Published in final edited form as:

Epidemiology. 2011 July ; 22(4): 524–531. doi:10.1097/EDE.0b013e31821c6c58.

Particulate Air Pollution Exposure and C-reactive Protein During Early Pregnancy

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Abstract

Background—It is not well understood how air pollution leads to adverse pregnancy outcomes. One pathway may be through C-reactive protein, a biomarker of systemic inflammation that has been reported to increase the risk of preterm delivery. We examined whether air pollution influences serum concentrations of C-reactive protein in early pregnancy.

Methods—We studied 1696 pregnant women in Allegheny County, PA, from 1997 through 2001. C-reactive protein concentrations were assayed in blood collected before the 22nd week of gestation. We estimated levels of particles of less than 10 μm (PM_{10}) and less than 2.5 μm diameter ($\text{PM}_{2.5}$), carbon monoxide, nitrogen dioxide, sulfur dioxide, and ozone at the maternal zip code using Kriging interpolation for measurements obtained from ambient stations. Associations between air pollution and high C-reactive protein concentrations ($> 8 \text{ ng/mL}$) were evaluated using logistic regression.

Results—Among nonsmokers, an observed 9.2 $\mu\text{g}/\text{m}^3$ increase in PM_{10} (averaged over 28 days prior to the blood sample) was associated with an odds ratios of 1.41 for high C-reactive protein concentrations (95% confidence interval = 0.99–2.00). Similarly, a 4.6 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was associated with an odds ratio of 1.47 (1.05–2.06). The odds ratio was 1.49 (0.75–2.96) per 7.9 ppb increase in ozone during summer. There were no associations in smokers or for other air pollutants, and there was no evidence for effect-measure modification by obesity.

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Conclusions—PM₁₀, PM_{2.5}, and ozone exposures were associated with increased C-reactive protein concentrations in early pregnancy, suggesting that these air pollutants contribute to inflammation and thereby possibly to adverse pregnancy outcomes.

Numerous studies have linked ambient air pollution to adverse pregnancy outcomes, such as preterm birth, low birth weight (LBW), small size for gestational age (SGA), whereas a few have also investigated preeclampsia, perinatal mortality, and cardiac birth defects.¹⁻⁷ Positive associations have been described most consistently for particulate matter exposures and preterm birth, especially particulate exposure during the first and third trimester of pregnancy.⁸ Some studies relying on measures of traffic density have suggested that motor vehicle exhaust may be an important source of particulates.^{9,10} The biologic mechanisms by which air pollution might affect pregnancy, however, are not well understood.

Inflammation is one pathway believed to be involved in particulate-induced adverse health outcomes (particularly cardiovascular diseases),^{11,12} and has also been hypothesized to influence birth outcomes.¹³ Animal studies provide strong evidence that particulate exposure can cause localized inflammation. Particles of less than 10 μm diameter (PM₁₀) and less than 2.5 μm diameter (PM_{2.5}) elicit pulmonary inflammation in rats.^{12,14} Similarly, exposures to diesel exhaust particles and ultrafine carbon particles have been reported to induce an inflammatory reaction in the lungs of mice.¹⁵ Growing epidemiologic evidence suggests that exposure to air pollution, especially particulates, is associated with not only pulmonary inflammatory and immune responses but also with systemic inflammation as measured by interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), C-reactive protein, fibrinogen, and white cell counts.¹⁶⁻²⁰ C-reactive protein is a sensitive marker of inflammation and infection.²¹ Previous studies have described positive associations of C-reactive protein with air pollution in various populations including healthy men, the elderly, and people with coronary heart disease.^{17-20,22}

To our knowledge, no studies have evaluated whether air pollution exposure increases the systemic inflammatory response in pregnant women. This is of particular interest because the special state of immune response during pregnancy allows the mother to tolerate the semi-allogeneic fetus.²³ Particulate exposure during pregnancy has been hypothesized to induce acute placental inflammation. Alternatively, systemic inflammatory responses may lead to alterations in maternal immunity, and in turn increase the risk of adverse birth outcomes.¹³ We explore this hypothesis in a cohort of pregnant women in Pennsylvania, among whom we have previously demonstrated that inflammation (measured by C-reactive protein) during early pregnancy is associated with increased risk of preterm delivery.²⁴

