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## Original Contribution

# Ambient Air Pollution and Preterm Birth in the Environment and Pregnancy Outcomes Study at the University of California, Los Angeles

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The authors conducted a case-control survey nested within a birth cohort and collected detailed risk factor information to assess the extent to which residual confounding and exposure misclassification may impact air pollution effect estimates. Using a survey of 2,543 of 6,374 women sampled from a cohort of 58,316 eligible births in 2003 in Los Angeles County, California, the authors estimated with logistic regression and two-phase models the effects of pregnancy period-specific air pollution exposure on the odds of preterm birth. For the first trimester, the odds of preterm birth consistently increased with increasing carbon monoxide exposures and also at high levels of exposure to particulate matter less than or equal to 2.5 μm in diameter (>21.4 μg/m$^3$), regardless of type of data (cohort/sample) or covariate adjustment (carbon monoxide exposures of >1.25 ppm increased the odds by 21–25%). Women exposed to carbon monoxide above 0.91 ppm during the last 6 weeks of pregnancy experienced increased odds of preterm birth. Crude and birth certificate covariate-adjusted results for carbon monoxide differed from each other. However, further adjustment for risk factors assessed in the survey did not change effect estimates for short-term pollutant averages appreciably, except for time-activity patterns, which strengthened the observed associations. These results confirm the importance of reducing exposure misclassification when evaluating the effect of traffic-related pollutants that vary spatially.

air pollution; confounding factors (epidemiology); misclassification; premature birth; two-phase regression; vehicle emissions

Abbreviations: CI, confidence interval; EPOS, Environment and Pregnancy Outcomes Study; OR, odds ratio; $PM_{2.5}$, particulate matter less than or equal to 2.5 μm in diameter ($PM_{10}$ and $PM_{0.1}$ defined analogously).

Similar to mortality studies of air pollution, previous pregnancy outcome studies have relied on birth certificate records as their primary or sole source of data (1–3). These studies have the advantage of using large sample sizes, which reduces uncertainty due to random error common to smaller studies that collect in-depth covariate information from mothers (4, 5). However, this increased precision comes at the expense of increased confounding bias, which is not reflected in the standard uncertainty estimates. The control of confounding by maternal or fetal risk factors depends on having adequate covariate information, but birth record studies are typically limited to routinely recorded information. Our previous studies of air pollution and low birth weight and preterm birth using data from the 1990s (6–9), as well as similar studies conducted worldwide, have lacked information on many potential confounding factors.

A case-control sample nested within the 2003 birth cohort in Los Angeles County, California, was selected, and detailed risk factor information was collected. The Environment and Pregnancy Outcomes Study (EPOS) at the University of California, Los Angeles, allowed us to estimate covariate-adjusted associations for preterm birth and gestational

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age-specific air pollution exposures, and to 1) assess the extent to which residual confounding may affect our new results and 2) explore whether exposure misclassification due to different mobility and time-activity patterns influences our results. Nesting our survey within a cohort with birth and air pollution data available for all its members made it possible to use a two-phase (two-stage) design, correct for possible selection/response bias, and improve the efficiency of the estimates compared with analyzing only the surveyed subsample (10).

## MATERIALS AND METHODS

### Subject selection

Our source population was the cohort of livebirths taking place from January 1, 2003, to December 31, 2003, to mothers who resided in a select group of 111 Los Angeles County ZIP codes, chosen on the basis of their proximity to South Coast Air Quality Management District monitoring stations ($n = 24$ ZIP codes) or major population centers and roadways ($n = 87$ ZIP codes), similar to our previous studies. Eligible births were to mothers residing in Los Angeles County at the time of delivery and were identified by use of California State and Los Angeles County electronic birth certificate records.

A total of 66,795 births occurred in these 111 study ZIP codes, representing 41 percent of all Los Angeles County births in the year 2003. From this group, we excluded births with recorded defects ($n = 202$), extreme gestational ages (missing, <140 days, or >320 days; $n = 5{,}948$), extreme birth weights (missing, <500 g, or >5,000 g; $n = 130$), multiple gestations ($n = 1{,}574$), births not eventually reported to the state ($n = 110$), and births taking place outside Los Angeles County ($n = 515$). Our final cohort consisted of 58,316 eligible births, 87 percent of the original total; we will refer to this group as the ''birth cohort'' throughout the paper.

Using the monthly Los Angeles County birth data sampling frame (refer to the Web Appendix (http://aje.oupjournals.org/)), we selected all cases of low birth weight (<2,500 g) or preterm birth (<37 completed weeks' gestation) and an equal number of randomly sampled controls (≥2,500-g weight and full term) from the set of 24 ZIP codes located in close proximity to South Coast Air Quality Management District air monitoring stations. We randomly selected 30 percent of cases and an equal number of controls from the set of 87 ZIP codes containing major population centers and located close to major roadways. Cases and controls were thus matched on ZIP Code set and birth month.

We interviewed 2,543 of the 6,374 women sampled from the birth cohort (40 percent response rate): 1,474 by telephone, 1,004 by mail, and 65 during visits to the mothers' homes (Web Appendix). Of the 3,831 nonresponders, 274 (7 percent) refused, 340 (9 percent) could not be reached because of incorrect addresses or telephone numbers, and 3,158 (82 percent) without a correct telephone number did not return our survey mailed to the address on the birth certificate. The remaining 59 (2 percent) nonresponders were out of the country, had a deceased infant, did not live at home, could not be reached after initial contact, or spoke neither English nor Spanish.

