.12–1.69) *	1.04 (0.83–1.32)
	SO ₂	1.10 (0.84–1.45)	1.46 (1.15–1.84) *	1.30 (1.08–1.56) *	0.90 (0.70–1.16)	0.83 (0.63–1.10)	0.93 (0.72–1.21)	1.14 (0.88–1.47)	0.95 (0.72–1.25)	1.10 (0.86–1.41)
PM _{2.5} constituents ^b	NO _x	1.30 (1.06–1.59) *	1.31 (1.12–1.54) *	1.38 (1.16–1.64) *	1.15 (0.99–1.35)	0.96 (0.78–1.17)	0.94 (0.78–1.15)	1.22 (1.04–1.43) *	1.33 (1.12–1.57) *	0.99 (0.83–1.19)
	Elemental carbon	0.71 (0.56–0.92)	0.82 (0.61–1.12)	0.85 (0.63–1.14)	1.03 (0.77–1.38)	0.72 (0.49–1.05)	0.63 (0.44–0.89) *	1.13 (0.83–1.53)	0.99 (0.71–1.39)	0.81 (0.61–1.07)

CVD (n)	Pollutant	Days before delivery								
		Week average	Lag 0	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6	Lag 7
Unspecified events (143)	Organic compounds	0.62 (0.45–0.85)	0.56 (0.31–1.03)	0.60 (0.40–0.89) *	0.79 (0.51–1.22)	0.58 (0.37–0.93) *	0.75 (0.40–1.41)	1.10 (0.76–1.60)	0.92 (0.60–1.42)	0.85 (0.57–1.26)
	Ammonium ions	0.77 (0.54–1.10)	1.93 (0.83–4.48)	2.13 (0.95–4.79)	1.00 (0.41–2.40)	2.16 (0.88–5.28)	2.33 (0.88–6.18)	0.98 (0.42–2.27)	0.96 (0.41–2.28)	2.16 (0.93–4.98)
	Sulfate particles	0.68 (0.46–1.02)	1.64 (1.15–2.33) *	1.19 (0.84–1.68)	1.09 (0.68–1.75)	1.26 (0.84–1.89)	1.02 (0.62–1.69)	0.29 (0.18–0.48)	0.69 (0.40–1.18)	1.06 (0.68–1.66)
	Nitrate particle	1.01 (0.85–1.19)	0.98 (0.80–1.19)	1.17 (0.95–1.44)	0.97 (0.80–1.18)	1.07 (0.89–1.29)	1.20 (0.99–1.45)	1.40 (1.18–1.66) *	1.18 (1.01–1.37)	1.08 (0.91–1.29)
	Dust particles	0.84 (0.69–1.03)	0.73 (0.54–0.98)	0.95 (0.74–1.22)	1.17 (0.92–1.48)	1.01 (0.78–1.30)	0.92 (0.64–1.32)	1.18 (0.92–1.51)	1.00 (0.78–1.27)	0.96 (0.73–1.25)
	Criteria pollutants ^a									
	Ozone	1.18 (0.71–1.98)	2.00 (1.14–3.49)	1.72 (1.01–2.93)	1.21 (0.71–2.08)	1.01 (0.62–1.64)	1.29 (0.80–2.08)	0.69 (0.41–1.16)	0.62 (0.35–1.08)	0.53 (0.30–0.94) *