METHODS

Study Population

The study population was drawn from the Prenatal Exposures and Preeclampsia Prevention study, which enrolled 2211 Pennsylvania women from clinics and private practices between 1997 and 2001. Briefly, this prospective study recruited healthy women, ages 14–44 years and pregnant for less than 16 weeks, and followed them to delivery. A comprehensive questionnaire was administered at baseline and postpartum. Information obtained in the

baseline questionnaire included maternal demographic characteristics, socioeconomic status, active and passive cigarette smoking, consumption of alcohol, other lifestyle factors, and medical history. We also obtained maternal residential zip code information at delivery from the hospital record. We excluded women with preexisting medical conditions ($n = 37$), including chronic hypertension, chronic diabetes, and HIV, to avoid large variations in C-reactive protein concentrations resulting from these conditions. Because we were interested in inflammation in the first half of pregnancy, we also excluded women without a blood sample taken before 22 weeks of gestation ($n = 145$). Additionally, we limited our analysis to singleton births and first-time participants in the study who had a maternal residence zip code in Allegheny County, PA. There were 1696 women included in this analysis.

Biomarker Assessment

Maternal nonfasting blood samples were stored and frozen at -80°C . We measured C-reactive protein concentrations with a high-sensitivity enzyme-linked immunosorbent assay (ELISA) on the SpectraMax Me analyzer (Molecular Devices, United States), as described elsewhere.²⁵ The detection limit of the assay was 0.03 ng/mL, with an intraassay variability of 7%.

Exposure Assessment

We obtained ambient air pollution data, from the Allegheny County Health Department and the Air Quality System (<http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloaddaqsdata.htm>) of the Environmental Protection Agency (EPA) for the years 1996–2001. These data included concentrations of carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), PM_{10} , and $\text{PM}_{2.5}$ for Allegheny County and its neighboring counties (within 50 km of the Allegheny County boundary). From 1999 to 2001, $\text{PM}_{2.5}$ data were collected at 23 monitoring stations, including 13 monitoring stations in Allegheny County and 10 monitoring stations in neighboring counties. PM_{10} measurements were available from 40 stations (18 monitoring stations in Allegheny County), SO_2 from 32 stations (7 monitoring stations in Allegheny County), and O_3 from 15 stations (3 monitoring stations in Allegheny County), whereas only 11 stations measured NO_2 and CO during the study period (3 and 2 monitoring stations, respectively, in Allegheny County). For each station, the data include 1-hour concentrations for CO, NO_2 , O_3 , and SO_2 , and 24-hour concentrations (some collected every day and others collected every third or sixth day) for $\text{PM}_{2.5}$ and PM_{10} . Although not every $\text{PM}_{2.5}$ and PM_{10} monitoring station collected information every day, there are very few days during our study period on which no monitoring station collected data. Meteorologic variables, including hourly temperature and daily relative humidity for the Pittsburgh International Airport, Pittsburgh, PA monitoring station, were obtained from the National Climate Data Center (<http://www.ncdc.noaa.gov/oa/ncdc.html>).

We used the space-time ordinary Kriging interpolation method to estimate daily air pollution concentrations at the zip code level by calculating the average estimated zip code concentration for each pollutant based on all grid centroid values (grid size = 13.4 m^2) that fall within a zip code. Spatial and temporal variograms were fitted into a spherical semivariogram model separately, based on temporally detrended residuals (eTable 1, <http://>

[links.lww.com/EDE/A478](https://www.lww.com/EDE/A478)). In addition, we combined the spatial and temporal variograms into a space-time variogram by fitting a general product-sum model.²⁶ This modification of space-time ordinary kriging has been shown to increase mean precision compared with ordinary kriging.²⁷

