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The effect of ambient air pollution on term birth weight and preterm birth in Kansas, 2005-2013

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Abstract

The effect of ambient air pollution on term birth weight and preterm birth in Kansas, 2005-2013

By Sodahm Yoo

Epidemiologic studies suggest that exposure to ambient air pollution during pregnancy increases the risk of low birth weight and preterm birth; however, the evidence remains inconsistent. We examined the relationship between ambient levels of particulate matter $< 2.5\ \mu m$ in diameter ($PM_{2.5}$), $PM_{2.5}$ chemical constituents [elemental carbon (EC), organic carbon (OC), and nitrate (NO_3), ozone (O_3) carbon monoxide (CO), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) and two birth outcomes, birth weight and preterm birth, between 2005 and 2013 in Kansas. Using a generalized additive modeling framework, we evaluated relationships between birth weight and pollutant concentrations during the first trimester, second trimester, third trimester, and total pregnancy. For preterm birth, we estimated the risk of preterm for both time-invariant and time-variant exposures with a discrete-time survival model. We also studied the potential modifying effect of pre-pregnancy hypertension, pre-pregnancy diabetes, and infant sex. In this statewide analysis, ambient levels of second-trimester $PM_{2.5}$, second-trimester O_3, total-pregnancy O_3, and total-pregnancy $PM_{2.5}$ were significantly associated with reductions in birth weight [-3.6 to -9.6 *g* per interquartile range (IQR) increase in pollutant concentrations]. Time-varying total pregnancy NO_3 was significantly associated with a 5% decreased risk of preterm birth per IQR increase. These findings suggest some support for an effect of ambient air pollution on term birth weight and preterm birth in Kansas.

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Introduction

Low birth weight and preterm birth are major causes of neonatal mortality and morbidity and long-term health conditions.[1–4] Recent epidemiological studies have suggested that ambient air pollution may increase the risk of such adverse birth outcomes, although the evidence remains inconsistent across different pollutants and exposure windows.[5,6] These differences may be due to variation in study design, statistical methods, and geographic region.

Ambient air pollution is a leading risk factor that contributes to respiratory and cardiovascular disease.[7–9] Prior studies have also suggested that air pollution exposure may exacerbate chronic conditions such as hypertension and diabetes, perhaps due to increased oxidative stress and inflammation.[10–13] Other studies have also shown that women with chronic hypertension and diabetes are at increased risk of adverse pregnancy outcomes.[14–18] Given that pregnancy is a period of greater susceptibility to oxidative stress and inflammation,[19] a potential relationship between maternal comorbidities, air pollution, and adverse birth outcomes would have important public health implications.

In addition, infant sex has been hypothesized as a potential effect modifier of the association between air pollution and adverse birth outcomes. Average birth weight has been observed to be higher in male infants than in female infants,[20,21] and epidemiologic studies have suggested that the incidence of preterm birth is higher for male fetuses than for female fetuses.[24] Differences in adverse birth outcomes due to infant sex should be examined to help identify potentially more vulnerable populations.

In this study, we investigated the association between eight different ambient air pollutants and two birth outcomes, term birth weight and preterm birth, in Kansas. These pollutants included particulate matter < 2.5 μm in diameter ($PM_{2.5}$), $PM_{2.5}$ chemical constituents [elemental carbon (EC), organic carbon (OC), and nitrate (NO_3), ozone (O_3) carbon monoxide (CO), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x). We also studied the potential effect modifying effect of pre-pregnancy hypertension, pre-pregnancy diabetes, and infant sex. To date, there have been no published studies on the potential role of ambient air pollution on birth weight and preterm birth in Kansas. The present study is the first to be conducted using Kansas state birth records and air pollutant concentration data to estimate the effect of air pollution on adverse birth outcomes.

Methods

Study population

Birth record data were obtained from the Bureau of Epidemiology and Public Health Informatics, Kansas Department of Health. We included singleton pregnancies with gestational lengths of 27 to 44 weeks with an estimated date of conception between January 1st 2005 and December 31st 2013. Birth outcomes examined in this study included term (gestational age > 37 weeks) birth weight and preterm birth (gestational age < 37 weeks). We restricted to births ≥ 27 weeks so that all pregnancies were followed for the entire duration of the first and second trimesters. The first trimester was defined as gestational weeks 3 to 13,

the second trimester as gestational weeks 14 to 26, and the third trimester as gestational weeks 27 until birth.

We further excluded births with (a) maternal age < 10 years or > 55 years (0.02%); (b) birth weight < 250 g or > 7500 g (0.04%); (c) missing geocode data at the census tract level (0.0005%); and (d) missing maternal and infant covariate data included in the analyses (2.5%). After exclusions, 302,647 term births were eligible for the birth weight analysis, and 318,845 births were eligible for the preterm birth analysis.

Exposure assessment

We obtained daily air pollution concentrations estimated by a data fusion product that combines monitoring measurements and simulations from the Community Multi-scale Air Quality model (CMAQ), which incorporates information on emission, meteorology, and atmospheric chemistry.[25] For each birth record, gridded air quality estimates at a 12km-by-12km spatial resolution were linked to the maternal residential address census tract.

Statistical analysis

For all analyses, we examined linear associations between pollutant concentration and birth outcome in single-pollutant models for each exposure window of interest. Due to the large geographic region, the primary analyses for birth weight and preterm birth were conducted in two stages to account for effect heterogeneity. In the first stage, separate models were fitted for each county with over 300 births (n = 57). Second, county-specific effect estimates were pooled

using a random-effect meta-analysis model. We assumed that the unknown true effect was normally distributed with mean μ (overall pooled effect across counties) and variance τ^2 (between-county heterogeneity). Between-county heterogeneity was estimated using the method of restricted maximum likelihood (REML). For the preterm analysis, we removed some samples due to sparsity of covariate data.

Linear regression models were used to analyze term birth weight as a continuous outcome and average pollutant concentrations for the first trimester, second trimester, third trimester, and total pregnancy exposure windows. For preterm birth, gestational age (in weeks) was treated as time-to-event data, and we estimated pollutant associations in a Cox proportional hazards model with time-dependent covariates. The Breslow method was used for ties in gestational weeks. We examined two fixed-time windows: trimester 1 and trimester 2. We also investigated four time-varying exposure windows. For each ongoing pregnancy at completed gestational week t, we defined: (1) trimester 3 (week 27 to t); (2) cumulative (week 1 to t); (3) a 1-week lag (week t); and (4) a 4-week lag (week t – 4 to t). Using this approach, each pregnancy enters the risk set at gestational week 27 until either (1) a preterm birth occurs before gestational week 37 or (2) the pregnancy reaches gestational week 37. Term births are censored at gestational week 37, and no births are censored during the at-risk period of gestational weeks 27 to 36. This design assumes that the risk of birth associated with the time-varying exposure is constant during the at-risk window after adjusting for all other covariates and the baseline hazard.