This research was approved by the Office for Protection of Research Subjects at the University of California, Los Angeles, and by the California State Committee for the Protection of Human Subjects.

### Exposure assessment

Each mother's residential ZIP Code at the time of delivery was linked to the nearest ''best'' South Coast Air Quality Management District air monitoring station, accounting for distance, geography, and wind flow patterns in the basin. Data on the infant's date of birth, gestational age, and daily (24-hour) mean pollutant measures for three gaseous pollutants (carbon monoxide, nitrogen dioxide, ozone) and daily or every third day measurements for fine particulate pollutants ($PM_{2.5}$) were used to calculate mean exposure levels for three gestational periods: the entire pregnancy, the first trimester, and the last 6 weeks before delivery.

### Statistical methods

We estimated crude and adjusted effects of air pollution exposure on the odds of preterm birth within our birth cohort and the nested case-control sample using single- and multiple-variable logistic regression models. Preterm infants were those delivered before 37 weeks, while control infants were delivered at 37 or more weeks of completed gestation.

Most risk factors of interest had very few missing values (<1–2 percent) (Web appendix table 1). (This information is described in the first of three supplementary tables; each is referred to as ''Web appendix table'' in the text and is posted on the *Journal*'s website (http://aje.oxfordjournals.org/).) However, because income information was missing for about 17 percent of our sample, we utilized IVEware software (11) and performed multiple imputation based on individual and census characteristics to replace missing values of all key confounder variables only in models adjusting for income. The final models were adjusted for nonimputed risk factors from birth certificates (maternal age, race/ethnicity, parity, education, and season of birth) and/or the EPOS survey (maternal smoking, alcohol consumption, living with a smoker, and marital status during pregnancy); these covariates (table 1) were selected because they were independent risk factors for the outcome and, in combination, changed the estimates for some of the pollutants of interest by more than 5–10 percent in one of our models. Other risk factors (e.g., occupation, pregnancy weight gain, income) resulted in no further changes of point estimates and were not included in the models presented.

We treated the pollutants as both continuous and categorical variables. Category cutpoints were determined by dividing the birth cohort's entire-pregnancy pollutant range into five evenly spaced intervals. If this caused the reference group to contain less than 10 percent or the highest category to contain less than 1 percent of the population for any of the exposure averaging periods, we combined the category with the adjacent category. This procedure guaranteed

**TABLE 1. Adjusted odds ratios and 95% confidence intervals for preterm births for phase 1 covariates in the 2003 Los Angeles (California) birth cohort and the Environment and Pregnancy Outcomes Survey responders and nonresponders**

| | Los Angeles birth cohort ($n = 58,316$) | | EPOS* nonresponders ($n = 3,831$) | | EPOS responders ($n = 2,543$) | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% confidence interval | Odds ratio | 95% confidence interval | Odds ratio | 95% confidence interval |
| Maternal age (years) | | | | | | |
| <20 | 1.16 | 1.05, 1.29 | 1.30 | 1.02, 1.66 | 1.16 | 0.87, 1.56 |
| 20–24 | 1.0 | | 1.0 | | 1.0 | |
| 25–29 | 0.94 | 0.87, 1.01 | 0.95 | 0.79, 1.14 | 0.83 | 0.65, 1.04 |
| 30–34 | 0.97 | 0.89, 1.05 | 1.00 | 0.83, 1.21 | 0.95 | 0.75, 1.20 |
| ≥35 | 1.20 | 1.10, 1.30 | 1.24 | 1.02, 1.66 | 1.23 | 0.95, 1.59 |
| Maternal race/ethnicity | | | | | | |
| White, non-Hispanic | 1.0 | | 1.0 | | 1.0 | |
| Hispanic | 1.47 | 1.35, 1.60 | 1.58 | 1.27, 1.98 | 1.36 | 1.09, 1.69 |
| African American | 2.13 | 1.90, 2.40 | 2.34 | 1.75, 3.13 | 1.72 | 1.21, 2.45 |
| Asian | 1.02 | 0.88, 1.18 | 1.10 | 0.79, 1.54 | 0.83 | 0.53, 1.32 |
| Other† | 1.51 | 1.29, 1.77 | 1.58 | 1.08, 2.29 | 1.38 | 0.89, 2.15 |
| Parity | | | | | | |
| 0 | 1.0 | | 1.0 | | 1.0 | |
| ≥1 | 0.86 | 0.81, 0.91 | 0.77 | 0.67, 0.88 | 0.87 | 0.74, 1.03 |
| Maternal education (years) | | | | | | |
| ≤8 | 1.06 | 0.98, 1.16 | 1.18 | 0.97, 1.43 | 0.92 | 0.71, 1.20 |
| 9–11 | 1.00 | 0.92, 1.07 | 1.11 | 0.93, 1.33 | 0.91 | 0.73, 1.15 |
| 12 | 1.0 | | 1.0 | | 1.0 | |
| 13–15 | 0.92 | 0.84, 1.00 | 1.14 | 0.93, 1.41 | 0.87 | 0.67, 1.11 |
| ≥16 | 0.65 | 0.60, 0.71 | 0.67 | 0.53, 0.83 | 0.67 | 0.53, 0.84 |
| Season of birth | | | | | | |
| April–June (spring) | 1.05 | 0.97, 1.13 | 0.97 | 0.81, 1.17 | 1.08 | 0.86, 1.35 |
| July–September (summer) | 0.94 | 0.88, 1.02 | 0.99 | 0.82, 1.18 | 0.91 | 0.73, 1.15 |
| October–December (fall) | 1.03 | 0.95, 1.11 | 1.03 | 0.86, 1.24 | 0.89 | 0.72, 1.11 |
| January–March (winter) | 1.0 | | 1.0 | | 1.0 | |
| First trimester air pollution exposures | | | | | | |
| Carbon monoxide (per 1 ppm*) | 1.10 | 1.04, 1.17 | 1.14 | 0.99, 1.31 | 1.15 | 0.96, 1.38 |
| Nitrogen dioxide (per 2 pphm*) | 1.02 | 0.99, 1.06 | 1.03 | 0.95, 1.13 | 1.05 | 0.94, 1.17 |
| Ozone (per 2 pphm) | 0.99 | 0.96, 1.02 | 0.95 | 0.88, 1.02 | 0.99 | 0.90, 1.08 |
| $PM_{2.5}$* (per 10 $\mu g/m^3$) | 1.00 | 0.94, 1.07 | 0.95 | 0.82, 1.10 | 1.23 | 1.02, 1.48 |