Statistical Analysis

We used logistic regression analyses to evaluate the associations between air pollution and C-reactive protein during early pregnancy. We dichotomized C-reactive protein concentrations at 8 ng/mL, a threshold we previously found associated with an increased risk of preterm birth.^{24,28} We also evaluated C-reactive protein as a continuous measure in linear regression models after log transformation, which was necessary to normalize the residuals of C-reactive protein and air pollution concentrations. We present our results from these models as percentage changes. For all regression models, we used the robust cluster variance estimator to account for clustering of maternal residences in zip codes. Our primary interest was to explore the influence of medium- to long-term pollutant concentrations for 3 periods before the blood draw (ie, 8-day averages [Day 0–7], 22-day averages [Day 0–21], and 29-day averages [Day 0–28 before blood collection]). These averaging periods were chosen a priori. In addition, we explored short-term (single-day) exposures; ie, on the same day (lag 0) and to a maximum of 7 days before a blood draw (lag 1–lag 7), based on previous reports suggesting that systemic inflammation may increase within 7 days after a pollutant exposure.^{18,22,29} To estimate the influence of both short- and longer- term exposures, we relied on continuous pollutant measures and interquartile ranges (IQR).

In all models, we controlled for gestational week in which the sample was collected (weeks), maternal body mass index (BMI) at enrollment or time of blood draw (kg/m^2), maternal age (years), maternal race (white, African American), maternal education (less than high school, high school, completed high school but did not complete college, completed college or greater), parity (first birth, second or subsequent birth), maternal cigarette exposure during early pregnancy (active smoker, nonactive smoker but exposed to cigarette smoke at home or indoors elsewhere, nonactive and nonpassive smoker), household income (< \$10,000, \$10,000 –\$19,999, \$20,000 –\$49,999, \$50,000), season of sample collection (spring, summer, fall, winter), and year entering the study (for PM_{10} and other pollutants, spanning 1997–2001; for $\text{PM}_{2.5}$, 1999–2001). We also evaluated other potential confounders including marital status, alcohol intake during pregnancy, multivitamin or prenatal vitamin use, aspirin use within a year prior to pregnancy, employment, public assistance, daily mean temperature, and relative humidity. Because these factors did not change the estimates for pollutants by more than 10%, they were not included in the models we present here.³⁰

Previous studies have suggested that obesity and smoking status may modify the influence of air pollution on inflammation.^{20,22,31,32} Thus, we also conducted stratified analyses for obesity (defined as $\text{BMI} \geq 30 \text{ kg/m}^2$) and analyses for nonsmokers only. Although women entered the study at various gestational ages, the mean BMI of women whose baseline blood was collected before 8 gestational weeks, at 8 to less than 12 weeks, and at 12 to 22 weeks of gestation were quite similar; (27.0 kg/m^2 [standard deviation = 7.4], 25.9 kg/m^2 [6.1], and 26.7 kg/m^2 [6.5], respectively). In addition, we performed sensitivity analyses restricting

analyses to nonsmokers without environmental tobacco smoke exposure (ETS; nonsmokers who reported exposure to cigarette smoke at home or indoors elsewhere). Only one monitoring station measured ozone between October and March in the study period; thus, the analysis for ozone was restricted to the summer months (April–September) when data were available for more stations.

RESULTS

Blood samples were collected at a mean of 10.2 (SD = 4.0) gestational weeks. The mean BMI in early pregnancy (at baseline) was 26.5 kg/m² (SD = 6.7). In univariate and adjusted models, the crude odds ratio for elevated C-reactive protein concentrations (> 8 ng/mL) was higher in women for whom samples were collected later in gestation, who had higher BMI, were older, or were African-American (Table 1), but not in women actively smoking or passively exposed to cigarette smoke during early pregnancy.

Table 2 summarizes means and correlations for mean pollutant concentrations 0 to 7 days before blood collection; correlations were very similar for longer averaging periods, but means were slightly lower. Average 8-day PM₁₀ concentrations were highly correlated with PM_{2.5} (r = 0.9) and moderately with O₃ (r = 0.5), but very weakly correlated with CO, SO₂, and NO₂. Similarly, PM_{2.5} was moderately correlated with O₃ (r = 0.5) but only weakly correlated with CO, SO₂, and NO₂.

