Effect of Air Pollution on Preterm Birth Among Children Born in Southern California Between 1989 and 1993

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We evaluated the effect of air pollution exposure during pregnancy on the occurrence of preterm birth in a cohort of 97,518 neonates born in Southern California. We used measurements of carbon monoxide (CO), nitrogen dioxide, ozone, and particulate matter less than 10 μm (PM_{10}) collected at 17 air-quality-monitoring stations to create average exposure estimates for periods of pregnancy. We calculated crude and adjusted risk ratios (RRs) for premature birth by period-specific ambient pollution levels. We observed a 20% increase in preterm birth per 50-μg increase in ambient PM_{10} levels averaged over 6 weeks before birth [RR_{crude} = 1.20; 95% confidence interval (CI) = 1.09–1.33] and a 16% increase when averaging over the first month of pregnancy (RR_{crude} = 1.16; 95% CI = 1.06–1.26). PM_{10} effects showed no regional pattern. CO exposure 6 weeks before birth consistently exhibited an effect only for the inland regions (RR_{crude} = 1.13; 95% CI = 1.08–1.18 per 3 parts per million), and during the first month of pregnancy, the effect was weak for all stations (RR_{crude} = 1.04; 95% CI = 1.01–1.09 per 3 parts per million). Exposure to increased levels of ambient PM_{10} and possibly CO during pregnancy may contribute to the occurrence of preterm births in Southern California. (Epidemiology 2000;11:502–511)

Keywords: air pollution, carbon monoxide, environmental hazard surveillance, health effects, preterm birth.

Preterm birth is an indicator of prenatal disturbances of the placenta and of fetal development. Like low birth weight (LBW), prematurity is an important predictor of infant mortality, childhood morbidity, and possibly adult morbidity.[1–3] In the United States, the prevalence of preterm birth (birth before the 37th week of gestation) has increased from 7.9% to 10.2% of all births over the last 2 decades.[4] Maternal risk factors that may shorten gestation have been scrutinized widely.[5] Nevertheless, the potential impact of environmental toxins such as air pollution has not been considered until recently. A study of Chinese women living in Beijing reported that exposure to elevated levels of sulfur dioxide (SO_2) and total suspended particles (TSP) during the last trimester shortened gestational length[6] and contributed to LBW.[7] A small Czech study restricted to the Teplice area[8] found that exposure to elevated levels of particulate matter less than 10 μm (PM_{10}) and less than 2.5 μm ($PM_{2.5}$) early in pregnancy resulted in intrauterine growth retardation (IUGR). Another Czech study including data for the whole republic observed increased risks for prematurity and LBW with increased levels of both SO_2 and TSP during all trimesters but not for IUGR.[9] We previously reported that exposure to high carbon monoxide (CO) concentrations during the last trimester of pregnancy was associated with increased risk of LBW for term infants born in Southern California.[10]

Although some overlap exists for common risk factors, several investigators recommend treating prematurity and IUGR as different etiologic entities related to distinct risk factor profiles and leading to different neonatal and postneonatal complications.[5,11,12] Previous studies evaluating the effects of air pollution on IUGR focused on term birth only.[7,8,10,11] Although both IUGR and preterm birth can result in LBW, prematurity does not have to result in low weight or small-for-gestational-age (SGA) babies. In fact, only about 23% of all infants born preterm in our population were also low weight. Thus, we explored the impact of air pollution on the occurrence of preterm birth in infants of adequate and low weight for gestational age.

Approximately 15 million people live in the South Coast Air Basin (SoCAB) a 16,000-km^2 area comprising the nondesert portions of Los Angeles, San Bernardino, Riverside, and Orange Counties. To evaluate the effects of several air pollutants on preterm birth in this large and densely populated region, we focused on the popu-

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lation living in the vicinity of 17 ambient air pollution-monitoring stations (Figure 1).

Subjects and Methods

Outcomes

We used birth certificates provided by the California Department of Health Services to identify subjects and to determine birth outcomes and potential risk factor information. About 5% of births had to be excluded because the certificates did not contain valid gestational age data, leaving us with 143,196 eligible study subjects who were singletons born between 1989 and 1993 at 26–44 weeks of gestation to women living in selected zip code areas around air-monitoring stations (see previous section). We excluded an additional 1,146 offspring whose mothers suffered from chronic hypertension, chronic renal, cardiac, or lung diseases, or diabetes during pregnancy, because we believe that effects of ambient air pollution on such pregnancies may be far outweighed by the influence of the mothers' high-risk medical conditions and/or treatment for those conditions. Including these children and controlling for maternal disease in the model did not change the exposure estimates reported below. Further exclusion of study subjects was necessary owing to missing data for variables included in our covariate-adjusted analyses, such as maternal age, infant sex, maternal race, prenatal care information, and maternal education (N = 1,959). Finally, we required that more than 10 days of CO measurements and at least one PM_{10} measurement be available for each infant for two periods during pregnancy, the last 6 weeks before birth and the first month of pregnancy (see also statistical methods below). Owing to monitoring gaps, mainly for PM_{10}, we had to exclude 11.2% of the eligible children. Because cesarean deliveries before 37 weeks of gestation are likely to be scheduled owing to maternal, fetal, and/or placental problems, we excluded 27,119 children delivered by cesarean section from our main analyses, leaving us with a total cohort of 97,158 children delivered vaginally. Among these vaginally delivered children, for very few cases (N = 48) birth was medically induced before the 37th week. Excluding these cases did not change the estimates reported below by much.

The outcome of interest, premature birth, was treated as a dichotomous variable (birth at <37 weeks of gestation) in most and as a continuous variable (gestational age) in some analyses. Finally, we tried to distinguish between factors affecting weight gain and those inducing premature labor. Thus, we conducted some analyses (1) excluding subjects considered SGA or LBW and (2) restricting preterm births to SGA or LBW children.