* EPOS, Environment and Pregnancy Outcomes Survey; ppm, part(s) per million; pphm, parts per hundred million; $PM_{2.5}$, particulate matter less than or equal to 2.5 $\mu$m in diameter.

† Includes Native American/American Indian, Indian, Filipino, Hawaiian, Guamanian, Samoan, Eskimo, Aleut, Pacific Islander, other (specified).

comparability of the estimated effect sizes across pregnancy periods while—unlike using quartiles—it also allowed us to explore the impact of high exposures and to maintain adequate precision.

Two-phase methods were used for some analyses of the EPOS survey responders (refer to Web Appendix). We used first-phase variables (including the outcome, covariates, and exposure) measured for all members of the population as stratification variables; the second-phase sample was drawn from within these strata with known probability. First, we used the detailed covariate data collected for our second-phase sample to assess their potential for confounding

and to further adjust air pollution estimates when needed. Second, we used the known sampling fractions to account for the stratified sampling to reduce potential selection bias and to increase the statistical efficiency of the case-control estimators, yielding standard errors closer to those that could be obtained using the entire first-phase population.

In summary, for EPOS survey respondents, we compared results from three models: 1) adjusting only for a limited set of confounders provided on birth certificates; 2) including additional covariates from our EPOS survey; and 3) using a two-stage analysis to increase the efficiency of the case-control estimators.

## RESULTS

Demographic information from birth certificates and our EPOS survey for the birth cohort, survey responders, and nonresponders is provided in Web appendix table 1. Over half of all responders identified as Hispanic and were foreign born, mostly in Mexico. Approximately 60 percent had 12 or fewer years of education, and 53 percent reported a household income below $30,000/year in 2002. Very few women used cigarettes or alcohol during pregnancy (5 percent and 9 percent, respectively), but 18 percent were exposed to household environmental tobacco smoke while pregnant. A majority of women were married or living with a partner (79 percent) and had previously given birth (60 percent), and almost all women received prenatal care starting in the first trimester (91 percent).

Odds ratios for potential risk factors for preterm birth collected in the EPOS survey are presented in Web appendix table 2. Odds ratios for the major risk factors recorded on birth certificates differed most for young maternal age, parity, and education when comparing the birth cohort, EPOS survey responders, and nonresponders (table 1).

Air pollutants closely tied to primary traffic emissions, carbon monoxide and nitrogen dioxide, were highly correlated for each pregnancy period and strongly negatively correlated with pregnancy-specific ozone exposures; carbon monoxide and $PM_{2.5}$ were moderately correlated (Web appendix table 3).

For the first trimester, we observed an increase in the odds of preterm birth with increasing carbon monoxide exposures, and a positive trend was suggested in the birth cohort ($p_{trend} < 0.001$). Adjusting for birth certificate and EPOS covariates, we estimated that the odds of preterm birth increased by 11–17 percent for women with average carbon monoxide levels of 0.59–1.25 ppm (vs. $\leq$0.58 ppm) and by as much as 21–25 percent for women with carbon monoxide exposures greater than 1.25 ppm (table 2). Similarly, single-pollutant models showed a 10–29 percent increase in the odds of preterm birth at the highest levels of first trimester $PM_{2.5}$ exposures ($>21.36$ $\mu g/m^3$). We observed no consistent patterns of increase in the odds of preterm birth for ozone or nitrogen dioxide exposures. Multipollutant models that included carbon monoxide and fine particle measures generally confirmed these associations; the odds of preterm birth increased 16–47 percent for women with high $PM_{2.5}$ exposures and remained between 7 and 25 percent in the cohort or the EPOS sample (results not shown).