Ambient Air Pollution and C-reactive protein

Longer averaging periods (ie, 0–21 and 0–28 day averages for PM₁₀) increased the odds of having a C-reactive protein concentration >8 ng/mL (Table 3). For an IQR increase in PM₁₀, the odds ratios of a C-reactive protein >8 ng/mL were 1.23 (95% CI = 0.97–1.57) based on a 22-day average and 1.18 (CI = 0.91–1.53) based on a 29-day average, in adjusted single-pollutant models for the entire population. PM_{2.5} exposures also increased the ORs for high C-reactive protein concentrations when using longer averaging periods; for a 22-day average, the ORs were 1.32 (95% CI = 1.05–1.67) and for a 29-day average, 1.26 (0.97–1.63) per IQR increase in adjusted single-pollutant models (Table 3). When we restricted our analyses to nonsmokers only, effect estimates were generally larger for both PM₁₀ and PM_{2.5}. For each IQR increase in PM₁₀ exposure, the ORs for elevated C-reactive protein concentrations were 1.47 (1.06–2.02) based on a 22-day average, and 1.41 (0.99–2.00), based on a 29-day average, in adjusted single-pollutant models for nonsmokers; for each IQR increase in PM_{2.5} exposure, they were 1.55 (1.15–2.11) and 1.47 (1.05–2.06), respectively (Table 3).

Generally, effect estimates for both PM₁₀ and PM_{2.5} were larger between lag days 2 and 5. For nonsmokers, a per-IQR increase in PM₁₀ exposure was associated with increased C-reactive protein during lag days 4 and 5, whereas PM_{2.5} exposure was associated with modestly increased C-reactive protein during lag days 1, 2, 4, and 5 (eTable 2, <http://links.lww.com/EDE/A478>). When we examined associations based on percentage change of log-transformed C-reactive protein in linear regression single-pollutant models, C-reactive protein increased by 6%–17% per IQR increase in PM₁₀ or PM_{2.5} among smokers (Figure). For nonsmokers, there was only a 2% increase in C-reactive protein per IQR increase in

PM_{2.5} during a 22-day average period, and 3%–5% increases for an IQR increase in PM₁₀ for longer periods (ie, 0–21 and 0–28 day averages). When we examined interactions between BMI and particulates, the 95% confidence intervals of the estimates included 1.0 (data not shown). We found no evidence for effect measure modification by obesity; ie, the effect estimates (ORs) for particulates on C-reactive protein were similar in women with a BMI >30 kg/m² and <30 kg/m² in early pregnancy.

Positive associations were also observed between O₃ and C-reactive protein for all longer averaging periods (Table 3). Generally, the estimates for particulates (PM₁₀ and PM_{2.5}) and O₃ air pollution were slightly larger for nonsmokers not exposed to ETS (eTable 3, <http://links.lww.com/EDE/A478>). However, excluding those with ETS exposure from the nonsmoking group greatly reduced the sample size and precision of our estimates. For CO, SO₂, and NO₂, associations were negligible for both the entire population and nonsmokers only (eg, per IQR increase in the 29-day average of CO in adjusted singlepollutant models, OR = 1.05 [CI = 0.86–1.30] in the entire population; for nonsmokers only, OR = 0.95 [0.71–1.27]).

DISCUSSION

We observed positive associations between particulate (both PM_{2.5} and PM₁₀) and O₃ air pollution and elevated concentrations of a systemic inflammatory biomarker, C-reactive protein, in nonsmoking women during early pregnancy. These findings support the hypothesis that these exposures during pregnancy induce an inflammatory response that may result in an increased risk for adverse birth outcomes—especially preterm birth, which we have previously shown to be associated with these higher C-reactive protein concentrations (>8 ng/mL).²⁴

To date, few studies have examined associations between air pollution and inflammation in pregnant women, even though this has been studied extensively in other susceptible populations such as the elderly and children.^{17,19,22,32} We found primarily medium-term particulate exposures (up to 28 days prior to blood collection) to be associated with C-reactive protein concentrations above 8 ng/mL, a level that previous studies had linked to an increase in preterm birth risk.^{24,28} However, because of insufficient sample size (99 preterm births among 1129 nonsmoking women) and thus low statistical power, we are unable to examine whether inflammation (specifically C-reactive protein) plays a mediating role for the associations between air pollutants and adverse birth outcomes. Nevertheless, our findings that particulates and O₃ increase the odds of having elevated C-reactive protein concentrations in early pregnancy provide some insight into pathways through which air pollution may influence birth outcomes.