For both birth outcomes, we adjusted for the following variables: maternal education (< High School, High School/GED, Some college/AA, Bachelors or above); maternal race (White, Black, Native American/Alaskan, API, Multiracial, Other); maternal ethnicity (Non-Hispanic, Hispanic); median household income quartiles; natural cubic splines for maternal age and body mass index (BMI) with 5 degrees of freedom; and indicators for infant sex, marital status, pre-pregnancy diabetes, and pre-pregnancy hypertension. Since ambient air pollution levels exhibit strong seasonal trends, we controlled for season of conception: winter (December – February), spring (March – May), summer (June – August), fall (September – November), and year of conception. For birth weight, we flexibly controlled for conception season and conception year as a factor-smooth interaction term using cubic regression splines, which allows a separate smooth for each category of conception season in a generalized additive modeling framework with R package *mgcv*. For preterm birth, conception season and conception year were included in the model as indicator variables; we also considered interaction terms for these temporal confounder indicators.

To investigate effect modification of the association between air pollution and each birth outcome, we stratified the data by (1) pre-pregnancy hypertension; (2) pre-pregnancy diabetes; and (3) infant sex. Separate regression models were fitted for each stratum in a similar two-stage procedure as the primary analyses. Sensitivity analyses included fitting whole-state models for birth weight and preterm birth with adjustment for county indicators. We also explored the

addition of gestational age as indicators for the birth weight model. All statistical analysis was conducted using R, version 4.0.4.

Results

The total study sample consisted of 325,003 singleton births across 57 counties in Kansas, of which 22,356 (6.9%) were preterm births. Table 1 shows the maternal and infant characteristics of the total study population. The cohort was majority non-Hispanic White. Compared to term births, preterm births had higher proportions of mothers with pre-pregnancy diabetes, pre-pregnancy hypertension, educational attainment below the high school level, unmarried marital status, and lower median household income. Term infants had a mean birth weight of 3403.9 grams (*g*), while preterm infants had a lower mean birth weight of 2496.6 *g*. For all infants over the study conception period from 2005 to 2013, average birth weight increased from 3335 *g* to 3354.4 *g*. The proportion of preterm births decreased slightly over the study period (from 7.2% to 6.9%). Compared to female infants, more male infants were born preterm (53.8%). (Refer to Supplementary Tables 1 and 2 for the maternal and infant characteristics of the birth weight and preterm birth samples used for each analysis, for which the distributions of characteristics were nearly identical.)

Table 2 summarizes total pregnancy exposure averages of daily pollutant concentrations for the whole state. Over the nine-year study period, total-pregnancy exposure averages for all pollutants decreased, except EC, which remained relatively constant from 2005 to 2013. Of all pollutants, NO_x had the largest decrease (33.8 to 23.8 *ppb*) in concentration. (Refer to Supplementary

Table 3 for the interquartile ranges (IQR) of each exposure metric used to scale the effect estimates for the birth weight and preterm analyses for comparability.)

Table 3 presents the adjusted regression estimates and 95% confidence intervals (CIs) of maternal risk factors associated with birth weight and preterm birth. Since we modeled each county separately, we report estimates for Sedgwick County, the region with the greatest number of births in our study sample, for the total-pregnancy exposure model with $PM_{2.5}$. Estimates were nearly identical across different pollutants and exposure windows.

On average, female infants weighed less than male infants, and compared to infants conceived in the winter, infants conceived in the spring had lower birth weight. Both BMI and maternal age were non-linearly associated with birth weight. Higher maternal education, maternal Hispanic ethnic background, and higher median household income were positively associated with birth weight. Compared to White mothers, Black, Asian Pacific Islander (API), and Multiracial mothers delivered infants with lower mean birth weight, with API mothers having infants with the lowest mean birth weight. Compared to infants born to married mothers, infants born to unmarried mothers also had lower mean birth weight. While pre-pregnancy diabetes was positively associated with birth weight, pre-pregnancy hypertension was negatively associated with birth weight.

For preterm birth, female infants had lower risk than male infants, and across maternal age groups, mothers aged 32 to 54 years had the highest risk of preterm birth (HR = 2.52; 95% CI: [1.09, 5.82]). Similar to birth weight, the risk of preterm birth decreased with higher levels of maternal education and for mothers

of Hispanic descent. In contrast to birth weight, the risk of preterm birth increased as median household income increased. Black mothers had the highest risk of delivering preterm (HR = 1.36; 95% CI: [1.25, 1.48]), and compared to mothers without pre-existing conditions, mothers with pre-pregnancy diabetes and hypertension were two times more likely to have preterm infants.

Figure 1 shows the statewide mean differences and 95% CIs for birth weight per IQR increase in each of the eight pollutant averages during the first, second, and third trimesters, and total pregnancy. A statistically significant association ($p < 0.05$) was observed for birthweight with an IQR increase in first-trimester O_3 (mean difference MD = 7.9 *g*; 95% CI: [0.2, 15.5]). Second-trimester $PM_{2.5}$ (MD = -3.6 *g*; 95% CI = [-7, -0.2]) and O_3 (MD = -9.6 *g*; 95% CI: [-14.6, -4.7]) were significantly associated with reduced birth weight per IQR increase, as well as third-trimester $PM_{2.5}$ (MD = -4.3 *g*; 95% CI: [-8, -0.6]). Second-trimester NO_x (MD = 8.5 *g*; 95% CI: [3.4, 13.5]) was significantly associated with increased birth weight per IQR increase. Total-pregnancy $PM_{2.5}$ (MD = -7 *g*; 95% CI: [-11.2, -2.7]) and O_3 (MD = -5.7 *g*; 95% CI = [-9.6, -1.9]) were both negatively associated with birth weight. All other pollutant associations were not significant.

Figure 2 summarizes statewide hazard ratios (HRs) and 95% CIs for the risk of preterm birth per IQR increase in each of the eight pollutants across all time-independent and time-dependent exposure windows. Time-varying total pregnancy NO_3 was significantly associated with a decreased risk of preterm birth (HR = 0.95; 95% CI: [0.91, 0.99]). The majority of pollutant exposures for both

fixed and time-varying windows were associated with an increased risk of preterm birth, although these associations were not significant.