An increase in the odds was also observed for women with average carbon monoxide exposures above 0.91 ppm (3–33 percent) during the last 6 weeks before birth. However, the exposure-response relation was not as consistently observed as for first trimester exposures. Odds ratios for all other pollutants late in pregnancy were close to the null value.

Overall, air pollution exposure estimates for the EPOS survey responders changed most strongly (>10 percent) upon adjustment for covariates provided on birth certificates: maternal age, race, education, parity, and infant's season of birth. Effect estimates for first trimester carbon monoxide averages increased while odds ratios for entire pregnancy carbon monoxide exposures were generally attenuated. In fact, after adjustment for these covariates, none of the air pollutants exhibited a consistently positive association with preterm birth when averaged over the entire pregnancy.

In EPOS responders, the point estimates were often larger, but because of the much-reduced sample size, the 95 percent confidence intervals were wider. Adding potential confounders from the EPOS survey to the birth certificate covariate-adjusted models generally did not change the pollutant point estimates but further widened the confidence intervals. Our two-stage models yielded point and interval estimates similar to the cohort estimates, except for carbon monoxide estimates averaged over the last 6 weeks or the entire pregnancy, which could be due to random variability and/or the differences between the two groups noted in table 1.

Finally, we restricted our analyses to EPOS survey women who reported not to have changed residence throughout pregnancy and found that the first trimester carbon monoxide exposures strengthened, although confidence intervals widened (0.59–0.91 ppm carbon monoxide: odds ratio (OR) = 1.12, 95 percent confidence interval (CI): 0.87, 1.45; 0.92–1.25 ppm carbon monoxide: OR = 1.22, 95 percent CI: 0.90, 1.65; >1.25 ppm carbon monoxide: OR = 1.29, 95 percent CI: 0.90, 1.85). Parous women also experienced strongly increased odds for delivering preterm at high exposures to carbon monoxide during the last 6 weeks of pregnancy (0.59–0.91 ppm carbon monoxide: OR = 1.13, 95 percent CI: 0.85, 1.51; >0.91 ppm carbon monoxide: OR = 1.54, 95 percent CI: 1.08, 2.19) compared with women with first pregnancies (0.59–0.91 ppm carbon monoxide: OR = 0.79, 95 percent CI: 0.55, 1.11; >0.91 ppm carbon monoxide: OR = 0.90, 95 percent CI: 0.58, 1.39). For parous women who worked outside the home at any point during pregnancy compared with those who did not, first trimester carbon monoxide results did not differ much. However, parous women who did not work outside their home and were exposed to high carbon monoxide levels during the last 6 weeks of pregnancy experienced strongly increased odds for delivering preterm (0.59–0.91 ppm carbon monoxide: OR = 1.40, 95 percent CI: 0.93, 2.10; >0.91 ppm carbon monoxide: OR = 1.96, 95 percent CI: 1.19, 3.23) compared with multiparas who reported working outside their home during pregnancy (0.59–0.91 ppm carbon monoxide: OR = 0.92, 95 percent CI: 0.60, 1.41; >0.91 ppm carbon monoxide: OR = 1.23, 95 percent CI: 0.73, 2.07).

**TABLE 2. Crude and adjusted (single pollutant) odds ratios and 95% confidence intervals for preterm delivery from one- and two-phase logistic models for birth cohort and Environment and Pregnancy Outcomes Survey responders residing in Los Angeles (California) in 2003**