Although the air pollutants related to gaseous combustion (CO, NO₂, and SO₂) have also previously been associated with adverse birth outcomes,^{1,2,8} we did not find associations with high C-reactive protein in our study. In Allegheny County, the major sources of CO, NO₂, and particles are motor vehicles and industrial plants. With the same sources of origin, we would expect particles, CO, and NO₂ to be positively correlated. However, we observed only very weak correlations between measures of particle, CO, and NO₂. This is most likely

due to a very small number of monitoring stations that measured CO and NO₂ (2 and 3 monitoring stations, respectively) in all of Allegheny County. Because CO is highly spatially heterogeneous (ie, its distributional peaks basically follow roadways), data from only 2 monitoring stations will not effectively represent these sources and their spatial distribution. Our findings that particulates were associated with inflammation indicate that particles from sources such as motor vehicles or industrial plants present potentially important adverse exposures for pregnant women and that our spatial model based on a larger number of particulate monitoring stations likely captured particulate exposures from these sources better than the monitoring for gaseous combustion products. However, ozone is spatially more homogeneously distributed than other gaseous pollutants, and we expect the 3 monitoring stations, combined with our spatial interpolation model, to have adequately represented ozone exposures.

Previous studies investigated various lag times for air pollution exposures and inflammatory markers and generally assumed effects to be acute and to occur within 7 days prior to sample collection. Only a few studies have examined longer periods (ie, months or years).^{20,31,33} Our results for particulate exposures are generally consistent with other studies. Zeka et al²⁰ reported that a 7.95 $\mu\text{g}/\text{m}^3$ increase in a 4-week average PM_{2.5} resulted in a 4.4% (95% CI = -3.3% to 12.0%) increase in C-reactive protein among 710 healthy men. Similarly, we observed that a 5.0 $\mu\text{g}/\text{m}^3$ increase in 29-day average PM_{2.5} before blood collection was associated with a 3.8% increase in C-reactive protein (95% CI = -6.7% to 15.6%) for the entire population. Rückerl et al¹⁹ studied the influence of air pollution on markers of inflammation and coagulation among 57 men with coronary heart disease. For a C-reactive protein concentration greater than 8.5 mg/L, they reported an odds ratio of 1.4 (95% CI = 0.9–2.3) for an IQR (12.2 $\mu\text{g}/\text{m}^3$) increase in 5-day average PM_{2.5}, and an odds ratio of 2.0 (1.2–3.7) for an IQR (12.8 $\mu\text{g}/\text{m}^3$) increase in 5-day average PM₁₀. In this repeated-measures panel study in men, the estimated effect for PM_{2.5} was in the range of our finding in nonsmoking women (OR = 1.17 [95% CI = 0.90–1.52] for C-reactive protein 8 ng/mL per 5.8 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} 8-day average); our estimated effect size for PM₁₀, however, was much smaller and did not suggest an association for this short averaging period (1.05 [0.77–1.44] per 11 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ 8-day average).

We also found consistent positive associations between O₃ in summer (April to September) and high C-reactive protein concentrations. Exposure to ozone has been associated with airway inflammation as well as systemic inflammation.^{16,34} O₃ has a strong oxidative potential and is likely to generate reactive oxygen and nitrogen species and to increase inflammatory reactions.³⁵ Ozone exposures are associated with increased concentrations of interleukin-8 (IL-8) and interleukin-6 (IL-6) in asthmatic children and nonsmoking adults.^{16,35} Recently, a longitudinal study³⁶ following 40 healthy persons reported a 5.9% (95% CI = -6.8% to 18.7%) increase in C-reactive protein for a 42 $\mu\text{g}/\text{m}^3$ increase on lag day 4 for O₃ exposure; this was similar to our finding (3.6% increase [95% CI = -8.5% to 17.3%] on lag day 4 per 14.0 ppb) in the summer months for nonsmokers.

We found no indication that BMI modifies the associations between particulates and C-reactive protein in pregnant women; ie, the sizes of our effect measures were similar for normal-weight and obese women. Our results are not consistent with previous studies in

which associations between short-term air pollution and inflammation markers (ie, C-reactive protein and interleukin-6) were more pronounced in obese persons and those with diabetes or hypertension.^{20,22} This inconsistency may be due to the fact that we excluded pregnant women with preexisting health conditions, such as chronic hypertension and chronic diabetes, and that our BMI measure was inaccurate, because our study weight at baseline was measured as early as 3 and as late as 22 weeks of gestation. However, very few women had their blood collected later than 20 weeks of gestation, when weight during pregnancy increases rapidly.