We did not find evidence for effect modification by pre-pregnancy hypertension, pre-pregnancy diabetes, or infant sex for either birth weight or preterm birth, despite adverse risk estimates in the primary regression models. Sensitivity analyses for whole-state models for $PM_{2.5}$ and birth weight showed associations in the same negative direction, although the effect sizes were smaller for all exposure windows except during the first trimester. Similar patterns were also found from the whole-state models for $PM_{2.5}$ and preterm birth, except for first-trimester and 1-week lag exposures, for which the associations were in the opposite direction and not significant. When we adjusted for gestational age in the birth weight model, we found significant negative associations during the second trimester, third trimester, and total pregnancy period for $PM_{2.5}$.

Discussion

In this study we conducted a statewide analysis to estimate the association between eight ambient air pollutants and two birth outcomes, term birth weight and preterm birth, in the state of Kansas. We found statistically significant adverse associations for $PM_{2.5}$ levels during the second trimester, third trimester, and total pregnancy. Significant adverse associations for O_3 levels during the second trimester and total pregnancy were also observed. In contrast, significant protective associations were found for trimester-1 O_3 and trimester-2 NO_x exposures. For the risk of preterm birth, we did not observe significant

associations for either short-term or long-term exposures, other than a protective effect for cumulative total-pregnancy NO_3 exposure.

Our study's reported estimates for the effect of $PM_{2.5}$ on birth weight are consistent with previous findings. In a study in Atlanta, Georgia, Darrow et al. found that ambient levels of $PM_{2.5}$ during the third trimester were associated with a decrease in term birth weight of -4.3 g per 4 $\mu g/m^3$ (95% CI: [-9.8, 1.2]).[26] For second-trimester $PM_{2.5}$ exposure, Sun et al. found a mean difference of -12.6 g per 10 $\mu g/m^3$ increment (95% CI: [-21.7, -3.1]) in a meta-analysis of 11 studies.[27] The same meta-analysis found a decrease of -10 g (95% CI: [-16.6, -3.5]) for third-trimester exposure and -15.9 g (95% CI: [-26.8, -5]) for total-pregnancy exposure. For second-trimester and total-pregnancy O_3, the California Children's Health Study found a decrease in birth weight of -25.7 g (95% CI: [-42.7, -8.7]) per 29 ppb increase and -49.9 g (95% CI: [-72, -27.8]) per 26 ppb increase, respectively.[28] However, our first-trimester estimate for O_3 exposure suggests an apparent protective effect for birth weight, which is in the opposite direction of the results from the California study and other studies that observed similar negative associations.[29–31] Survival bias is one possible explanation for this finding, as the pregnancies included in our analysis are potentially those that survived high levels of exposure during critical periods of gestation. A previous study in Florida also found similar protective effects of O_3 on term birth weight.[32] This explanation may also account for the protective effect observed for NO_x, which contrasts the adverse effect found in a cohort study of Mexican newborns.[33] Differences in geographic region and average air pollutant

concentrations may also influence this discrepancy. Further, given the large number of comparisons conducted in the present study, any of the associations observed may be due to random chance.

We also observed a protective effect for cumulative total-pregnancy NO_3 exposure and the risk of preterm birth. This finding is consistent with the observed protective effect found for NO_3 in a study examining air pollution and preterm birth in Georgia, although this association was not significant.[34] Additionally, our null estimates for all exposure windows for $PM_{2.5}$, EC, OC, NO_2, and CO contradict the findings from the same study. In our study we found a null association between O_3 and preterm birth, which is also consistent with many prior studies.[35] A possible explanation for these null findings may be that exposure concentration levels in Kansas are not high enough to influence fetal development. For example, Kansas' total-pregnancy $PM_{2.5}$ level was 9.5 $\mu g/m^3$. This exposure average is substantially lower than the total-pregnancy average of 71.8 $\mu g/m^3$ for a recent study in China, which observed a strong association between $PM_{2.5}$ and preterm birth risk during this exposure window (HR = 12.66; 95% CI = [8.2, 19.53]) per 10% increase in the proportion of days with daily average $PM_{2.5}$ concentrations exceeding 25 $\mu g/m^3$. [36] Several studies have found significant associations between both short-term and long-term exposures of $PM_{2.5}$ and the risk of preterm birth.[37,38] Fewer studies have examined the effect of $PM_{2.5}$ chemical constituents and NO_x for either term birth weight or preterm birth. More research is needed in this area.

A limited number of studies have examined the potential modifying effect of pre-existing maternal conditions on the association between air pollution and adverse birth outcomes. Both chronic hypertension and pre-gestational diabetes have been associated with low birth weight and preterm delivery. However, in our study we did not find evidence of effect modification of ambient air pollution by pre-pregnancy hypertension or pre-pregnancy diabetes on either term birth weight or preterm birth. One prior study, which treated preterm birth as multiple categories and combined pre-pregnancy and gestational diabetes as one outcome, found a protective effect of third-trimester $PM_{2.5}$ among women with diabetes per IQR increase of 12.4 $\mu g/m^3$ (OR = 0.86; 95% CI: [0.76, 0.97]) during gestational weeks 34-36.[39] The same study observed increased risk for total-pregnancy $PM_{2.5}$ among women with diabetes during gestational weeks 32-33, although the risk was higher among women without diabetes. Other studies have examined the effect of gestational hypertensive disorders but not chronic hypertension.[40–42] Additionally, our study revealed no differences in the relationship between air pollution and both birth outcomes by infant sex, which is consistent with the conclusions of a previous study that used Massachusetts and Connecticut birth record data.[43]

Our study had several strengths. First, our analysis was based on a large sample population of over 300,000 births, and exposure assignments used ambient air pollutant data with high temporal and spatial resolutions, which provided complete coverage over Kansas' entire geographic region. This method contrasts with several previous studies that were limited to air quality metrics from only

stationary monitors, which restricts spatial coverage.[44–46] Second, our regression models flexibly controlled for temporal confounders, limiting the potential bias associated with seasonality in adverse birth outcomes.[47] Third, we used a time-to-event framework to model the effect of short-term and long-term air pollutants on the risk of preterm birth. This design allowed us to efficiently estimate risk for time-varying exposure windows by avoiding the potential bias resulting from treating these exposures as fixed windows in logistic regression models.[48] Last, the Kansas birth records contain comprehensive maternal information, specifically clinical estimates of gestational age, which removes the potential recall bias associated with gestational age based on last menstrual period (LMP).[49,50]

This study had several limitations. Although exposure assignments for all eight pollutants had high spatial resolution at the census tract level, assigning pollutant levels to individual pregnancies may be subject to measurement error. Since exposures are assigned according to maternal residence at the time of delivery, we also assumed that mothers remained at the reported address throughout the pregnancy. For example, it is possible that mothers spent time away from home, such as at the workplace, or moved residences during the pregnancy, which could introduce bias away or toward the null depending on whether maternal mobility is nondifferential with respect to air pollutant levels and both birth outcomes. While we controlled for multiple risk factors in our birth weight and preterm birth models, including maternal clinical characteristics and census-tract level median household income, the possibility of individual and neighborhood-level

confounding presents another source of error in this study. Known risk factors, such as maternal tobacco use and illicit drug use, were unavailable from the birth record data. In addition, it is possible that our study's spatiotemporal controls did not completely remove the effects of unmeasured confounding. Hence, residual confounding may account for the protective effects observed for total-pregnancy NO_3 in the preterm birth analysis and for first-trimester O_3 and second-trimester NO_x in the birth weight analysis.