	PM ₁₀	1.13 (0.88–1.46)	1.09 (0.76–1.57)	0.95 (0.67–1.36)	1.14 (0.82–1.60)	1.37 (1.05–1.79)	1.22 (0.92–1.60)	1.13 (0.83–1.53)	0.94 (0.68–1.30)	0.97 (0.71–1.32)
	PM _{2.5}	1.30 (0.97–1.74)	1.31 (0.95–1.81)	1.11 (0.76–1.63)	1.21 (0.88–1.66)	1.30 (1.02–1.65)	1.16 (0.84–1.58)	1.29 (0.95–1.75)	1.21 (0.84–1.74)	1.11 (0.79–1.55)
	CO	1.14 (0.72–1.78)	1.15 (0.76–1.75)	0.87 (0.56–1.36)	0.80 (0.51–1.27)	1.22 (0.81–1.84)	1.11 (0.73–1.68)	1.76 (1.14–2.72) *	0.95 (0.60–1.52)	1.12 (0.74–1.68)
	SO ₂	0.96 (0.76–1.22)	1.09 (0.88–1.36)	0.75 (0.54–1.05)	0.99 (0.79–1.23)	0.85 (0.64–1.12)	0.96 (0.76–1.21)	1.08 (0.89–1.31)	1.08 (0.89–1.32)	0.98 (0.78–1.23)
	NO _x	1.14 (0.75–1.73)	1.05 (0.77–1.43)	0.69 (0.46–1.04)	0.94 (0.69–1.29)	1.11 (0.82–1.51)	1.02 (0.74–1.41)	1.47 (1.15–1.88) *	1.19 (0.87–1.63)	1.05 (0.80–1.37)
	PM _{2.5} constituents ^b									
	Elemental carbon	0.57 (0.39–0.84) *	0.56 (0.33–0.94)	0.43 (0.19–0.94) *	0.73 (0.42–1.29)	0.56 (0.36–0.88) *	0.37 (0.22–0.64) *	0.67 (0.40–1.14)	0.71 (0.42–1.19)	0.53 (0.31–0.90) *
Organic compounds	0.90 (0.61–1.34)	0.73 (0.41–1.27)	0.44 (0.24–0.82)	1.06 (0.67–1.67)	1.20 (0.88–1.62)	0.94 (0.56–1.58)	1.23 (0.76–2.01)	1.06 (0.67–1.68)	1.18 (0.77–1.81)	
Ammonium ions	0.89 (0.55–1.46)	0.93 (0.26–3.25)	5.79 (1.32–25.4) *	0.93 (0.34–2.51)	1.17 (0.52–2.62)	1.00 (0.36–2.76)	0.60 (0.20–1.78)	0.84 (0.29–2.48)	0.96 (0.32–2.90)	
Sulfate particles	1.08 (0.65–1.82)	1.69 (1.03–2.79)	1.87 (1.09–3.22) *	1.29 (0.78–2.12)	0.94 (0.66–1.35)	1.12 (0.70–1.80)	1.12 (0.73–1.71)	0.92 (0.57–1.50)	1.42 (0.93–2.19)	
Nitrate particle	0.90 (0.74–1.10)	0.83 (0.62–1.12)	0.96 (0.73–1.27)	0.87 (0.71–1.07)	0.98 (0.83–1.16)	0.91 (0.75–1.11)	0.87 (0.71–1.06)	1.02 (0.83–1.24)	0.78 (0.62–0.98)	
Dust particles	0.96 (0.74–1.24)	0.98 (0.73–1.33)	0.75 (0.43–1.30)	0.94 (0.71–1.26)	1.11 (0.91–1.36)	1.25 (0.96–1.63)	1.03 (0.78–1.36)	0.74 (0.49–1.11)	0.76 (0.52–1.10)	