Much evidence has accumulated to demonstrate that maternal exposure to air pollution is associated with adverse birth outcomes or pregnancy complications. C-reactive protein concentrations are generally higher in pregnant than in nonpregnant women,³⁷ and placentally derived microparticles or soluble products from the placenta are suspected of driving systemic inflammation during normal pregnancy.²³ An increased inflammatory response during pregnancy is present for preeclampsia, small-for-gestational-age infants, and preterm birth.^{24,28,38,39} Two studies have examined the associations between maternal plasma C-reactive protein concentrations in early pregnancy (before 21 weeks of gestation) and the risk of preterm delivery; they found 2.6- to 2.9-fold increases in risk of preterm delivery with early pregnancy inflammation (C-reactive protein ≥ 8 ng/mL).^{24,28} Cord blood concentrations of inflammatory markers such as interleukin-6, tumor necrosis factor- α , thrombopoietin, and C-reactive protein were reported to be higher in SGA infants compared with appropriate-for-gestational-age controls.³⁸ Thus, our findings provide some evidence that inflammation is one possible pathway through which air pollution may increase the risk of adverse birth outcomes.

The primary strength of our study is that we were able to examine potential confounders including active and passive smoking, maternal nutrition (ie, multivitamin or prenatal vitamin use), and BMI. Our BMI information was based on measurements in early pregnancy, not self-report. Our study also has several limitations. First, we did not have maternal infection information during the period when blood was collected. Because we were unable to control for acute infections, this may have confounded our short-term results (0–7 lag days). However, some infections, such as respiratory infections, are likely to be on the same causal pathway as air pollution and C-reactive protein increases, and it would be inappropriate to control for intermediate factors. Second, when performing Kriging interpolation for estimating PM_{2.5} and PM₁₀ concentrations, we relied on data collected in different monitoring cycles (ie, every day, every third or sixth day) and with different EPA reference or equivalent sampling methods (ie, the Federal Reference Method and Tapered Element Oscillating Microbalance). This might also have contributed to measurement error. Because in Allegheny County only one PM₁₀ and PM_{2.5} monitoring station collected data every day with the same sampling method, restricting our exposure measures to these everyday ones would not have captured the spatial variability of particles when performing Kriging. (Many EPA particle monitoring sites used in previous publications have the same restrictions.) Third, we relied on residential information at birth rather than at the time we collected the blood samples, and we assumed that mothers did not move during pregnancy and that the estimates of residential air pollution were representative of the woman's

personal exposures—all of which may have resulted in exposure measurement error. Because our study population was drawn from a longitudinal cohort, in which participants received their prenatal care and delivered in the same hospital, we believe that it is reasonable to assume that most women in our study either did not move or moved only within the same neighborhood (or zip code) during pregnancy, as was also suggested by Chen et al.⁴⁰ Furthermore, we do not have maternal residential address available for this cohort; thus, we were unable to evaluate traffic-related air pollution exposures. While we conducted a large number of statistical tests, the consistency and magnitude of our findings for the relationships of particulates and O₃ air pollution with high C-reactive protein concentrations make it less likely that our results are due to chance only.

Our study suggests that particulate matter (PM₁₀ and PM_{2.5}) air pollution and ozone exposures during early pregnancy contribute to systemic inflammation, as measured by C-reactive protein. Our findings provide some new evidence that effects of particulate air pollution on adverse birth outcomes may be mediated by systemic inflammation.

Acknowledgments

We thank all the Prenatal Exposures and Preeclampsia study participants for their participation, Marcia Gallaher for help measuring the C-reactive protein, and Shawn Brown of the Pittsburgh Supercomputer Center for providing the access to the server. We also thank Kirit Dalal and Jason Maranche of the Pennsylvania Department of Health, and the Allegheny County Health Department for providing electronic air monitoring data.

Supported by the Department of Epidemiology, University of Pittsburgh.

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FIGURE.