In summary, our findings indicate significant associations for several different air pollutants and decreased birth weight among term infants. We also observed a significant decreased risk of preterm birth for NO_3 exposure. While some of these associations aligned with the existing literature, other associations were not consistent across different pollutants and exposure windows. These inconsistencies merit additional investigation into the effects of ambient air pollution to inform policy for effective air pollution control. Although our analysis did not reveal evidence for effect modification by either pre-pregnancy hypertension or pre-pregnancy diabetes, these relationships warrant further study in other populations given the plausibility of the biological mechanisms that may underlie these relationships.

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Table 1: Characteristics of the study population in Kansas, 2005-2013

	Preterm infants (N=22356)	Term infants (N=302647)	Total (N=325003)
Birth weight (g)			
Mean (SD)	2496.6 (643.4)	3403.9 (454.3)	3341.5 (522.9)
Gestational age (weeks)			
Mean (SD)	34.5 (2.1)	39.1 (1.0)	38.7 (1.6)
Infant sex			
Male	12036 (53.8%)	153921 (50.9%)	165957 (51.1%)
Female	10320 (46.2%)	148726 (49.1%)	159046 (48.9%)
Conception season			
Winter	5594 (25.0%)	76840 (25.4%)	82434 (25.4%)
Spring	5678 (25.4%)	73931 (24.4%)	79609 (24.5%)
Summer	5545 (24.8%)	74928 (24.8%)	80473 (24.8%)
Autumn	5539 (24.8%)	76948 (25.4%)	82487 (25.4%)
Body mass index (BMI)			
Mean (SD)	26.5 (6.9)	26.3 (6.4)	26.3 (6.4)
Maternal age (years)			
Mean (SD)	26.9 (6.1)	27.0 (5.7)	27.0 (5.7)
Maternal education			
< High school	4254 (19.0%)	49647 (16.4%)	53901 (16.6%)
High school/GED	5945 (26.6%)	71335 (23.6%)	77280 (23.8%)
Some college/AA	6808 (30.5%)	91099 (30.1%)	97907 (30.1%)
BA+	5349 (23.9%)	90566 (29.9%)	95915 (29.5%)
Maternal race			
White	17746 (79.4%)	248220 (82.0%)	265966 (81.8%)
Black	2271 (10.2%)	21079 (7.0%)	23350 (7.2%)
Native American/Alaskan	131 (0.6%)	1969 (0.7%)	2100 (0.6%)
API	633 (2.8%)	9381 (3.1%)	10014 (3.1%)
Multiracial	455 (2.0%)	5723 (1.9%)	6178 (1.9%)
Other	1120 (5.0%)	16275 (5.4%)	17395 (5.4%)
Maternal ethnicity			
Non-Hispanic	19116 (85.5%)	253720 (83.8%)	272836 (83.9%)

Hispanic	3240 (14.5%)	48927 (16.2%)	52167 (16.1%)
Marital status			
Married	12758 (57.1%)	191754 (63.4%)	204512 (62.9%)
Unmarried	9598 (42.9%)	110893 (36.6%)	120491 (37.1%)
Pre-pregnancy diabetes			
Absent	21904 (98.0%)	300887 (99.4%)	322791 (99.3%)
Present	452 (2.0%)	1760 (0.6%)	2212 (0.7%)
Pre-pregnancy hypertension			
Absent	21784 (97.4%)	299806 (99.1%)	321590 (98.9%)
Present	572 (2.6%)	2841 (0.9%)	3413 (1.1%)
Median household income($)			
[9,380-36,900]	6641 (29.7%)	77106 (25.5%)	83747 (25.8%)
(36,900-45,600]	4830 (21.6%)	62377 (20.6%)	67207 (20.7%)
(45,600-59,800]	5276 (23.6%)	77305 (25.5%)	82581 (25.4%)
(59,800-172,000]	5609 (25.1%)	85859 (28.4%)	91468 (28.1%)

Table 2: Exposure characteristics for total pregnancy and by selected years of conception in Kansas, 2005-2013

	Total Pregnancy	2005	2009	2013
$PM_{2.5}$ $(\mu g/m^3)$				
Mean (SD)	9.4 ± 1.4	10.6 ± 1.6	9.3 ± 1.4	8.4 ± 0.9
EC $(\mu g/m^3)$				
Mean (SD)	0.4 ± 0.2	0.4 ± 0.1	0.4 ± 0.2	0.4 ± 0.2
NO_3 $(\mu g/m^3)$				
Mean (SD)	1.7 ± 0.5	1.8 ± 0.5	1.9 ± 0.7	1.7 ± 0.5
OC $(\mu g/m^3)$				
Mean (SD)	2.2 ± 0.9	3.1 ± 0.9	2.2 ± 0.8	1.5 ± 0.4
NO_x (ppb)				
Mean (SD)	26.3 ± 14.9	33.8 ± 18.1	22.8 ± 12.9	23.8 ± 12.7
NO_2 (ppb)				
Mean (SD)	15.7 ± 6.5	18.6 ± 7.4	14.3 ± 6.0	14.2 ± 5.7
CO (ppm)				
Mean (SD)	0.4 ± 0.2	0.6 ± 0.2	0.4 ± 0.2	0.3 ± 0.1
O_3 (ppm)				
Mean (SD)	0.041 ± 0.004	0.043 ± 0.004	0.038 ± 0.004	0.040 ± 0.003

Table 3: Adjusted regression estimates and associated 95% confidence intervals of risk factors associated with term birth weight (*g*) and preterm birth in Sedgwick County, Kansas, 2005-2013