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CVD (n)	Pollutant	Days before delivery								
		Week average	Lag 0	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6	Lag 7
PM _{2.5} constituents ^b	Elemental carbon	1.20 (0.69–2.09)	2.38 (1.22–4.63) [*]	0.77 (0.40–1.47)	0.74 (0.43–1.28)	0.81 (0.43–1.54)	1.98 (0.97–4.05)	1.81 (0.98–3.34)	1.92 (1.05–3.54) [*]	0.97 (0.54–1.75)
	Organic compounds	0.86 (0.56–1.32)	1.66 (0.89–3.09)	1.05 (0.61–1.81)	0.96 (0.54–1.73)	1.70 (0.99–2.94)	0.98 (0.54–1.79)	0.48 (0.25–0.95)	0.58 (0.33–1.03)	0.66 (0.34–1.30)
	Ammonium ions	0.71 (0.37–1.35)	0.19 (0.04–0.84)	1.47 (0.34–6.28)	0.91 (0.25–3.30)	0.18 (0.03–1.00)	0.59 (0.15–2.32)	1.04 (0.30–3.65)	1.32 (0.40–4.35)	2.21 (0.54–9.00)
	Sulfate particles	0.77 (0.44–1.34)	0.84 (0.34–2.10)	0.79 (0.39–1.59)	0.57 (0.28–1.20)	0.88 (0.39–1.98)	1.00 (0.51–1.95)	1.11 (0.62–1.97)	1.03 (0.63–1.71)	0.47 (0.20–1.10)
	Nitrate particle	0.90 (0.66–1.23)	0.82 (0.55–1.24)	0.95 (0.68–1.33)	1.10 (0.85–1.41)	0.87 (0.61–1.23)	0.84 (0.62–1.15)	1.02 (0.81–1.29)	1.08 (0.84–1.40)	1.37 (1.04–1.79)
	Dust particles	0.94 (0.64–1.38)	1.06 (0.70–1.59)	0.98 (0.64–1.52)	1.02 (0.64–1.64)	1.23 (0.68–2.21)	1.27 (0.73–2.19)	0.91 (0.54–1.54)	0.82 (0.47–1.41)	1.24 (0.92–1.67)
	Criteria pollutants ^a									
Stroke (70)	Ozone	1.46 (0.79–2.70)	0.98 (0.51–1.87)	0.88 (0.44–1.75)	2.13 (1.01–4.49)	2.14 (1.09–4.19) [*]	1.89 (0.96–3.72)	1.58 (0.83–3.02)	0.78 (0.40–1.53)	1.14 (0.59–2.20)
	PM ₁₀	0.91 (0.68–1.21)	0.85 (0.55–1.34)	0.86 (0.57–1.29)	0.73 (0.49–1.08)	0.83 (0.56–1.21)	1.08 (0.76–1.52)	0.98 (0.66–1.43)	1.03 (0.73–1.45)	1.14 (0.83–1.57)
	PM _{2.5}	0.82 (0.61–1.12)	0.97 (0.66–1.44)	0.84 (0.56–1.26)	0.64 (0.43–0.95)	0.64 (0.43–0.95)	0.84 (0.57–1.23)	0.94 (0.64–1.39)	1.10 (0.76–1.59)	1.03 (0.72–1.47)
	CO	0.97 (0.56–1.69)	1.03 (0.59–1.79)	1.60 (0.97–2.63)	0.53 (0.22–1.30)	0.50 (0.20–1.24)	1.04 (0.62–1.76)	1.22 (0.79–1.90)	1.20 (0.71–2.03)	1.07 (0.60–1.90)
	SO ₂	0.77 (0.48–1.23)	0.83 (0.51–1.34)	0.87 (0.54–1.40)	0.43 (0.24–0.77) [*]	0.92 (0.60–1.41)	1.08 (0.70–1.65)	0.91 (0.55–1.49)	1.00 (0.64–1.57)	1.14 (0.76–1.72)
	NO _x	0.72 (0.43–1.21)	0.87 (0.52–1.47)	1.37 (0.84–2.23)	0.37 (0.16–0.84) [*]	0.66 (0.38–1.15)	0.94 (0.61–1.46)	0.77 (0.47–1.25)	1.05 (0.67–1.64)	1.10 (0.73–1.67)
	PM _{2.5} constituents ^b									
	Elemental carbon	1.05 (0.57–1.94)	1.35 (0.63–2.89)	2.13 (0.90–5.05)	0.92 (0.43–1.97)	1.09 (0.55–2.15)	1.75 (0.74–4.14)	0.67 (0.33–1.36)	1.28 (0.53–3.07)	0.96 (0.45–2.06)
	Organic compounds	1.08 (0.65–1.80)	0.63 (0.25–1.59)	1.06 (0.49–2.28)	1.17 (0.53–2.55)	1.37 (0.67–2.82)	1.41 (0.66–3.02)	1.03 (0.50–2.09)	1.25 (0.76–2.04)	0.89 (0.51–1.57)
	Ammonium ions	1.00 (0.57–1.77)	9.18 (1.04–80.9)	0.38 (0.06–2.35)	2.83 (0.57–14.0)	0.81 (0.16–4.04)	0.78 (0.20–3.06)	0.45 (0.09–2.23)	1.53 (0.40–5.85)	1.94 (0.52–7.17)
	Sulfate particles	0.93 (0.51–1.68)	0.38 (0.15–0.98)	0.85 (0.36–2.02)	1.28 (0.56–2.91)	0.52 (0.20–1.35)	0.64 (0.23–1.81)	1.42 (0.85–2.38)	1.21 (0.67–2.19)	1.22 (0.61–2.45)
	Nitrate particle	0.92 (0.63–1.35)	2.16 (1.28–3.66) [*]	1.24 (0.72–2.13)	0.91 (0.55–1.52)	0.92 (0.56–1.52)	0.89 (0.56–1.41)	0.72 (0.49–1.06)	0.77 (0.56–1.05)	0.77 (0.53–1.11)
	Dust particles	1.08 (0.64–1.83)	1.15 (0.45–2.93)	1.24 (0.54–2.87)	1.26 (0.68–2.35)	2.03 (1.22–3.39) [*]	1.72 (0.95–3.13)	0.52 (0.12–2.23)	0.66 (0.32–1.35)	0.88 (0.47–1.65)