Percentage change for C-reactive protein with average ambient PM_{2.5} and PM₁₀ exposures (per IQR increase) in (A) smokers and (B) nonsmokers. All models were adjusted for gestational week at sample collection, maternal BMI at enrollment, maternal age, race, education, parity, cigarette smoke exposure during early pregnancy (for the entire population)/passive cigarette smoke exposure during early pregnancy (for nonsmokers), household income, season of sample collection, and year of enrollment (for PM₁₀: 1997 to 2001; for PM_{2.5}: 1999 to 2001).

TABLE 1

Demographic Characteristics of Study Population by C-reactive Protein Concentration (n = 1696)

	C-reactive Protein		Crude OR (95% CI)	Adjusted OR ^a (95% CI)
	<8 ng/mL	8 ng/mL		
Gestational weeks at sample collection (weeks); mean (SD)	10.0 (3.9)	11.6 (4.2)	1.10 (1.07–1.14)	1.13 (1.09–1.17)
Maternal BMI at baseline ^b (kg/m ²); mean (SD)	25.4 (5.9)	32.5 (7.8)	1.14 (1.12–1.17)	1.15 (1.12–1.18)
Maternal age (years); mean (SD)	24.6 (5.8)	26.4 (6.1)	1.05 (1.03–1.08)	1.07 (1.03–1.11)
Maternal race/ethnicity ^b ; no. (%)				
White	905 (64)	128 (52)	1.00	1.00
African American	509 (36)	118 (48)	1.64 (1.25–2.15)	1.31 (0.91–1.87)
Maternal education; no. (%)				
Less than high school	302 (21)	46 (19)	1.15 (0.72–1.83)	1.26 (0.62–2.55)
High school	544 (37)	107 (43)	1.48 (0.99–2.22)	1.46 (0.81–2.61)
Less than 4-year college	332 (23)	58 (23)	1.32 (0.84–2.05)	1.02 (0.57–1.84)
Bachelor's degree or above	271 (19)	36 (15)	1.00	1.00
Parity; no. (%)				
First birth	913 (63)	110 (45)	1.00	1.00
Second or subsequent birth	536 (37)	137 (55)	2.12 (1.62–2.79)	0.99 (0.68–1.43)
Maternal cigarette exposure during early pregnancy ^b ; no. (%)				
Active (smokers)	480 (33)	73 (30)	0.72 (0.50–1.02)	0.88 (0.57–1.37)
Passive (nonsmokers)	610 (43)	97 (40)	0.75 (0.54–1.04)	0.93 (0.63–1.38)
None	348 (24)	74 (30)	1.00	1.00
Household income; no. (%)				
<\$10,000	360 (25)	74 (30)	1.00	1.00
\$10,000–\$19,999	287 (20)	55 (22)	0.93 (0.64–1.37)	1.02 (0.64–1.62)
\$20,000–\$49,999	289 (20)	52 (21)	0.88 (0.59–1.29)	1.06 (0.66–1.71)
\$50,000	259 (18)	38 (16)	0.71 (0.47–1.09)	1.13 (0.61–2.11)
Unknown	254 (17)	28 (11)	0.54 (0.34–0.85)	0.67 (0.38–1.18)
Year entering the study; no. (%)				
1997	187 (13)	18 (7)	1.00	1.00
1998	272 (19)	34 (14)	1.30 (0.71–2.37)	1.21 (0.60–2.45)
1999	331 (23)	49 (20)	1.54 (0.87–2.72)	1.04 (0.53–2.04)
2000	396 (27)	92 (37)	2.41 (1.41–4.11)	1.63 (0.85–3.13)
2001	263 (18)	54 (22)	2.13 (1.21–3.75)	1.63 (0.82–3.24)
Season of sample collected; no. (%)				
Spring (March–May)	451 (31)	84 (34)	1.00	1.00
Summer (June–August)	367 (25)	61 (25)	0.89 (0.62–1.28)	0.73 (0.48–1.11)
Fall (September–November)	321 (22)	49 (20)	0.82 (0.56–1.20)	0.75 (0.48–1.19)
Winter (December–February)	310 (22)	53 (21)	0.92 (0.63–1.33)	0.96 (0.62–1.48)

^a Adjusted for all other covariates in the table.

^b Missing observations for maternal BMI at enrollment (n = 72); maternal race other than white and African American (n = 36); and maternal cigarette exposure during early pregnancy (n = 14).