	Mean Difference in tBW	Hazard Ratio for PTB
Infant sex		
Female	-123.4 (-130.2, -116.5)	0.89 (0.85, 0.95)
Conception season		
Spring	-7.6 (-17.6, 2.3)	1.00 (0.93, 1.09)
Summer	-0.4 (-10.3, 9.5)	1.00 (0.92, 1.08)
Autumn	-4.3 (-14.2, 5.5)	0.99 (0.91, 1.07)
Body mass index (BMI)		
[13.2 - 20.9]	392.6 (341.3, 443.9)	0.36 (0.26, 0.51)
(20.9 - 23.3]	436.8 (378.9, 494.6)	0.33 (0.23, 0.48)
(23.3 - 26.3]	406.1 (364.3, 447.9)	0.69 (0.51, 0.92)
(26.3 - 30.9]	822.5 (691.8, 953.3)	0.16 (0.07, 0.38)
(30.9 - 74]	414.9 (292.1, 537.8)	0.68 (0.3, 1.54)
Maternal age (years)		
[12 - 21]	-91.8 (-142.6, -41)	1.02 (0.7, 1.49)
(21 - 25]	-86.1 (-144.9, -27.2)	1.00 (0.64, 1.55)
(25 - 28]	16.1 (-24.2, 56.4)	1.38 (1.01, 1.87)
(28 - 32]	-222.1 (-355.5, -88.7)	1.77 (0.66, 4.72)
(32 - 54]	-97.6 (-217.4, 22.1)	2.52 (1.09, 5.82)
Maternal education		
High school/GED	20.3 (9.3, 31.2)	0.90 (0.83, 0.98)
Some college/AA	45.7 (33.9, 57.6)	0.80 (0.73, 0.88)
BA+	87.9 (74.4, 101.4)	0.64 (0.57, 0.71)
Maternal race		
Black	-172.9 (-185, -160.9)	1.36 (1.25, 1.48)
Native American/Alaskan	11.2 (-36, 58.5)	1.08 (0.76, 1.52)
API	-176.7 (-194.3, -159.1)	1.08 (0.94, 1.24)
Multiracial	-36.5 (-61.2, -11.8)	0.96 (0.78, 1.17)
Other	-19.6 (-43.1, 3.9)	1.30 (1.09, 1.56)
Maternal ethnicity		
Hispanic	24.1 (13.6, 34.5)	0.77 (0.71, 0.84)
Marital status		
Unmarried	-52.3 (-60.9, -43.6)	1.18 (1.1, 1.26)
Pre-pregnancy diabetes		
Present	201.2 (155.1, 247.2)	2.78 (2.27, 3.39)
Pre-pregnancy hypertension		

Present	-184.3 (-218.8, -149.8)	2.31 (1.96, 2.73)
Median household income ($)		
(36,900, 45,600]	14.7 (4.5, 24.8)	0.97 (0.89, 1.05)
(45,600, 59,800]	24.4 (13.2, 35.7)	0.86 (0.79, 0.95)
(59,800, 172,000]	32.6 (22.5, 42.7)	0.88 (0.81, 0.96)

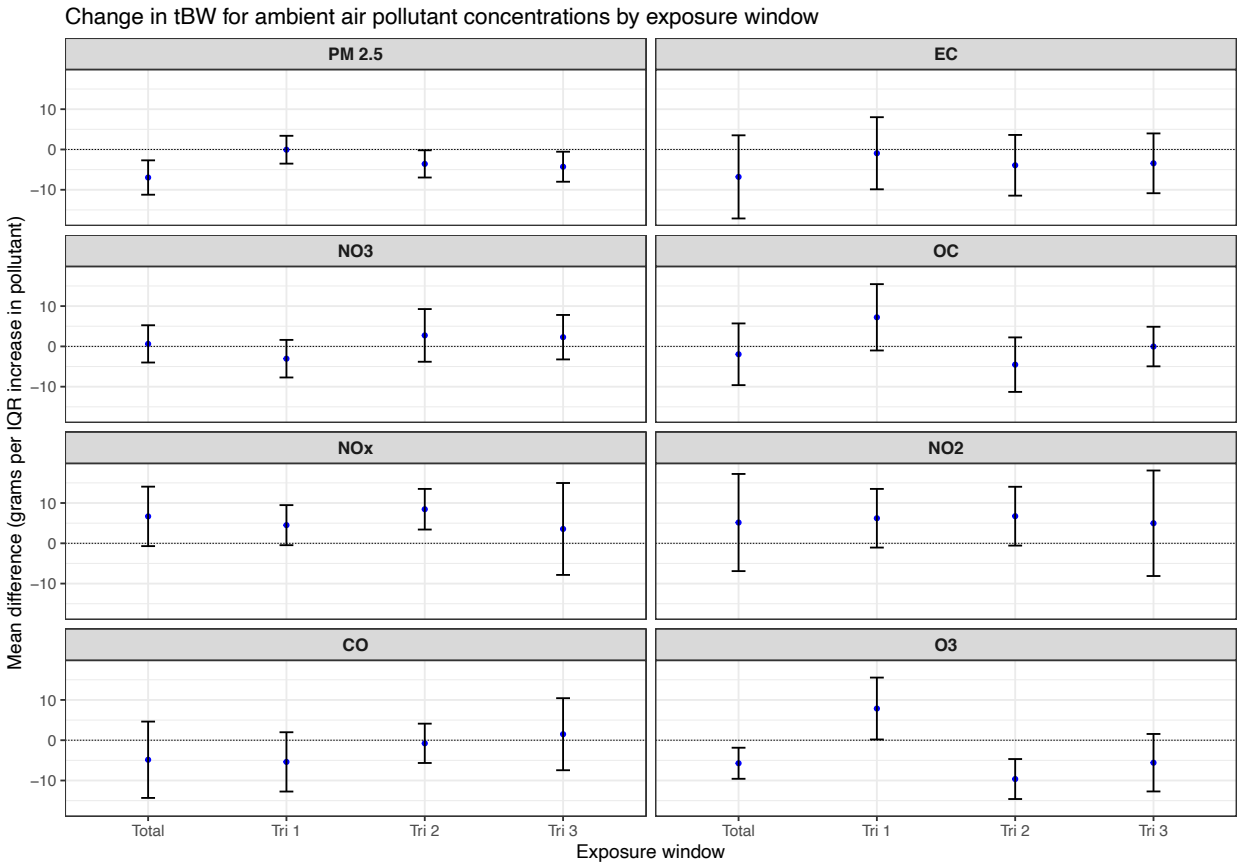

Figure 1: Panel plots of the mean change in term birth weight across eight different ambient air pollutants