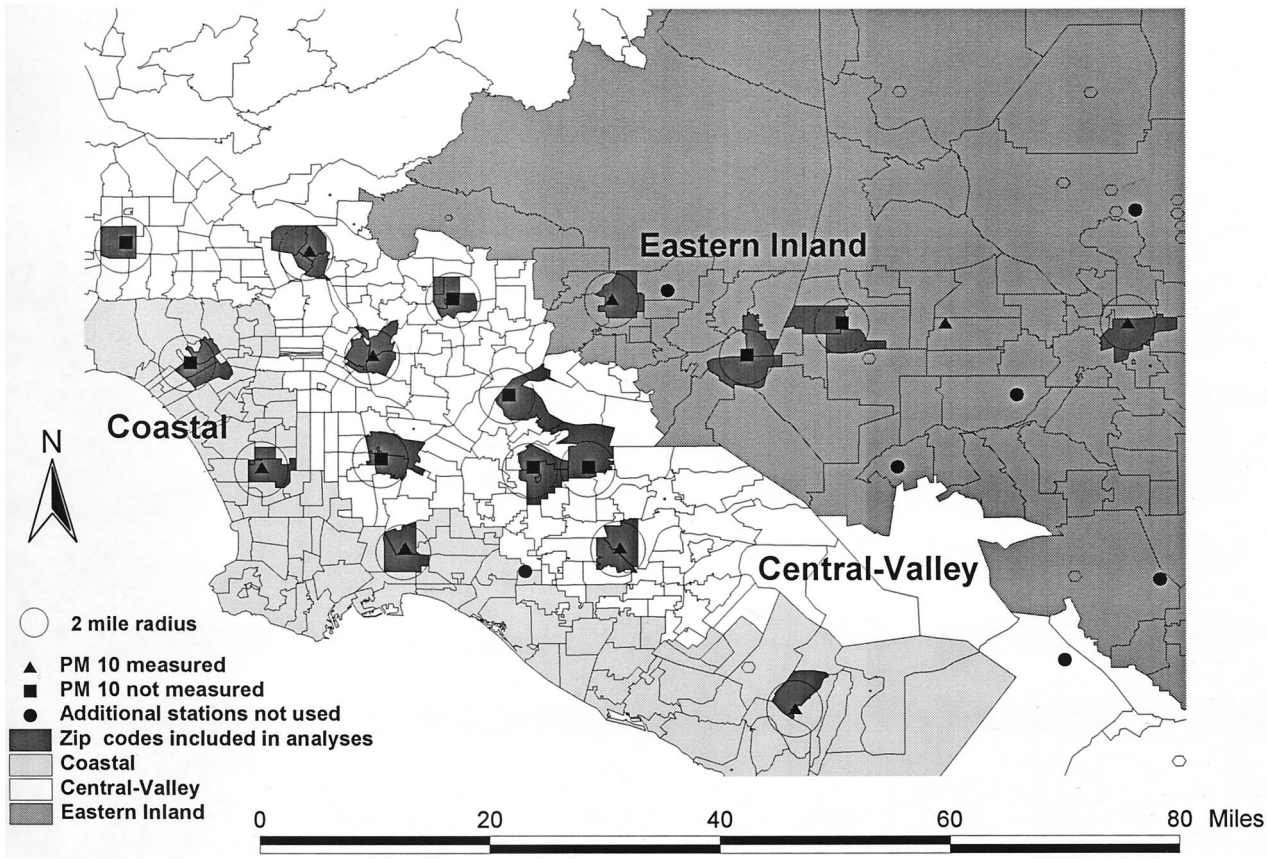

FIGURE 1. Map of the South Coast Air Quality Management District monitoring stations and zip codes included in the analyses.

Exposure Assessment

Monitoring data for at least one of the four ambient air pollutants of interest [CO, nitrogen dioxide (NO_2), ozone (O_3), and PM_{10}] were collected at 32 locations by South Coast Air Quality Management District between 1989 and 1993. A total of 17 stations collected data for at least three of the four pollutants of interest and, in addition, fulfilled the requirement that zip code areas be small enough to be located within a 2-mile radius of a station (as discussed further below). Yet, among these stations, only six collected data simultaneously for all four pollutants, two stations lacked NO_2 data, and nine additional stations lacked PM_{10} data (Figure 1). In general, stations measuring gaseous pollutants were located predominantly in the western and coastal areas of the SoCAB, while those maintaining PM_{10} samplers concentrated in the eastern and inland (central and valley) areas (Figure 1). Thus, there was little overlap between stations monitoring for the three gaseous pollutants and those monitoring for PM_{10}.

We relied on data from all 17 stations mentioned above to examine the effect of CO exposures in single-pollutant models. Sharp CO gradients can occur near sources such as areas of high vehicle density, and staff from the air quality management district recommended not to extrapolate CO measures to areas located farther than 2 miles from a monitoring station (J. Cassmassi, 1998, personal communication). Because maternal address was only reported as zip code area on birth certificates, we restricted our study population to the infants of mothers residing in 35 zip code areas closely surrounding the 17 monitoring stations. These zip codes were selected so that their boundaries fell largely within 2 miles of one of the monitoring stations. Eleven of these zones lay entirely within 2 miles of a monitoring station; 20 zones are situated such that more than 80% and 4 so that 60–80% of their area falls within the 2-mile radius (Figure 1).

To be consistent, we estimated the effect of all air pollutants in single- and multiple-pollutant models for the same population living in these 35 zip code areas. Because PM_{10} was measured at only 8 of the 17 stations, only half of the eligible population contributed to the PM_{10} models. For some analyses, we replaced missing PM_{10} data with data sampled at the nearest monitoring station providing PM_{10} data for the period.