| | Birth cohort | | | | EPOS* responders | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Adjusted | | | | | |
| | Crude | | Adjusted† | | Crude | | Adjusted for state covariates† | | Adjusted for state and EPOS covariates‡ | | Two-phase model‡ | |
| | Odds ratio | 95% confidence interval | Odds ratio | 95% confidence interval | Odds ratio | 95% confidence interval | Odds ratio | 95% confidence interval | Odds ratio | 95% confidence interval | Odds ratio | 95% confidence interval |
| First trimester carbon monoxide (ppm*) | | | | | | | | | | | | |
| ≤0.58 | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| 0.59–0.91 | 1.16 | 1.08, 1.25 | 1.17 | 1.08, 1.26 | 1.11 | 0.90, 1.37 | 1.11 | 0.89, 1.38 | 1.11 | 0.89, 1.39 | 1.15 | 1.03, 1.29 |
| 0.92–1.25 | 1.13 | 1.05, 1.23 | 1.15 | 1.05, 1.26 | 1.19 | 0.95, 1.50 | 1.17 | 0.90, 1.52 | 1.17 | 0.89, 1.52 | 1.15 | 0.97, 1.38 |
| >1.25 | 1.14 | 1.05, 1.23 | 1.25 | 1.12, 1.38 | 1.18 | 0.94, 1.50 | 1.21 | 0.89, 1.65 | 1.21 | 0.88, 1.65 | 1.25 | 0.96, 1.63 |
| Last 6 weeks carbon monoxide (ppm) | | | | | | | | | | | | |
| ≤0.58 | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| 0.59–0.91 | 1.02 | 0.95, 1.09 | 1.00 | 0.93, 1.08 | 0.94 | 0.77, 1.16 | 0.95 | 0.77, 1.19 | 0.97 | 0.78, 1.21 | 1.06 | 0.96, 1.17 |
| 0.92–1.25 | 1.12 | 1.03, 1.22 | 1.08 | 0.98, 1.20 | 1.22 | 0.96, 1.54 | 1.29 | 0.97, 1.72 | 1.33 | 0.99, 1.78 | 1.23 | 1.02, 1.47 |
| >1.25 | 1.06 | 0.98, 1.15 | 1.03 | 0.93, 1.14 | 1.03 | 0.83, 1.29 | 1.14 | 0.84, 1.55 | 1.13 | 0.83, 1.55 | 1.23 | 0.98, 1.54 |
| Entire pregnancy carbon monoxide (ppm) | | | | | | | | | | | | |
| ≤0.58 | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| 0.59–0.91 | 0.84 | 0.78, 0.91 | 0.76 | 0.70, 0.82 | 0.77 | 0.62, 0.97 | 0.65 | 0.51, 0.83 | 0.66 | 0.52, 0.84 | 0.73 | 0.65, 0.83 |
| 0.92–1.25 | 0.93 | 0.86, 1.00 | 0.84 | 0.77, 0.91 | 0.99 | 0.79, 1.25 | 0.82 | 0.64, 1.07 | 0.85 | 0.65, 1.10 | 0.82 | 0.71, 0.94 |
| >1.25 | 1.22 | 1.09, 1.37 | 1.03 | 0.91, 1.17 | 1.13 | 0.82, 1.56 | 0.82 | 0.57, 1.18 | 0.83 | 0.57, 1.19 | 0.90 | 0.74, 1.10 |
| First trimester nitrogen dioxide (pphm*) | | | | | | | | | | | | |
| ≤2.61 | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| 2.62–3.12 | 1.23 | 1.14, 1.32 | 1.22 | 1.13, 1.31 | 1.04 | 0.84, 1.29 | 1.04 | 0.83, 1.31 | 1.04 | 0.83, 1.30 | 1.23 | 1.11, 1.37 |
| 3.13–3.64 | 1.09 | 1.00, 1.18 | 1.09 | 1.00, 1.19 | 1.15 | 0.91, 1.44 | 1.11 | 0.87, 1.41 | 1.13 | 0.88, 1.45 | 1.07 | 0.93, 1.23 |
| >3.64 | 1.09 | 1.02, 1.18 | 1.09 | 1.00, 1.19 | 1.03 | 0.82, 1.28 | 0.92 | 0.71, 1.20 | 0.94 | 0.72, 1.23 | 1.03 | 0.86, 1.23 |
| First trimester ozone (pphm) | | | | | | | | | | | | |
| ≤2.17 | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| 2.18–2.86 | 1.03 | 0.97, 1.10 | 0.98 | 0.91, 1.06 | 1.08 | 0.89, 1.31 | 1.07 | 0.85, 1.35 | 1.08 | 0.86, 1.37 | 0.99 | 0.84, 1.17 |
| 2.87–3.54 | 0.98 | 0.92, 1.06 | 0.96 | 0.88, 1.06 | 0.91 | 0.73, 1.13 | 0.94 | 0.72, 1.24 | 0.95 | 0.72, 1.25 | 0.95 | 0.78, 1.17 |
| >3.54 | 0.93 | 0.83, 1.03 | 0.93 | 0.82, 1.06 | 1.08 | 0.80, 1.46 | 1.17 | 0.81, 1.68 | 1.16 | 0.80, 1.68 | 0.92 | 0.70, 1.20 |
| First trimester $PM_{2.5}$* ($\mu g/m^3$) | | | | | | | | | | | | |
| ≤18.63 | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| 18.64–21.36 | 0.96 | 0.90, 1.03 | 1.01 | 0.93, 1.09 | 1.11 | 0.90, 1.36 | 1.14 | 0.90, 1.46 | 1.15 | 0.90, 1.47 | 0.98 | 0.84, 1.15 |
| >21.36 | 1.05 | 0.99, 1.12 | 1.10 | 1.01, 1.20 | 1.27 | 1.06, 1.53 | 1.27 | 0.99, 1.64 | 1.29 | 1.00, 1.67 | 1.07 | 0.85, 1.35 |

* EPOS, Environment and Pregnancy Outcomes Survey; ppm, part(s) per million; pphm, parts per hundred million; $PM_{2.5}$, particulate matter less than or equal to 2.5 $\mu$m in diameter.
† Adjusted for state covariates: birth season, parity, and mother's age, race, and education.
‡ Adjusted for both state covariates (birth season, parity, and mother's age, race, and education) and EPOS covariates (active and passive smoking, marital status, and alcohol use during pregnancy).

## DISCUSSION

We conducted the first case-control study nested within a birth cohort that collected detailed risk factor information to assess the extent to which residual confounding and exposure misclassification due to time activity and mobility may affect birth certificate-based studies of air pollution and adverse pregnancy outcomes. Our extensively adjusted analyses conducted with new 2003 data for both the birth cohort and our EPOS sample confirmed that carbon monoxide associations are strongest and suggestive of an exposure-response relation during the first pregnancy trimester; our analyses further suggested that higher exposures during the last 6 weeks of pregnancy may also increase the odds of preterm birth.