TABLE 2

Descriptive Statistics of Air Pollution (0–7 Day Averages)

	Mean (SD)	Percentile							Pearson Correlation				
		0th	25th	50th	75th	95th	100th	PM ₁₀	PM _{2.5}	O ₃	CO	SO ₂	NO ₂
PM ₁₀ (μg/m ³)	26.1 (8.3)	10.7	19.9	24.4	31.2	42.2	58.7	1					
PM _{2.5} (μg/m ³)	16.4 (5.3)	7.1	12.8	15.2	18.7	26.2	40.8	0.9	1				
O ₃ (ppb) ^a	29.9 (7.1)	4.4	25.6	30.3	34.3	41.6	51.4	0.5	0.5	1			
CO (ppm)	0.5 (0.2)	0.0	0.3	0.5	0.6	0.9	1.4	0.1	0.0	−0.1	1		
SO ₂ (ppb)	8.4 (3.3)	1.5	6.1	7.9	10.1	14.4	25.4	0.1	0.2	0.1	0.3	1	
NO ₂ (ppb)	18.8 (3.8)	8.2	15.9	18.7	21.1	25.1	33.4	0.1	0.1	0.0	0.6	0.4	1

^aFor summer season only (April to September).

TABLE 3

Associations Between C-reactive Protein (<8 vs. 8 ng/mL), Particulates, and O₃ Air Pollution per IQR Increase by Lag Period for the Entire Population (n = 1696) and Nonsmokers (n = 1129)

Pollutant/Lag Periods	IQR	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
For the entire population			
PM ₁₀ (μg/m ³)		(n = 1696)	(n = 1576)
Day 0–7	11.3	1.02 (0.84–1.24)	1.05 (0.81–1.36)
Day 0–21	9.8	1.06 (0.88–1.28)	1.23 (0.97–1.57)
Day 0–28	9.2	1.03 (0.85–1.26)	1.18 (0.91–1.53)
PM _{2.5} (μg/m ³)		(n = 1189)	(n = 1084)
Day 0–7	6.0	1.17 (1.00–1.38)	1.21 (1.02–1.43)
Day 0–21	5.2	1.19 (1.01–1.40)	1.32 (1.05–1.67)
Day 0–28	5.0	1.16 (0.96–1.41)	1.26 (0.97–1.63)
O ₃ ^b (ppb)		(n = 909)	(n = 833)
Day 0–7	8.7	1.02 (0.83–1.24)	1.27 (0.87–1.86)
Day 0–21	8.2	0.96 (0.76–1.23)	1.26 (0.78–2.03)
Day 0–28	7.7	0.91 (0.72–1.15)	1.05 (0.65–1.71)
For nonsmokers			
PM ₁₀ (μg/m ³)		(n = 1129)	(n = 1060)
Day 0–7	11.0	0.98 (0.78–1.24)	1.05 (0.77–1.44)
Day 0–21	9.9	1.13 (0.88–1.45)	1.47 (1.06–2.02)
Day 0–28	9.2	1.10 (0.86–1.42)	1.41 (0.99–2.00)
PM _{2.5} (μg/m ³)		(n = 786)	(n = 726)
Day 0–7	5.8	1.15 (0.93–1.43)	1.17 (0.90–1.52)
Day 0–21	5.2	1.29 (1.04–1.62)	1.55 (1.15–2.11)
Day 0–28	4.6	1.25 (0.98–1.60)	1.47 (1.05–2.06)
O ₃ ^b (ppb)		(n = 579)	(n = 539)
Day 0–7	9.0	1.03 (0.75–1.40)	1.15 (0.69–1.89)
Day 0–21	8.3	1.06 (0.72–1.58)	1.60 (0.83–3.09)
Day 0–28	7.9	1.05 (0.72–1.55)	1.49 (0.75–2.96)

^a Adjusted for gestational week at sample collection, maternal BMI at enrollment, maternal age, race, education, parity, cigarette smoke exposure during early pregnancy, household income, season of sample collection (only adjusted in PM₁₀ and PM_{2.5} models), and year of enrollment (for PM₁₀ and O₃: 1997 to 2001; for PM_{2.5}: 1999 to 2001); month of enrolment was also adjusted in O₃ models.

^b Restricted to participants enrolled in the study in the months of April–September only.