Hourly measurements were available for CO, NO_2, and O_3. To estimate O_3 exposure, we averaged daytime measures taken between 9 am and 5 pm. For NO_2, we averaged over the whole 24-hour period. Following the recommendation of the South Coast Air Quality Management District staff, we averaged measurements of CO only for the morning hours between 6 am and 9 am, to obtain peak CO concentrations during periods of low wind speed in the SoCAB. For PM_{10}, only 24-hour average measurements at 6-day intervals were available (see also Statistical Methods, below).

Statistical Methods

To evaluate air pollution effects on prematurity, we calculated average exposure over various periods before birth. Using the birth date and gestational age of each child, we averaged pollutant measures taken at the closest air-monitoring station over distinct periods such as 1, 2, 4, 6, 8, 12, and 26 weeks before birth and the whole pregnancy period. In addition, we calculated average exposures for the first and second months of pregnancy. We evaluated the effect of ambient air pollution on preterm birth using logistic regression models for the dichotomous outcome and linear regression models for a continuous outcome, respectively. We examined the adequacy of a linear or log-linear relation using indicator terms (dummy variables) for pollutant-average quartiles and report continuous measures for period-specific pollutant averages to compare results of crude with adjusted and multiple- with single-pollutant models. The most influential exposure periods were identified according to the strength of the effect and width of confidence interval (CI).

We examined and controlled several known risk factors for preterm birth[13–15] that could potentially modify or confound the relation with neighborhood air pollution levels in our models. We adjusted for maternal age (in categories: <19, 20–29, 30–34, 35–39, or >40 years), race (African-American, White, Hispanic, or Asian), education (in categories: 0–8, 9–11, 12, 13–15, or >15 years), parity (first *vs* second or subsequent birth), interval since the previous livebirth (≤12 or >12 months), access to prenatal care (none, first trimester, or later), infant sex, previous low weight or preterm births, and tobacco smoking during pregnancy reported as "pregnancy complications" on Californian birth certificates. All of these risk factors are included in all adjusted regression models. Some models, in addition, included season of birth or conception. We conducted stratified analyses by region (coastal *vs* inland); birth and conception seasons; maternal age, race, and education; and infant gender to evaluate the consistency of the air pollution associations across strata, that is, to identify any effect modification by these factors. Risk factors for preterm birth that are not registered on California birth certificates include maternal passive smoking, marital status, and maternal height and pregnancy weight gain. Although weather factors such as inversions, lack of rain, abundance of sun, and wind speed influence the levels of air pollutants in the SoCAB and pollutants exhibit seasonal patterns, we did not include weather variables in our models, because none of these is known to be a risk factor for preterm birth.

Results

The mean gestational age of all 97,158 children included in our analyses is 277 days. Among these singleton children, 9.0% are born preterm and 4.0% are LBW (<2,500 gm). Although the mean birth weight of preterm children is about 500 gm less than the average weight of children born at term, only 23.2% of the preterm children are LBW.

The incidence proportions and 95% CI of preterm birth are presented in Table 1 by known risk factors and

TABLE 1. Incidence Proportion of Preterm Births by Demographic Characteristics and Air Pollution Exposure in a Cohort of 97,158 Children Delivered Vaginally between 1989 and 1993 in Southern California; Mothers Lived in the Vicinity of 17 Air-Monitoring Stations