Therefore, we corroborated our earlier birth-certificate-only–based results that implicated traffic-related pollutants. We first reported carbon monoxide and particle associations for preterm birth in the South Coast Air Basin using data from 1989 to 1993 (7). For the later period from 1994 to 2000 (9), we reported an 8–24 percent increase in risk of preterm birth per 1-ppm increase in carbon monoxide during the first trimester among women who lived close to stations measuring carbon monoxide. Depending on the distance to the monitoring station, we also observed a 9–30 percent increase in the risk of preterm birth when average carbon monoxide concentrations were high ($\geq$1.9 ppm) 6 weeks before birth. For particles ($PM_{10}$), a risk increase of 17–20 percent during both the early and late pregnancy periods was seen only for women in the highest exposure quartile ($\geq$51.2 $\mu g/m^3$) and residing within one mile (1.6 km) of a station, and no association was seen beyond this distance from a station that measured these particles.

Complete $PM_{10}$ measurements were available only for five of the nine stations measuring particles and—as previously—these were recorded every 6 days. A denser $PM_{2.5}$ monitoring network was established in the Los Angeles Basin in 1999 with one third of the stations taking daily measurements, the rest recording every third day. Thus, for the first time, we were able to use fine particle measures in our analyses. We found that $PM_{2.5}$ exposures during the first trimester, but not the last 6 weeks before birth, paralleled the carbon monoxide results. These consistent associations for carbon monoxide and $PM_{2.5}$ suggest that smaller primary exhaust particles may play an important role in the Los Angeles Basin; that is, the observed associations for carbon monoxide may be attributable to toxins sorbed to primary exhaust particles. This further supports our results that proximity to traffic sources is related to these birth outcomes (8).

The majority of fine and ultrafine ($<PM_{0.1}$) particles found in the urban atmosphere derive from engine combustion (12–15). Ultrafine particles have very low mass but provide a high surface area for the adsorption of toxic species, such as polycyclic aromatic hydrocarbons (16). These particles deposit in the lung (17, 18), escape phagocytosis by alveolar macrophages, and translocate to extrapulmonary organs (19), and they may transfer sorbed toxic compounds to the fetus and the placenta. Experimental and human data indicate that polycyclic aromatic hydrocarbons can cross the placenta and reach fetal organs (20–27). It has been suggested that such compounds may interfere with placental development and subsequent nutrient and oxygen delivery to the fetus (28, 29), and the DNA-adduct levels of polycyclic aromatic hydrocarbons in cord blood leukocytes have been linked with decreased birth weights, lengths, and head circumferences (4, 30).

Another potential mechanism of developmental toxicity is through activation of the oxidative stress pathway. Polycyclic aromatic hydrocarbons, metals, and related compounds can induce the production of cytotoxic reactive oxygen species and, ultimately, inflammatory and oxidant stress responses (16, 31). Ultrafine particles were found to be potent inducers of cellular heme oxygenase-1 expression and to deplete intracellular glutathione, both important in oxidant stress responses (32). Furthermore, while increasing concentrations of inflammatory cytokines may be part of the body's normal preparation for parturition, it has been hypothesized that preterm birth can be triggered by abnormal cytokine production favoring inflammation (33, 34); for example, common genetic variants increasing expression of proinflammatory cytokine genes have recently been associated with spontaneous preterm birth. Susceptibility to preterm delivery may be increased by an early activation of components normally associated with delivery (33, 35).

As explained previously (9), carbon monoxide may be a better marker of vehicle exhaust toxins than $PM_{2.5,}$ since the latter includes both particles directly emitted in vehicular exhaust and those created secondarily through atmospheric reactions (36). Thus, the newly available $PM_{2.5}$ measures cannot be as easily interpreted as a primary exhaust proxy, and carbon monoxide may still be the better indicator of primary exhaust toxins' contributions.

Two-phase designs nesting a sample within a cohort for which both outcome and some exposure information are available have a long history in epidemiology (37). Yet, they have not been widely used and, to our knowledge, have never been applied in studies of birth outcomes and air pollution. The advantage of a two-phase analysis is better control of confounding by use of survey data and minimization of any selection or response bias. Based on our results, we recommend that researchers consider this design in the future.

One limitation to our study was the low response rate, mostly because of our inability to find and/or contact the women randomly selected from birth records. However, when the pollutant estimates from the birth cohort, EPOS responders, and nonresponders were contrasted, the evidence for selection/response bias was modest, even though responders differed from nonresponders and the birth cohort in some aspects of exposure, as well as major risk factors for preterm birth (maternal education and age, being foreign born) (Web appendix tables 1 and 2). Adjustment for birth certificate covariates had the strongest influence on pollutant estimates, while additional adjustment for EPOS-collected covariates changed the estimates little (table 2). This confirmed our hypotheses that 1) estimates of effect for pollutants that change with season and are averaged over short time intervals, such as months or pregnancy trimesters, are likely not confounded by behavioral variables that do not

change seasonally, and 2) state covariates are sufficient to remove most confounding for the short- to moderate-term averages. This was further emphasized by our results for entire pregnancy averages that rely more on spatial rather than temporal contrasts. The large changes in estimates observed for the entire-pregnancy carbon monoxide averages (table 2) when adjusting for state covariates seem to support that these longer term averages are more sensitive to confounding bias due to population differences in other risk factors but, again, indicate that adjustment for additional behavioral risk factors is not necessary.