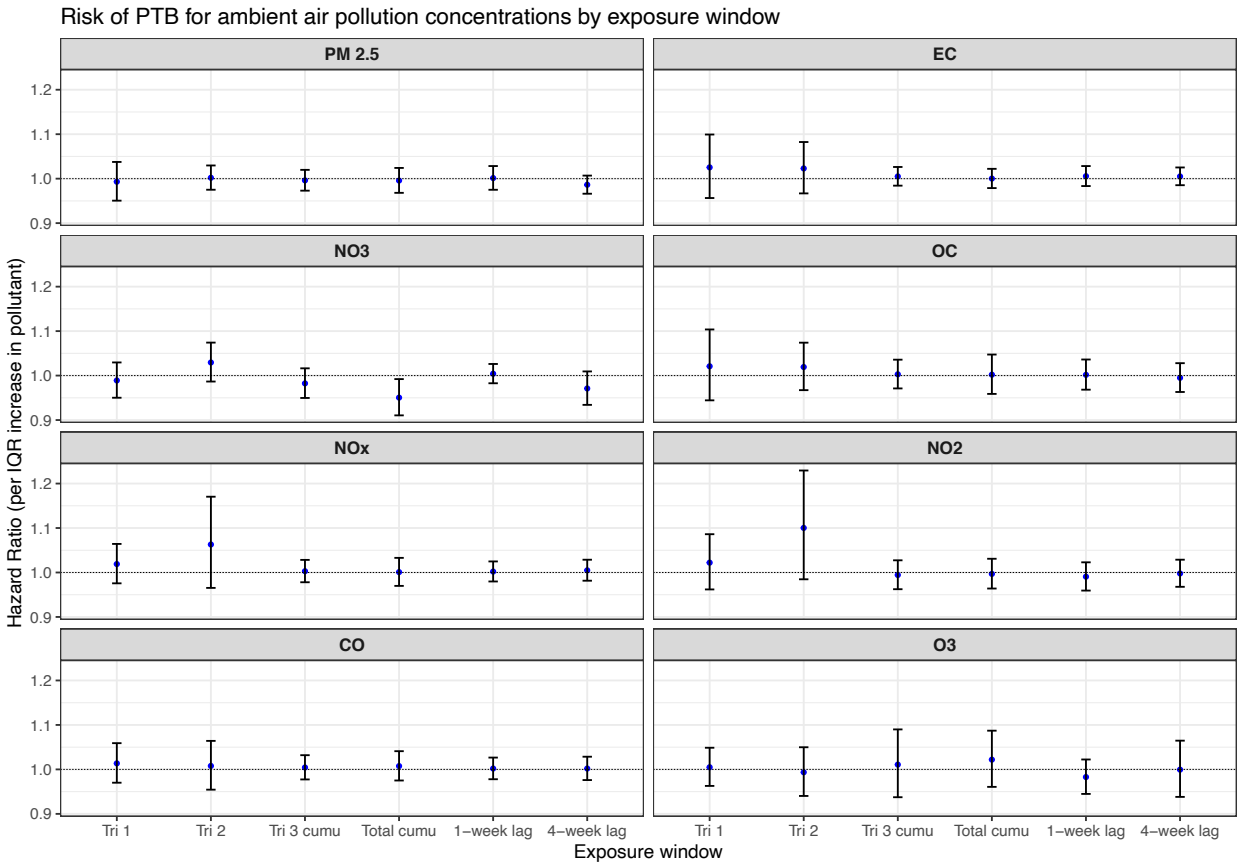

Figure 2: Panel plots of the risk of preterm birth across eight different ambient air pollutants

Supplementary Table 1: Characteristics of the study population for term birth weight analysis in Kansas, 2005-2013

	Overall (N=302647)
Birth weight (g)	
Mean (SD)	3403.870 (454.297)
Gestational age (weeks)	
Mean (SD)	39.051 (1.047)
Infant sex	
Male	153921 (50.9%)
Female	148726 (49.1%)
Conception season	
Winter	76840 (25.4%)
Spring	73931 (24.4%)
Summer	74928 (24.8%)
Autumn	76948 (25.4%)
Body mass index (BMI)	
Mean (SD)	26.267 (6.353)
Maternal age (years)	
Mean (SD)	27.021 (5.715)
Maternal education	
< High School	49647 (16.4%)
High School/GED	71335 (23.6%)
Some college/AA	91099 (30.1%)
Bachelors+	90566 (29.9%)
Maternal race	
White	248220 (82.0%)
Black	21079 (7.0%)
Native American/Alaskan	1969 (0.7%)
API	9381 (3.1%)
Multiracial	5723 (1.9%)
Other	16275 (5.4%)
Maternal ethnicity	
Non-Hispanic	253720 (83.8%)
Hispanic	48927 (16.2%)
Marital status	
Married	191754 (63.4%)

Unmarried	110893 (36.6%)
Pre-pregnancy diabetes	
Absent	300887 (99.4%)
Present	1760 (0.6%)
Pre-pregnancy hypertension	
Absent	299806 (99.1%)
Present	2841 (0.9%)
Median household income ($)	
[9,380, 36,900]	77106 (25.5%)
(36,900, 45,600]	62377 (20.6%)
(45,600, 59,800]	77305 (25.5%)
(59,800, 172,000]	85859 (28.4%)

Supplementary Table 2: Characteristics of the study population for preterm birth analysis in Kansas, 2005-2013

	Overall (N=318485)
Birth weight (g)	
Mean (SD)	3340.479 (524.013)
Preterm birth	
Non-preterm	296129 (93.0%)
Preterm	22356 (7.0%)
Gestational age (weeks)	
Mean (SD)	38.734 (1.639)
Infant sex	
Male	162602 (51.1%)
Female	155883 (48.9%)
Conception season	
Winter	80857 (25.4%)
Spring	77948 (24.5%)
Summer	78862 (24.8%)
Autumn	80818 (25.4%)
Body mass index (BMI)	
Mean (SD)	26.264 (6.382)
Maternal age (years)	
Mean (SD)	27.027 (5.737)
Maternal education	
< High School	52627 (16.5%)
High School/GED	75502 (23.7%)
Some college/AA	95699 (30.0%)
BA+	94657 (29.7%)
Maternal race	
White	262031 (82.3%)
Black	22993 (7.2%)
Native American/Alaskan	1517 (0.5%)
API	9600 (3.0%)
Multiracial	5577 (1.8%)
Other	16767 (5.3%)
Maternal ethnicity	

Non-Hispanic	267691 (84.1%)
Hispanic	50794 (15.9%)
Marital status	
Married	200572 (63.0%)
Unmarried	117913 (37.0%)
Pre-pregnancy diabetes	
Absent	316490 (99.4%)
Present	1995 (0.6%)
Pre-pregnancy hypertension	
Absent	315490 (99.1%)
Present	2995 (0.9%)
Median household income ($)	
[9,380, 36,900]	82500 (25.9%)
(36,900, 45,600]	64774 (20.3%)
(45,600, 59,800]	80070 (25.1%)
(59,800, 172,000]	91141 (28.6%)