	Number of Births or Mean ± SD	Number of Cases or Mean ± SD	Incidence Proportion	95% CI
Mean gestational age (days)	277 ± 15	244 ± 14		
Mean birth weight (gm)	3,376 ± 504	2,931 ± 664		
Preterm (<37 weeks)	97,158	8,745	9.0	8.8–9.2
Low birth weight (<2,500 gm)	3,897	2,028	52.0	50.7–53.4
Child of female gender	47,756	4,050	8.5	8.2–8.7
Prenatal care				
None	1,743	388	22.3	20.4–24.2
Started after first trimester	27,668	2,947	10.7	10.3–11.0
No siblings	37,251	3,423	9.2	8.9–9.5
Time to previous livebirth ≥12 months	39,600	3,833	9.7	9.4–10.0
Maternal race				
White	80,209	6,755	8.4	8.2–8.6
Hispanic among whites	62,391	5,572	8.9	8.7–9.2
African American	8,827	1,276	14.5	13.7–15.2
Asian	5,148	434	8.4	7.7–9.2
Maternal education (years)				
0–8	24,430	2,347	9.6	9.2–10.0
9–11	22,837	2,271	9.9	9.6–10.3
12	25,908	2,425	9.4	9.0–9.7
13–15	13,894	1,120	8.1	7.6–8.5
≥16	10,089	582	5.8	5.3–6.2
Maternal age group (years)				
<15	269	51	19.0	14.8–24.0
15–19	13,198	1,552	11.8	11.2–12.3
20–24	28,454	2,602	9.1	8.8–9.5
25–29	28,051	2,273	8.1	7.8–8.4
30–34	18,15	1,440	7.8	7.4–8.2
35–39	7,416	674	9.1	8.5–9.8
≥40	1,355	153	11.3	9.7–13.1
Tobacco use during pregnancy reported as "pregnancy complications"	1,308	179	13.7	11.9–15.6
Previous birth				
Preterm	26,883	2,151	8.0	7.7–8.3
Low weight (<2,500 gm)	433	110	25.4	21.6–29.6
Season of birth				
Winter	22,770	2,091	9.2	8.8–9.6
Spring	23,468	2,151	9.2	8.8–9.5
Summer	25,010	2,140	8.6	8.2–8.9
Fall	25,910	2,363	9.1	8.8–9.5
Quartile of average CO exposure during the last 6 weeks before birth (ppm)				
1 (<1.55)	24,254	2,030	8.4	8.0–8.7
2 (1.55–<2.22)	24,328	2,148	8.8	8.5–9.2
3 (2.22–<3.35)	24,312	2,246	9.2	8.9–9.6
4 (≥3.35)	24,264	2,321	9.6	9.2–9.9
Quartile of average CO exposure during the first month of pregnancy (ppm)				
1 (<1.60)	24,311	2,065	8.5	8.2–8.8
2 (1.60–<2.28)	24,269	2,168	8.9	8.6–9.3
3 (2.28–<3.48)	24,283	2,254	9.3	8.9–9.7
4 (≥3.48)	24,295	2,258	9.3	8.9–9.7
Quartile of average PM_{10} exposure during the last 6 weeks before birth ($\mu g/m^3$)				
1 (<36)	24,333	2,050	8.4	8.1–8.8
2 (36–<45)	24,163	2,189	9.1	8.7–9.4
3 (45–<57)	24,336	2,235	9.2	8.8–9.6
4 (≥57)	24,326	2,271	9.3	9.0–9.7
Quartile of average PM_{10} exposure during the first month of pregnancy ($\mu g/m^3$)				
1 (<37)	24,240	2,137	8.8	8.5–9.2
2 (37–<47)	24,309	2,138	8.8	8.4–9.2
3 (47–<60)	24,247	2,238	9.2	8.9–9.6
4 (≥60)	24,362	2,232	9.2	8.8–9.5
Quartile of average ozone exposure during the last 6 weeks before birth (pphm)				
1 (<2.12)	24,290	2,194	9.0	8.7–9.4
2 (2.12–<3.57)	24,283	2,268	9.3	9.0–9.7
3 (3.57–<4.80)	24,280	2,182	9.0	8.6–9.4
4 (≥4.80)	24,305	2,101	8.6	8.3–9.0
Quartile of average ozone exposure during the first month of pregnancy (pphm)				
1 (<2.01)	24,297	2,103	8.7	8.3–9.0
2 (2.01–<3.58)	24,285	2,323	9.6	9.2–9.9
3 (3.58–<4.84)	24,285	2,215	9.1	8.8–9.5
4 (≥4.84)	24,291	2,104	8.7	8.3–9.0
Quartile of average NO_2 exposure during the last 6 weeks before birth (pphm)				
1 (<3.20)	22,931	2,018	8.8	8.4–9.2
2 (3.20–<4.09)	22,929	2,045	8.9	8.6–9.3
3 (4.09–<5.04)	22,928	2,069	9.0	8.7–9.4
4 (≥5.04)	22,934	2,175	9.5	9.1–9.9
Quartile of average NO_2 exposure during the first month of pregnancy (pphm)				
1 (<3.33)	22,929	2,085	9.1	8.7–9.5
2 (3.33–<4.23)	22,933	2,093	9.1	8.8–9.5
3 (4.23–<5.21)	22,927	2,067	9.0	8.7–9.4
4 (≥5.21)	22,932	2,062	9.0	8.6–9.4

by quartiles of air pollution exposure during pregnancy periods. We found the highest incidence of preterm birth among mothers lacking prenatal care, who are of young and old age, who are of African-American race, who experienced previous low-weight births, and who used tobacco during pregnancy. High maternal educational level, higher-order parity, increased length of time between two births, and being born in the summer protects against prematurity (Table 1).

Examining the Pearson correlation coefficients (r) of air pollutant averages for the two pregnancy periods most important for predicting preterm birth, we found PM_{10} and CO averages most strongly correlated with NO_2 ($r > 0.6$) and less with each other ($r = 0.37$ and 0.43) (Table 2). O_3 is only weakly correlated with PM_{10} ($r = 0.20$ and 0.23) and not or negatively correlated with CO and NO_2. These patterns may reflect the fact that a large percentage of PM_{10}, CO, and NO_2 in the SoCAB are produced by the same vehicular sources and accumulate when trapped over the city by inversion layers during the colder seasons. O_3, however, is a secondary pollutant generated in the troposphere from the precursors NO_2 and hydrocarbons during clear, sunny summer days.

Figure 2 displays adjusted risk ratios (RRs) per quartile of PM_{10} and CO exposure derived from logistic regression models using indicator variables and controlling for NO_2 and O_3 exposures. We observed a dose-response effect for all stations for the last 6 weeks PM_{10} average and the first month exposure to CO. All estimates show an increase with increasing pollution level at inland stations. Trends for the last 6 weeks CO and first month PM_{10} at coastal stations are ambiguous, and all results for coastal stations are based on a relatively small number of births.

Using a continuous exposure variable, we estimated that the risk of preterm birth increases by 20% ($RR_{crude} = 1.20$; 95% CI = 1.09–1.33) per 50-μg increase in PM_{10} averaged over 6 weeks before birth and by 16% averaged over the first month of pregnancy ($RR_{crude} = 1.16$; 95% CI = 1.06–1.26) among mothers residing around eight stations monitoring PM_{10} (Table 3). Results reported in Table 3 also show that the effect size varied only slightly between single- and multiple-pollutant models, when we adjusted for other risk factors, and when we modeled coastal and inland regions separately. We found smaller or no effects for PM_{10} (6 weeks $RR_{crude} = 1.07$, 95% CI = 0.98–1.17; first month $RR_{crude} = 1.00$, 95% CI = 0.93–1.09) for children whose mothers lived near nine stations not measuring PM_{10}, which required us to substitute the missing information with PM_{10} data from another station.