CVD (n)	Pollutant	Days before delivery								
		Week average	Lag 0	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6	Lag 7
	NO _x	0.99 (0.58–1.68)	0.92 (0.55–1.53)	0.81 (0.49–1.36)	0.68 (0.38–1.19)	0.97 (0.63–1.48)	1.15 (0.81–1.64)	1.15 (0.68–1.95)	1.34 (0.70–2.54)	0.94 (0.57–1.54)
	PM _{2.5} constituents ^b									
	Elemental carbon	1.49 (0.43–5.19)	0.74 (0.20–2.79)	0.49 (0.20–1.19)	0.46 (0.15–1.38)	0.99 (0.19–5.13)	0.69 (0.18–2.57)	1.80 (0.40–8.11)	0.55 (0.11–2.79)	0.31 (0.06–1.48)
	Organic compounds	6.47 (1.16–36.0) [*]	3.93 (0.59–26.1)	2.43 (0.44–13.5)	4.36 (0.57–33.2)	9.00 (2.08–39.0)	6.01 (1.10–32.7) [*]	4.59 (0.85–24.8)	0.49 (0.09–2.63)	0.99 (0.25–3.91)
	Ammonium ions	6.42 (0.27–152.1)	0.51 (0.01–32.5)	0.89 (0.01–60.4)	10.6 (0.32–347.4)	0.20 (0.01–5.24)	1.17 (0.05–25.8)	0.26 (0.01–5.52)	0.74 (0.03–18.7)	2.02 (0.14–30.2)
	Sulfate particles	5.87 (0.94–36.5)	1.61 (0.28–9.16)	1.68 (0.21–13.3)	1.43 (0.18–11.4)	1.94 (0.23–16.4)	5.08 (0.67–38.2)	0.20 (0.03–1.44)	2.54 (0.63–10.2)	1.35 (0.36–5.10)
	Nitrate particle	0.72 (0.17–3.02)	0.21 (0.05–0.91)	0.48 (0.08–2.84)	0.61 (0.17–2.19)	0.08 (0.01–0.48) [*]	0.09 (0.01–0.64) [*]	0.90 (0.43–1.87)	0.77 (0.28–2.13)	1.26 (0.70–2.29)
	Dust particles	1.64 (0.69–3.86)	1.22 (0.46–3.20)	2.70 (0.83–8.79)	0.89 (0.31–2.52)	0.73 (0.29–1.84)	0.74 (0.21–2.59)	1.16 (0.28–4.73)	0.45 (0.11–1.76)	0.67 (0.35–1.32)

Abbreviations: CO, carbon monoxide; CI, confidence interval; CVD, cardiovascular event; NO_x, nitrogen oxides; OR, odds ratio; PM10, particulate matter 10 µm in aerodynamic diameter; PM2.5, particulate matter 2.5 µm in aerodynamic diameter; SO2, sulfur dioxide.

^a Odds ratios were estimated for an IQR increase for each pollutant at each lag. Analyses on criteria pollutants were based on modeled pollutant estimates fused with observed air quality data.

^b Odds ratios were estimated for an IQR increase for each pollutant at each lag, adjusting for total PM2.5 concentration. Models were based on modeled air pollution estimates.

^{*} Indicates statistical significance after false discovery rate adjustments