Supplementary Table 3: Exposure characteristics for term birth weight sample

	Total Pregnancy	Trimester 1	Trimester 2	Trimester 3
$PM_{2.5}$ $(\mu g/m^3)$				
Mean (SD)	9.43 ± 1.40	9.52 ± 1.86	9.44 ± 1.72	9.35 ± 1.66
IQR	1.77	2.41	2.26	2.18
EC $(\mu g/m^3)$				
Mean (SD)	0.41 ± 0.16	0.41 ± 0.17	0.41 ± 0.17	0.41 ± 0.17
IQR	0.2	0.22	0.22	0.22
NO_3 $(\mu g/m^3)$				
Mean (SD)	1.72 ± 0.52	1.75 ± 1.16	1.73 ± 1.08	1.70 ± 1.08
IQR	0.82	1.84	1.76	1.74
OC $(\mu g/m^3)$				
Mean (SD)	2.18 ± 0.89	2.23 ± 0.99	2.18 ± 0.95	2.13 ± 0.91
IQR	1.33	1.42	1.33	1.24
NO_x (ppb)				
Mean (SD)	26.33 ± 14.90	26.81 ± 17.65	26.33 ± 17.07	25.94 ± 16.97
IQR	24.07	23.81	23.35	22.73
NO_2 (ppb)				
Mean (SD)	15.70 ± 6.52	15.87 ± 7.05	15.72 ± 6.96	15.53 ± 6.89
IQR	11.03	11.81	11.71	11.51
CO (ppm)				
Mean (SD)	0.41 ± 0.19	0.42 ± 0.21	0.41 ± 0.20	0.40 ± 0.20
IQR	0.3	0.3	0.29	0.28
O_3 (ppm)				
Mean (SD)	0.041 ± 0.004	0.040 ± 0.009	0.041 ± 0.009	0.041 ± 0.008
IQR	0.006	0.015	0.014	0.013

Supplementary Table 4: Fixed-time exposure characteristics for preterm birth sample

	Trimester 1	Trimester 2
$PM_{2.5}$ $(\mu g/m^3)$		
Mean (SD)	9.55 ± 1.85	9.47 ± 1.71
IQR	2.4	2.24
EC $(\mu g/m^3)$		
Mean (SD)	0.41 ± 0.17	0.41 ± 0.17
IQR	0.22	0.21
NO_3 $(\mu g/m^3)$		
Mean (SD)	1.75 ± 1.16	1.73 ± 1.09
IQR	1.85	1.77
OC $(\mu g/m^3)$		
Mean (SD)	2.25 ± 0.99	2.20 ± 0.95
IQR	1.43	1.34
NO_x (ppb)		
Mean (SD)	27.11 ± 17.66	26.62 ± 17.08
IQR	23.93	23.43
NO_2 (ppb)		
Mean (SD)	16.01 ± 7.03	15.87 ± 6.94
IQR	11.74	11.65
CO (ppm)		
Mean (SD)	0.42 ± 0.21	0.41 ± 0.20
IQR	0.31	0.29
O_3 (ppm)		
Mean (SD)	0.040 ± 0.009	0.041 ± 0.009
IQR	0.015	0.014

Supplementary Table 5: Time-varying exposure characteristics for preterm birth sample

	Trimester 3 (time-varying)	Total Pregnancy (time-varying)	1-week lag (time-varying)	4-week lag (time-varying)
$PM_{2.5}$				
Mean (SD)	9.40 ± 2.21	8.88 ± 1.36	9.38 ± 3.01	9.40 ± 2.20
IQR	2.78	1.71	3.78	2.93
EC				
Mean (SD)	0.41 ± 0.18	0.39 ± 0.15	0.41 ± 0.21	0.41 ± 0.18
IQR	0.23	0.19	0.25	0.23
NO_3				
Mean (SD)	1.70 ± 1.28	1.62 ± 0.65	1.70 ± 1.52	1.70 ± 1.28
IQR	1.85	1.01	1.83	1.86
OC				
Mean (SD)	2.16 ± 1.01	2.07 ± 0.85	2.15 ± 1.15	2.15 ± 1.01
IQR	1.35	1.26	1.43	1.36
NO_x				
Mean (SD)	26.29 ± 18.20	25.03 ± 14.45	26.23 ± 20.38	26.26 ± 18.14
IQR	22.93	22.63	22.44	22.96
NO_2				
Mean (SD)	15.70 ± 7.19	14.87 ± 6.18	15.67 ± 7.79	15.69 ± 7.18
IQR	11.6	10.51	11.67	11.57
CO				
Mean (SD)	0.40 ± 0.21	0.39 ± 0.18	0.40 ± 0.23	0.40 ± 0.21
IQR	0.28	0.28	0.28	0.28
O_3				
Mean (SD)	0.041 ± 0.010	0.038 ± 0.005	0.041 ± 0.010	0.041 ± 0.010
IQR	0.015	0.007	0.016	0.015

Supplementary Table 6: Unadjusted regression estimates and associated 95% confidence intervals of risk factors associated with term birth weight (*g*) and preterm birth in Sedgwick County, Kansas, 2005-2013

	Mean Difference in tBW	Hazard Ratio for PTB
Infant sex		
Female	-122.7 (-129.9, -115.6)	0.89 (0.84, 0.94)
Conception season		
Spring	-8.9 (-19.1, 1.3)	1.01 (0.93, 1.09)
Summer	2.5 (-7.7, 12.7)	0.99 (0.91, 1.07)
Autumn	-1.7 (-11.8, 8.4)	0.98 (0.91, 1.06)
Body mass index (BMI)		
[13.2 - 20.9]	487.6 (434.8, 540.4)	0.30 (0.22, 0.42)
(20.9 - 23.3]	520.7 (461.1, 580.3)	0.29 (0.2, 0.42)
(23.3 - 26.3]	454.4 (411.5, 497.4)	0.69 (0.51, 0.92)
(26.3 - 30.9]	939.9 (805.2, 1074.7)	0.19 (0.08, 0.43)
(30.9 - 74]	365.4 (238.8, 492)	1.49 (0.67, 3.3)
Maternal age (years)		
[12 - 21]	91.5 (41.3, 141.6)	0.71 (0.5, 1.01)
(21 - 25]	122.8 (64.2, 181.4)	0.61 (0.4, 0.93)
(25 - 28]	202.5 (162.2, 242.9)	0.89 (0.66, 1.19)
(28 - 32]	85.4 (-49.3, 220.1)	1.06 (0.41, 2.74)
(32 - 54]	54.0 (-70.3, 178.3)	2.16 (0.94, 4.95)
Maternal education		
High school/GED	21.7 (11.2, 32.3)	0.93 (0.86, 1)
Some college/AA	75.1 (64.3, 85.8)	0.81 (0.75, 0.88)
BA+	151.1 (140.3, 161.9)	0.60 (0.55, 0.65)
Maternal race		
Black	-220.6 (-232.1, -209.1)	1.67 (1.55, 1.8)
Native American/Alaskan	-14.5 (-63.2, 34.3)	1.35 (0.96, 1.9)
API	-211.1 (-228.9, -193.3)	1.16 (1.01, 1.33)
Multiracial	-67.8 (-93.2, -42.5)	1.07 (0.87, 1.31)
Other	-32.5 (-55.8, -9.2)	1.26 (1.06, 1.5)
Maternal ethnicity		
Hispanic	16.9 (7.5, 26.2)	0.89 (0.82, 0.96)
Marital status		
Unmarried	-126.0 (-133.2, -118.8)	1.40 (1.33, 1.48)
Pre-pregnancy diabetes		
Present	242.7 (194.6, 290.7)	3.34 (2.75, 4.07)
Pre-pregnancy hypertension		