Using a continuous measure, we estimated that the risk of preterm birth increases by about 12% ($RR_{crude} = 1.12$; 95% CI = 1.08–1.17) per increase of 3 parts per million (ppm) in CO averaged over 6 weeks before birth and by 4% when averaged over the first month of pregnancy ($RR_{crude} = 1.04$; 95% CI = 1.01–1.09; Table 4). Including other covariates and/or other pollutants in the models for CO, however, caused effect estimates to fluctuate, and, unless we controlled simultaneously for all other air pollutants, exposure to CO during the last 6 weeks of pregnancy did not exhibit a clear dose-response pattern. For both pollutants, PM_{10} and CO, the point estimates of effect changed only slightly when extending the averaging period back in time until they eventually covered the whole pregnancy. Yet, the most precise estimates with the shortest CI was obtained for the last 6 weeks before birth (results for other intervals not shown). Furthermore, when exploring PM_{10} effects by season of birth or conception, winter and spring seasons seemed to be more strongly related to the effects observed for the last 6 weeks before birth, but wide CIs for all seasonal effect estimates did not allow us to draw clear conclusions about seasonality (crude estimates for last 6 weeks: $RR_{fall} = 1.08$, 95% CI = 0.88–1.31; $RR_{summer} = 1.06$, 95% CI = 0.87–1.29; $RR_{winter} = 1.33$, 95% CI = 1.07–1.65; $RR_{spring} = 1.81$, 95% CI = 1.41–2.31). Stratification on any other risk factor such as maternal age or race did not suggest effect modification by these factors. We found no consistent effects for O_3 and NO_2 over any of the pregnancy periods in single- or multiple-pollutant models (Table 1 presents crude risks by exposure quartile; adjusted effect estimates not shown).

TABLE 2. Pollutant Averages (Ranges) and Pearson Correlation Coefficients for All Pollutants by Pregnancy Period

	All Children (N = 97,158)			Pearson Correlation Coefficient for 6 or 8 Stations Measuring 3 or 4 Pollutants Simultaneously						
				PM_{10}		CO		NO_2		Ozone
Pollutant	Mean	SD	Range	Coefficient	N	Coefficient	N	Coefficient	N	N
6 weeks before birth										
PM_{10} ($\mu g/m^3$)	47.5	15.0	12.3–152.3	1						
CO (ppm)	2.61	1.45	0.37–8.81	0.43	48,904	1				
NO_2 (pphm)	4.13	1.25	0.22–9.01	0.74	43,468	0.64	43,468	1		
Ozone (pphm)	3.69	1.94	0.33–11.7	0.20	48,904	−0.45	48,904	−0.12	43,468	1
First month of pregnancy										
PM_{10} ($\mu g/m^3$)	49.3	16.9	9.5–178.8	1						
CO (ppm)	2.70	1.54	0.36–9.12	0.37	48,904	1				
NO_2 (pphm)	4.28	1.32	0.16–8.70	0.71	43,468	0.60	43,468	1		
Ozone (pphm)	3.69	2.07	0.26–12.4	0.23	48,904	−0.44	48,904	−0.08	43,468	1

SD = standard deviation; PM_{10} = particulate matter less than 10 μm; ppm = parts per million; pphm = parts per hundred million.

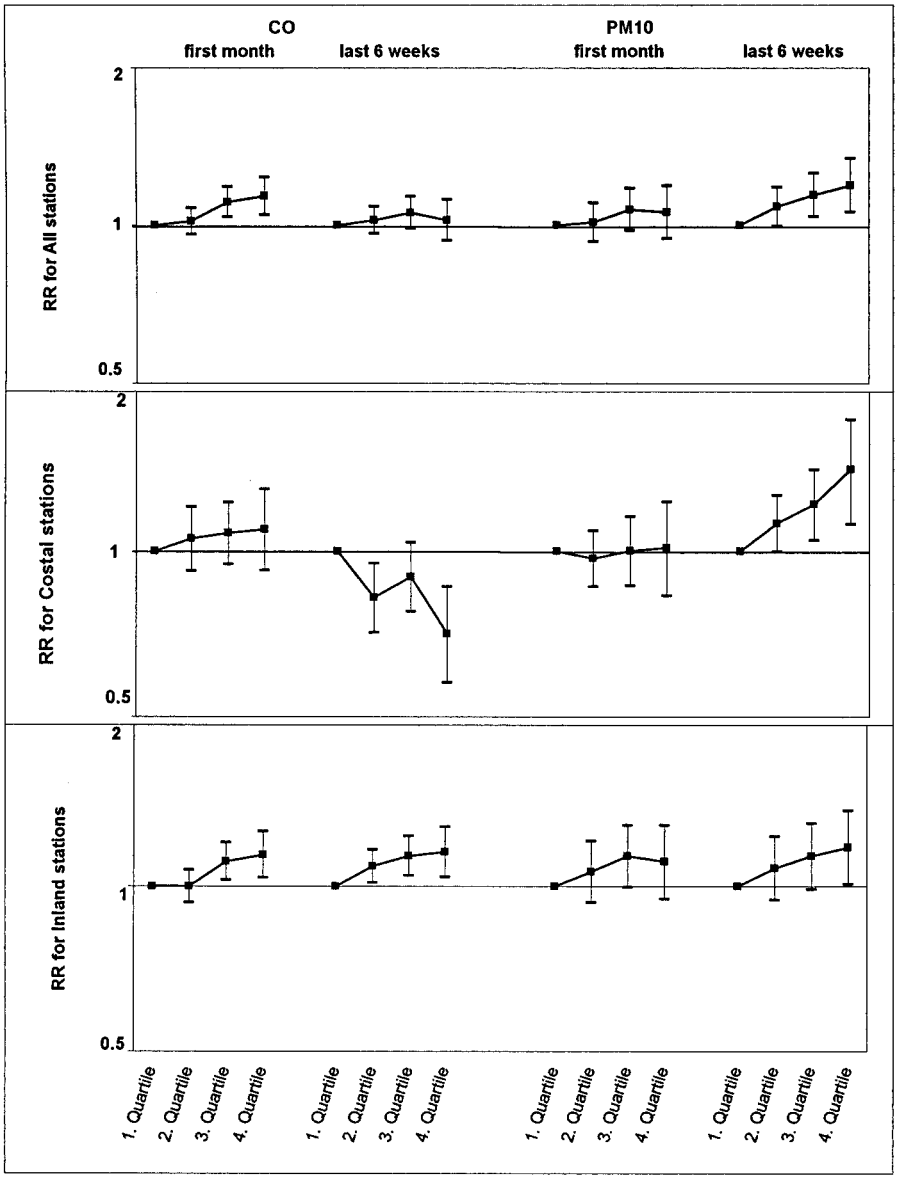

FIGURE 2. Risk ratios and 95% CIs for quartiles of average exposure to CO (17 stations) and PM_{10} (8 stations) from logistic regression models adjusted for all covariates and air pollutants.