Furthermore, we performed a number of sensitivity analyses including adjustment for additional EPOS variables: pregnancy weight gain, occupation, and imputed income. Addition of these variables to the models did not change the effect estimates appreciably. We restricted our analyses to women who had not moved during pregnancy, and our results remained unchanged or were slightly strengthened, as one would expect, assuming that nonmovers suffered less from exposure misclassification and that misclassification was nondifferential. Stratifying by whether or not women worked outside their homes during pregnancy was important for estimates of carbon monoxide averaged over the last 6 weeks before birth, suggesting that shorter-term averages are sensitive to exposure misclassification (likely nondifferential) introduced by a woman's actual location. This is particularly important for primary exhaust pollutants, such as carbon monoxide, whose concentrations have been shown to vary substantially over short distances (12, 14, 15, 38–51). We previously argued that a multiparous woman is more often at home during pregnancy, possibly taking care of other children (6). For the last 6 weeks before birth, the strongest and most consistent carbon monoxide exposure results were estimated for multiparas who did not work outside the home during pregnancy, again raising this supposition. Our survey data confirmed that women being pregnant for the first time were more likely to be employed outside the home during pregnancy (63 vs. 47 percent), and those who had another child within the previous year were more likely to not work outside their home during pregnancy (76 vs. 46 percent).

In conclusion, we confirmed our previous results that exposure to the traffic-related pollutants—carbon monoxide and fine particles—mostly during the first trimester but also possibly high exposures prior to delivery are associated with preterm birth in the Los Angeles metropolitan area. Importantly, the results were not confounded by well-known risk factors missing from California birth certificates. The additional information obtained by survey enabled us to also confirm that local heterogeneity of pollutants may influence results for traffic-related exposures, and that it might be important to consider time-activity patterns and to know where women spend their time to avoid exposure misclassification.

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## REFERENCES

1. Glinianaia SV, Rankin J, Bell R, et al. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiology 2004;15:36–45.
2. Maisonet M, Correa A, Misra D, et al. A review of the literature on the effects of ambient air pollution on fetal growth. Environ Res 2004;95:106–15.
3. Sram RJ, Binkova B, Dejmek J, et al. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect 2005;113:375–82.
4. Perera FP, Rauh V, Tsai WY, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect 2003;111:201–5.
5. Jedrychowski W, Bendkowska I, Flak E, et al. Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland. Environ Health Perspect 2004;112:1398–402.
6. Ritz B, Yu F. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ Health Perspect 1999;107:17–25.
7. Ritz B, Yu F, Chapa G, et al. Effect of air pollution on preterm birth among children born in southern California between 1989 and 1993. Epidemiology 2000;11:502–11.
8. Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994–1996. Environ Health Perspect 2003;111:207–16.
9. Wilhelm M, Ritz B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. Environ Health Perspect 2005;113:1212–21.
10. Breslow N, Chatterjee N. Design and analysis of two-phase studies with binary outcome applied to Wilms tumor prognosis. Appl Stat 1999;48:451–68.
11. Raghunathan T, Solenberger P, Van Hoewyk J. IVEware: imputation and variance estimation software. Ann Arbor, MI: University of Michigan, 2002.
12. Hitchins J, Morawska L, Wolff R, et al. Concentrations of submicrometre particles from vehicle emissions near a major road. Atmos Environ 2000;34:51–9.
13. Schauer J, Rogge W, Hildeman L, et al. Source apportionment of airborne particulate matter using organic compounds as tracers. Atmos Environ 1996;30:3837–55.
14. Shi J, Khan A, Harrison R. Measurements of ultrafine particle concentration and size distribution in the urban atmosphere. Sci Total Environ 1999;235:51–64.