Present	-115.2 (-151, -79.4)	2.85 (2.43, 3.35)
Median household income ($)		
(36,900, 45,600]	42.3 (32.1, 52.5)	0.89 (0.82, 0.96)
(45,600, 59,800]	77.3 (66.3, 88.4)	0.75 (0.69, 0.82)
(59,800, 172,000]	103.2 (94.4, 112)	0.71 (0.66, 0.76)

Supplementary Table 7: Mean difference in term birth weight (*g*) by exposure window from meta-analysis of 57 counties in Kansas, 2005-2013

	Total Pregnancy	Trimester 1	Trimester 2	Trimester 3
$PM_{2.5}$				
Pooled effect	-6.96 (-11.23, -2.69)	-0.06 (-3.51, 3.4)	-3.58 (-6.96, -0.2)	-4.28 (-8, -0.55)
Variance	0	3.813	0	4.59
EC				
Pooled effect	-6.80 (-17.12, 3.52)	-0.94 (-9.89, 8.01)	-3.93 (-11.45, 3.6)	-3.44 (-10.86, 3.98)
Variance	128.553	145.894	62.152	57.321
NO_3				
Pooled effect	0.62 (-4, 5.25)	-3.05 (-7.72, 1.61)	2.72 (-3.81, 9.26)	2.28 (-3.23, 7.8)
Variance	15.914	0	85.503	26.957
OC				
Pooled effect	-1.96 (-9.61, 5.7)	7.22 (-1.01, 15.45)	-4.53 (-11.29, 2.23)	-0.04 (-4.95, 4.87)
Variance	20.001	163.509	39.299	0
NO_x				
Pooled effect	6.68 (-0.7, 14.06)	4.50 (-0.47, 9.47)	8.46 (3.41, 13.5)	3.56 (-7.85, 14.97)
Variance	3.904	0	0	166.451
NO_2				
Pooled effect	5.15 (-6.9, 17.21)	6.22 (-1.06, 13.5)	6.73 (-0.57, 14.03)	4.97 (-8.12, 18.07)
Variance	95.689	0	0	243.429
CO				
Pooled effect	-4.85 (-14.32, 4.63)	-5.38 (-12.74, 1.98)	-0.77 (-5.65, 4.11)	1.49 (-7.45, 10.43)
Variance	108.764	53.379	0	127.434
O_3				
Pooled effect	-5.72 (-9.58, -1.86)	7.86 (0.18, 15.54)	-9.63 (-14.59, -4.67)	-5.58 (-12.72, 1.55)
Variance	0	147.38	0	115.895

Supplementary Table 8: Risk of preterm birth by time-independent exposure window from meta-analysis of 57 counties in Kansas, 2005-2013

	Trimester 1	Trimester 2
$PM_{2.5}$		
Pooled effect	0.99 (0.95, 1.04)	1.00 (0.98, 1.03)
Variance	0.005	0
EC		
Pooled effect	1.03 (0.96, 1.1)	1.02 (0.97, 1.08)
Variance	0.005	0.002
NO_3		
Pooled effect	0.99 (0.95, 1.03)	1.03 (0.99, 1.07)
Variance	0	0
OC		
Pooled effect	1.02 (0.94, 1.1)	1.02 (0.97, 1.07)
Variance	0.016	0.001
NO_x		
Pooled effect	1.02 (0.98, 1.06)	1.06 (0.97, 1.17)
Variance	0	0.01
NO_2		
Pooled effect	1.02 (0.96, 1.09)	1.10 (0.98, 1.23)
Variance	0	0.015
CO		
Pooled effect	1.01 (0.97, 1.06)	1.01 (0.95, 1.06)
Variance	0	0.001
O_3		
Pooled effect	1.00 (0.96, 1.05)	0.99 (0.94, 1.05)
Variance	0	0.004

Supplementary Table 9: Risk of preterm birth by time-dependent exposure window from meta-analysis of 57 counties in Kansas, 2005-2013

	Total Pregnancy (time-varying)	Cumulative Trimester 3 (time-varying)	1-week lag	4-week lag
$PM_{2.5}$				
Pooled effect	1.00 (0.97, 1.02)	1.00 (0.97, 1.02)	1.00 (0.98, 1.03)	0.99 (0.97, 1.01)
Variance	0.001	0	0.002	0
EC				
Pooled effect	1.00 (0.98, 1.02)	1.01 (0.98, 1.03)	1.01 (0.98, 1.03)	1.01 (0.99, 1.03)
Variance	0.001	0	0.001	0
NO_3				
Pooled effect	0.95 (0.91, 0.99)	0.98 (0.95, 1.02)	1.00 (0.98, 1.03)	0.97 (0.93, 1.01)
Variance	0.001	0	0	0.001
OC				
Pooled effect	1.00 (0.96, 1.05)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)	0.99 (0.96, 1.03)
Variance	0.003	0.001	0.002	0.001
NO_x				
Pooled effect	1.00 (0.97, 1.03)	1.00 (0.98, 1.03)	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)
Variance	0.002	0.001	0.001	0.001
NO_2				
Pooled effect	1.00 (0.96, 1.03)	0.99 (0.96, 1.03)	0.99 (0.96, 1.02)	1.00 (0.97, 1.03)
Variance	0.002	0.002	0.003	0.001
CO				
Pooled effect	1.01 (0.98, 1.04)	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)
Variance	0.002	0.001	0.001	0.001
O_3				
Pooled effect	1.02 (0.96, 1.09)	1.01 (0.94, 1.09)	0.98 (0.94, 1.02)	1.00 (0.94, 1.06)
Variance	0.012	0.017	0.002	0.012