Furthermore, effect estimates for PM_{10} and CO remained stable when we excluded SGA or LBW children or restricted preterm births to SGA or LBW children only (results not shown). Linear regression analyses suggested a small reduction of mean gestational length by 0.66 (±0.24; crude estimate) days or 0.90 (±0.27) days (adjusting for covariates) for each 50-μg PM_{10} increase during the last 6 weeks before births.

For births delivered by cesarean section, we observed increases in risk for premature delivery with increasing PM_{10} and CO exposure during the first month of pregnancy (for each 50-μg increase in PM_{10}, $RR_{adjusted}$ = 1.35, and 95% CI = 1.06–1.69; for each 3-ppm increase in CO, $RR_{adjusted}$ = 1.08, and 95% CI = 0.97–1.20), but no effect for exposures received before birth.

Discussion

The biological mechanisms whereby air pollution might cause preterm births remain to be determined, but may include disturbances of the pituitary-adrenocortico-placental system, disturbances of the uterine blood flow, and/or increased maternal susceptibility to infections. Air pollutants contributing to these pathogenic pathways could trigger premature contractions and/or premature rupture of membranes, resulting in preterm birth. For example, PM_{10} exposure may increase maternal susceptibility to infections during the weeks before birth. Or, toxic components of PM_{10} or unmeasured compounds that are correlated with particulate matter such as polycyclic aromatic hydrocarbons (PAHs) from ve-

TABLE 3. Risk Ratios (and 95% Confidence Intervals) for Vaginally Delivered Preterm Birth (Including Small-for-Gestational-Age Births) by Average Ambient PM_{10} Concentration (per 50 $\mu g/m^3$) for Two Pregnancy Periods

	Crude Risk Ratio	95% CI	Single-Pollutant Models Adjusted for: Two Exposure Periods Risk Ratio*	95% CI	Other Risk Factors Risk Ratio*	95% CI	Other Risk Factors and Season of Birth and Conception Risk Ratio*	95% CI	Multiple-Pollutant Model† Adjusted for Other Risk Factors Risk Ratio	95% CI
All eight stations‡ (N = 48,904)										
6 weeks before birth	1.20	1.09–1.33	1.18	1.07–1.31	1.15	1.04–1.26	1.15	1.03–1.29	1.19	1.01–1.40
1st month of pregnancy	1.16	1.06–1.26	1.13	1.04–1.24	1.09	1.00–1.19	1.09	0.99–1.20	1.12	0.97–1.29
Coastal stations only‡ (N = 18,859)										
6 weeks before birth	1.22	1.00–1.49	1.28	1.04–1.56	1.13	0.93–1.38	1.18	0.92–1.51	1.42	0.97–2.01
1st month of pregnancy	1.28	1.06–1.54	1.32	1.09–1.59	1.17	0.97–1.40	0.99	0.79–1.24	1.09	0.83–1.41
Inland stations only‡ (N = 30,045)										
6 weeks before birth	1.27	1.12–1.44	1.27	1.11–1.44	1.19	1.05–1.35	1.27	1.10–1.48	1.18	0.97–1.43
1st month of pregnancy	1.16	1.04–1.29	1.16	1.04–1.29	1.09	0.98–1.21	1.09	0.97–1.24	1.11	0.93–1.33

* Includes all covariates listed in Table 1 except season.
† N is slightly smaller owing to missing data for NO_2 at some stations.
‡ Exposures during both pregnancy periods are included in each model.

hicular exhaust could interfere with processes affecting the development and nutrition of the fetus and cause fetal distress. If such components are inhaled and absorbed into the maternal bloodstream, they could affect the placental function or cross the placenta and affect the fetus directly. For example, Polish studies found increased PAH-DNA adduct levels in umbilical cord blood in areas with high air pollution, and newborns were at increased risk for low weight, reduced head circumference, and reduced birth length.[16,17] Furthermore, Huel *et al*[18] observed increased activity of placental aryl hydrocarbon hydroxylase—an enzyme induced by PAHs—among French women who were diagnosed with threatened preterm delivery. Male rats exposed to the particulate and gaseous components of diesel exhaust showed signs of endocrine disruption resulting in increased levels of adrenal cortex hormonal secretions and of testosterone and estradiol in the blood.[19] Concerning uterine blood flow, Peters *et al*[20] recently showed that air pollution episodes, specifically ambient TSP increases, were able to induce increases in blood pressure and heart rate in a cohort of healthy subjects.