15. Zhu Y, Hinds W, Kim S, et al. Study of ultrafine particles near a major highway with heavy-duty diesel traffic. Atmos Environ 2002;36:4323–35.
16. Sioutas C, Delfino RJ, Singh M. Exposure assessment for atmospheric ultrafine particles (UFPs) and implications in epidemiologic research. Environ Health Perspect 2005;113: 947–55.
17. Jaques PA, Kim CS. Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhal Toxicol 2000;12:715–31.
18. Yeh H, Muggenburg B, Harkema J. In vivo deposition of inhaled ultrafine particles in the respiratory tract of rhesus monkeys. Aerosol Sci Technol 1997;27:465–70.
19. Oberdorster G, Utell MJ. Ultrafine particles in the urban air: to the respiratory tract—and beyond? (Editorial). Environ Health Perspect 2002;110:A440–1.
20. Manchester DK, Parker NB, Bowman CM. Maternal smoking increases xenobiotic metabolism in placenta but not umbilical vein endothelium. Pediatr Res 1984;18:1071–5.
21. Huel G, Godin J, Moreau T, et al. Aryl hydrocarbon hydroxylase activity in human placenta of passive smokers. Environ Res 1989;50:173–83.
22. Huel G, Girard F, Nessmann C, et al. Placental aryl hydrocarbon hydroxylase activity and placental calcifications. Toxicology 1992;71:257–66.
23. Huel G, Godin J, Frery N, et al. Aryl hydrocarbon hydroxylase activity in human placenta and threatened preterm delivery. J Expo Anal Environ Epidemiol 1993;3(suppl 1):187–99.
24. Hatch MC, Warburton D, Santella RM. Polycyclic aromatic hydrocarbon-DNA adducts in spontaneously aborted fetal tissue. Carcinogenesis 1990;11:1673–5.
25. Sram RJ, Binkova B, Rossner P, et al. Adverse reproductive outcomes from exposure to environmental mutagens. Mutat Res 1999;428:203–15.
26. Madhavan ND, Naidu KA. Polycyclic aromatic hydrocarbons in placenta, maternal blood, umbilical cord blood and milk of Indian women. Hum Exp Toxicol 1995;14:503–6.
27. Arnould JP, Verhoest P, Bach V, et al. Detection of benzo[a]pyrene-DNA adducts in human placenta and umbilical cord blood. Hum Exp Toxicol 1997;16:716–21.
28. Dejmek J, Selevan SG, Benes I, et al. Fetal growth and maternal exposure to particulate matter during pregnancy. Environ Health Perspect 1999;107:475–80.
29. Dejmek J, Solansky I, Benes I, et al. The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environ Health Perspect 2000;108:1159–64.
30. Perera FP, Whyatt RM, Jedrychowski W, et al. Recent developments in molecular epidemiology: a study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. Am J Epidemiol 1998;147: 309–14.
31. Nel AE, Diaz-Sanchez D, Li N. The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. Curr Opin Pulm Med 2001;7:20–6.
32. Li N, Sioutas C, Cho A, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 2003;111:455–60.
33. Engel SA, Erichsen HC, Savitz DA, et al. Risk of spontaneous preterm birth is associated with common proinflammatory cytokine polymorphisms. Epidemiology 2005;16:469–77.
34. Keelan JA, Blumenstein M, Helliwell RJ, et al. Cytokines, prostaglandins and parturition—a review. Placenta 2003; 24(suppl A):S33–46.
35. Crider KS, Whitehead N, Buus RM. Genetic variation associated with preterm birth: a HuGE review. Genet Med 2005; 7:593–604.
36. Kim S, Shen S, Sioutas C. Size distribution and diurnal and seasonal trends of ultrafine particles in source and receptor sites of the Los Angeles basin. J Air Waste Manag Assoc 2002;52:297–307.
37. White J. A two stage design for the study of the relationship between a rare exposure and a rare disease. Am J Epidemiol 1982;115:119–28.
38. Ott W, Eliassen R. A survey technique for determining the representativeness of urban air monitoring stations with respect to carbon monoxide. J Air Pollut Control Assoc 1973;23:685–90.
39. Sivacoumar R, Thanasekaran K. Line source model for vehicular pollution prediction near roadways and model evaluation through statistical analysis. Environ Pollut 1999; 104:389–95.
40. Rodes C, Holland D. Variations of NO, NO2 and O3 concentrations downwind of a Los Angeles freeway. Atmos Environ 1981;15:243–50.
41. Kuhler M, Krafr J, Koch W, et al. Dispersion of car emissions in the vicinity of a highway, environmental meteorology. Dordrecht, Netherlands: Kluwer Academic Publishers, 1988: 39–47.
42. Nitta H, Sato T, Nakai S, et al. Respiratory health associated with exposure to automobile exhaust. I. Results of cross-sectional studies in 1979, 1982, and 1983. Arch Environ Health 1993;48:53–8.
43. Roorda-Knape MC, Janssen NA, de Hartog J, et al. Traffic related air pollution in city districts near motorways. Sci Total Environ 1999;235:339–41.
44. Monn C, Carabias V, Junker R, et al. Small-scale spatial variability of particulate matter $<10$ μm (PM10) and nitrogen dioxide. Atmos Environ 1997;31:2243–7.
45. Horvath H, Kriener I, Norek C, et al. Diesel emissions in Vienna. Atmos Environ 1988;22:1255–69.
46. Janssen NA, Hoek G, Harssema H, et al. Childhood exposure to PM10: relation between personal, classroom, and outdoor concentrations. Occup Environ Med 1997;54:888–94.
47. Kingham S, Briggs D, Elliot P, et al. Spatial variations in the concentrations of traffic-related pollutants in indoor and outdoor air in Huddersfield, England. Atmos Environ 2000; 34:905–16.
48. Wrobel A, Rokita E, Maenhaut W. Transport of traffic-related aerosols in urban areas. Sci Total Environ 2000;257: 199–211.
49. Zhu Y, Hinds W, Kim S, et al. Concentration and size distribution of ultrafine particles near a major highway. J Air Waste Manag Assoc 2002;52:1032–42.
50. Kinney PL, Aggarwal M, Northridge ME, et al. Airborne concentrations of PM(2.5) and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. Environ Health Perspect 2000;108:213–18.
51. Levy JI, Bennett DH, Melly SJ, et al. Influence of traffic patterns on particulate matter and polycyclic aromatic hydrocarbon concentrations in Roxbury, Massachusetts. J Expo Anal Environ Epidemiol 2003;13:364–71.