It has also been suggested that certain changes resulting in fetal growth retardation may occur in early pregnancy, that is, around the time of implantation, caused by an abnormal reaction between the trophoblast and uterine tissues.[21,22] A defective trophoblast invasion, resulting in suboptimal placentation and maternal hemodynamic maladaptation, can alter growth and development of the fetus. Such a growth-retarded fetus may exhibit a greater susceptibility to events that trigger premature labor, because ultrasound studies showed that preterm infants weigh less than infants of the same gestational age who remain *in utero*.[23]

CO may interfere with metabolic and transport functions of the placenta and, after crossing the placental barrier, concentrates more in the fetus than in its mother.[24] Moreover, animal studies showed that CO exhibits a toxic effect on the developing nervous system at moderate to low levels. Rat fetuses exposed to CO during gestation showed a marked reduction of the concentration of brain protein, DNA, norepinephrine, and serotonin at birth.[25]

Only two epidemiologic studies examined the effects of ambient air pollutants on preterm births; one was a cohort study of nonsmoking Chinese women delivering their first child in Beijing in 1988,[6] and the other was a large cohort of children born in the Czech republic during 1990–1991.[8] The authors of the Chinese study[6] reported a dose-response relation between ambient SO_2 and total suspended particulates (TSP) and preterm birth. The risk of delivering prematurely increased by 21% for each $\ln(\mu g/m^3)$ increase in SO_2 [odds ratio (OR) = 1.21; 95% CI = 1.01–1.46] and by about 10% for each 100 $\mu g/m^3$ increase in TSP (OR = 1.10; 95% CI = 1.01–1.20). Furthermore, regression coefficients reached a maximum when they considered a 7- to 8-day lag for these exposures, and TSP exposure shortened the mean gestational age by 0.43 (±0.12) days. Beijing monitoring stations measured SO_2 and TSP only. Thus,

TABLE 4. Risk Ratios (and 95% Confidence Intervals) for Vaginally Delivered Preterm Births (Including Small-for-Gestational-Age Births) by Average Ambient CO Concentration (Per 3 Parts Per Million) for Two Pregnancy Periods

			Single-Pollutant Models Adjusted for							
			Two Exposure Periods		Other Risk Factors		Other Risk Factors and Season of Birth and Conception		Multiple-Pollutant Model† Adjusted for Other Risk Factors	
	Crude Risk Ratio	95% CI	Risk Ratio*	95% CI	Risk Ratio*	95% CI	Risk Ratio*	95% CI	Risk Ratio	95% CI
All 17 stations‡ (N = 97,158)										
6 weeks before birth	1.12	1.08–1.17	1.13	1.08–1.17	1.06	1.02–1.10	1.04	0.99–1.10	1.05	0.97–1.12
1st month of pregnancy	1.04	1.01–1.09	1.05	1.01–1.09	1.01	0.97–1.04	1.04	0.99–1.09	1.03	0.96–1.10
Coastal stations‡ (N = 21,885)										
6 weeks before birth	1.08	0.99–1.18	1.11	1.01–1.21	0.97	0.89–1.06	0.99	0.87–1.12	0.77	0.64–0.91
1st month of pregnancy	1.14	1.05–1.24	1.16	1.07–1.26	1.03	0.95–1.12	0.88	0.78–0.98	1.04	0.91–1.19
Inland stations‡ (N = 75,273)										
6 weeks before birth	1.13	1.08–1.18	1.13	1.08–1.18	1.08	1.03–1.13	1.06	0.99–1.13	1.12	1.04–1.21
1st month of pregnancy	1.01	0.97–1.06	1.02	0.97–1.06	0.99	0.95–1.03	1.05	0.99–1.11	1.03	0.96–1.11

* Includes all covariates listed in Table 1 except season.
† N is slightly smaller owing to missing data for NO_2 at some stations.
‡ Exposures at both periods are included in each model.

it is not possible to determine whether these compounds may have served primarily as proxy measures for other pollutants concomitantly released from the same sources, such as other combustion products of coal used for heating and cooking. Similarly, the Czech study also reported increased risks for prematurity and LBW with increases in TSP and SO_2, but the effect of air pollution on LBW seemed to be mostly accounted for by low gestational age. For both pollutants, an increased risk for preterm birth was observed for exposure during each trimester, for SO_2 the increase was consistently about 25% per 50 $\mu g/m^3$, and for TSP the increase was between 11% and 18% per 50 $\mu g/m^3$ ($OR_{1st\ trimester} = 1.18$, 95% CI = 1.05–1.31; $OR_{2nd\ trimester} = 1.11$, 95% CI = 0.97–1.26; $OR_{3rd\ trimester} = 1.12$, 95% CI = 0.97–1.28 per 50 $\mu g/m^3$). Furthermore, the author reported that every 50 $\mu g/m^3$ TSP increase during the first trimester shortened mean gestational age by 0.53 ($\pm$0.18) days.

A small number of studies evaluated the effects of air pollution on several other adverse pregnancy outcomes, such as LBW, growth retardation, and intrauterine death. The first study reporting effects in a human population was conducted in Los Angeles, California, in the early 1970s and found lower mean birth weights in infants of nonsmoking mothers who lived in areas of high air pollution.[26] Alderman *et al*[27] observed a small increase in LBW rates for Denver, CO, residents when average last-trimester CO exposures exceeded 3 ppm at stations considered to provide the most accurate measurements of ambient CO concentrations (OR = 1.5; 95% CI = 0.7–3.5). The researchers examining the cohort of Beijing women found that increased levels of SO_2 and TSP, in addition to preterm birth, were also associated with an increase in the risk of delivering low-weight (<2,500 gm) full-term neonates.[7] For Southern California, we previously reported that increased third-trimester CO levels were responsible for low-weight term birth. Pereira *et al*[28] linked increased ambient concentrations of NO_2 to daily counts of intrauterine mortality. The effect size in this Brazilian study increased when an index of the combined concentration of three pollutants (NO_2, CO, and SO_2) was used. Dejmek *et al*[9] evaluated the association between ambient concentrations of PM_{10} and $PM_{2.5}$ and IUGR in infants born in the Teplice District of the Czech Republic. The investigators reported an association between increased ambient levels of PM_{10} during the first month of gestation and IUGR at birth (OR = 1.62, 95% CI = 1.07–2.46, and OR = 2.64, 95% CI = 1.48–4.71, for medium- and high-exposure tertiles, respectively). The effect size was smaller for $PM_{2.5}$.

As mentioned previously, preterm births may result from pathophysiological processes different from or similar to those responsible for IUGR and low weight. When we examined our results after excluding SGA or LBW babies and only for SGA or LBW children, we observed little difference in effect estimates.

We included in our analyses residents living throughout the SoCAB. We previously reported that the populations living around the air-monitoring stations show

distinct differences in racial composition and socioeconomic status reflected by mean educational level; the percentage of women who did not receive prenatal care; and, according to census data, the percentage of women with children whose income fell below the poverty limit.[10] Yet, when controlling for these risk factors in our analyses, our effect estimates for air pollutants did not change considerably, which suggests that the observed effects are not attributable to regional variations of these confounders. We lacked information, however, for other known risk factors for preterm birth, such as marital status and psychosocial stressors, and the birth records did not allow us to address adequately factors such as maternal weight, occupation, nutrition, mobility, and active and passive smoking.

The maternal smoking information provided under "pregnancy complications" on California birth certificates seemed incomplete. About 2% of all mothers were listed as smokers, whereas a California based pregnancy survey reports that 18.2% of women smoke during pregnancy, but only about 3% smoke more than 11 cigarettes during the last trimester.[29] Thus, we concluded that on California birth certificates smoking is most likely underreported or selectively reported for only the heaviest smokers who continue to smoke throughout pregnancy. Because we adjusted for maternal age, race, and education—factors that the National Center for Health Statistics has identified as influencing the smoking behavior of pregnant women—we may have indirectly adjusted for more moderate smoking behavior as well.

Although much of the PM_{10} in the LA metropolitan area is due to motor vehicle-related sources, particulate matter is not a single or exactly defined toxicant, and its dispersion and composition depends on the source and particle size. Smaller PM_{10} components such as fine (PM less than 2.5 μm) and ultrafine particles are dispersed more homogeneously over the SoCAB, although the composition of the fine-particle fraction can depend on local phenomena and on season.[30] Coarse-particle (PM more than 2.5 μm) concentrations tend to be derived from localized emission events rather than from basin-wide phenomena; for example, in the eastern regions, they contain more dust (crustal particles), and along the coast they contain more sea salt.[30] In addition, ambient air pollution levels for CO and PM_{10} follow a distinct pattern of winter highs and summer lows (with different ranges for stations), related to seasonal variations in average wind speed that affect dilution and dispersion of emissions, with low temperatures reducing surface vertical mixing and causing near-surface inversions to be stronger and last longer.[31] The seasonal fluctuation of ambient CO levels is, in addition, caused by an increase in CO emissions per mile for vehicles driven in cold weather.

Therefore, if considerable variation in air pollution exposures during pregnancy is attributable to seasonal and not to regional differences, risk factors would also have to vary seasonally to confound the relation we observed with air pollution. Although confounding by unknown seasonal factors is possible, such as a seasonal increase in the prevalence of respiratory infections or the use of gas heaters or air conditioners, we found that our effect estimates were stable or even strengthened when we included a term for season of birth and/or conception in our models. When we examined effect estimates for PM_{10} by season of birth or conception, our data indicated a larger effect-per-unit increase for fall and winter births and conceptions. The observed fall/winter effects may reflect a larger contribution of primary and secondary fine combustion-source particles common during stagnant air mass conditions. As previously suggested by Pope *et al*,[32] these particle components may impose a greater health risk than windblown crustal-derived particles that contribute more to the PM_{10} mass in the SoCAB in summer and fall.[33]

An important source of uncertainty in our study stems from misclassification of personal exposure when relying on ambient measurements only. Our estimates of individual exposure to air pollutants were based on average measures for residents living in close proximity to air-monitoring stations. Nevertheless, factors expected to contribute to differences between area-wide and individual exposures include time spent in the proximity of vehicles and indoor sources of CO and PM_{10}. The most important indoor sources of both pollutants are gas- and wood-burning stoves, second-hand cigarette smoke, and housecleaning activities for particulate matter.[34,35] Because ventilation rates influence indoor pollution levels, and residential air exchange rates are on average higher for the Los Angeles region than for the rest of California and the United States,[36] outdoor concentrations may determine a larger percentage of the indoor levels than in other parts of the country, as long as no indoor sources exist.[35–37]

Another measurement error in our study would occur if mothers spent substantial amounts of time during pregnancy outside the perimeter of the residential air-monitoring district—while working, for example. Moreover, those who worked outside the area may have been exposed to high levels of CO inside vehicles in the course of commuting.[38] Unfortunately, we had no information about these factors. A recent study showed that when area-wide measures of exposure to air pollution such as those obtained from fixed-site monitoring stations are used as proxies for personal exposures, the estimates of pollutant effects were generally smaller than those based on exposure levels determined by personal sampling.[39] Some studies showed that nondifferential exposure misclassification can be reduced by supplementing ambient air-monitoring data with human time-activity-pattern information.[40,41] Such refinements resulted in increased estimates of effect for the air pollutants studied. Nondifferential exposure misclassification might explain the much smaller PM_{10} effects observed for the nine monitoring stations for which we used data from the closest neighboring PM_{10} sampler. Stations could have been as much as 10 miles apart and, depending on wind patterns, may not have provided good surrogate measures for lacking PM_{10} data, because they ignored local variations of particle levels. This

concern may also apply to the first-month averages, because residential addresses reported on birth certificates are probably more accurate for the last than the first month of pregnancy.

In conclusion, the birth data we analyzed for Southern California suggest that increased ambient PM_{10} and, to a lesser degree, CO concentrations may contribute to the occurrence of preterm births.

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