HHS Public Access
Author manuscript
*Ann Epidemiol*. Author manuscript; available in PMC 2015 December 07.

Published in final edited form as:
*Ann Epidemiol*. 2015 November ; 25(11): 874–876. doi:10.1016/j.annepidem.2015.08.005.

# Role of infant sex in the association between air pollution and preterm birth

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### Keywords

Preterm birth; Air pollution; Sex differences

## Introduction

Preterm birth (less than 37 weeks of gestation) is the leading cause of perinatal morbidity and mortality in developed countries. Its prevalence is 12%–13% in the United States. Several studies have demonstrated a disproportionate number of males among preterm births (1–3). Underlying mechanisms for this sex disparity are not well understood. One reason could be a sex difference in intrauterine inflammation and/or infection response where there are studies reporting higher concentrations of pro-inflammatory markers in male infants (4–7). Furthermore, environmental exposures, such as ambient air pollution, may impact risk of adverse birth outcomes (8–14), including preterm birth, through inflammatory processes (15,16), and these associations may differ between male and female infants.

To our knowledge, few studies have accounted for infant sex while examining air pollution impact on preterm birth (17,18). We used data from several regularly monitored ambient air pollutants to investigate whether a previously described association between air pollution and preterm birth (19) differs between male and female infants.

## Methods

Our study population consists of all births ($n$ = 321,029) during 2000–2006, in the four most populated counties in the San Joaquin Valley of California, which are Fresno, Kern, Stanislaus, and San Joaquin. Gestational age at birth was determined from the last menstrual period reported on the birth certificate. Prematurity was categorized into the following gestational ages: 20–27 weeks, 28–31 weeks, 32–33 weeks, and 34–36 weeks. In all analyses, term birth, defined as births between 37 and 42 weeks, was the reference.

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Daily metrics of all pollutants carbon monoxide (CO), nitrogen dioxide ($NO_2$), particulate matter with aerodynamic diameter less than 2.5 microns ($PM_{2.5}$) and less than 10 microns ($PM_{10}$) were used to create an average for the entire pregnancy and for each trimester at each geocoded residence. Further details on exposure assessment were published previously (14,19). Briefly, air quality data were spatially interpolated using inverse distance-squared weighting. Data from up to four air quality measurement stations from US Environmental Protection Agency's Air Quality System database were included in each interpolation.

Exposures were categorized as "high" if they were above the 75 percentile of entire pregnancy averages to correspond to previous analyses. We used logistic regression to examine the association between each pollutant and each of the five gestational definitions of preterm birth versus term. To address the primary hypothesis of this analysis, we stratified analyses by infant sex to determine if there was a difference of the association between air pollution and preterm birth. The statistical differences were evaluated with the Wald test of homogeneity.

We adjusted models for the following covariates: maternal age, maternal race and/or ethnicity, education, infant birth weight, prenatal care in the first trimester, and Medi-Cal payment of birth expenses to be consistent with previous analyses. We excluded subjects missing data on any exposure of pollutants and those with pregnancy complications. This research was approved by institutional review boards from the University of California, Berkeley, Stanford University, and the California State Committee for the Protection of Human Subjects.

## Results

The study population ($n$ = 253,704) has been described (19). Preterm birth was 11.5%. The male to female ratio of all births was 1.05. Most women were 20–29 years of age, of Hispanic ethnicity, had a previous birth and had a high school education or higher. Prenatal care in the first trimester was 81%, and birth expenses were paid by Medi-Cal or other government program for approximately 55% of women.

Previous analysis of these data found significant odds of birth at 20–27 weeks of gestation for high exposure to each of the examined air pollutants during the second trimester of pregnancy (19). Odds were strongest for particulate matter with a more than two-fold increased risk of birth at 20–27 weeks gestation. There were increased odds of birth in all the preterm categories for particulate matter during the second trimester (19).

We compared adjusted odds ratios for preterm birth of males and for preterm birth of females associated with high versus low levels of pollutant exposures during the second trimester. Table 1 presents data on each pollutant exposure (during second trimester) for each of six gestational age categories. We did observe a statistically significant higher risk for males to be born at 20–27 weeks of gestation, as compared to females, when exposed to $NO_2$ during the second trimester ($P$ = 0.01).

Odds ratios were elevated for the earlier preterm gestational ages but did not appear to differ between males and females in terms of magnitude, except for being born in week 32–33 for those exposed during entire pregnancy to high $PM_{10}$, where the odds ratio was significantly higher for males compared to females (Wald test for homogeneity, $P = 0.04$; data not shown).

Results for the first and third trimesters were more variable, with an inverse association between air pollution and preterm birth in some cases (data not shown).

## Discussion

In this large study, we investigated whether there were sex differences in a previously observed association between preterm birth and gestational exposure to several air pollutants. Male and female infants showed similar risks for pollution associated with preterm birth.

Few studies have examined whether infant sex modifies the association between gestational air pollution exposure and premature birth, and results are inconsistent. In a systematic review, Ghosh et al. used data from Wilhelm and Ritz (9) to calculate the odds of preterm for several pollutants stratified by infant sex. The odds were slightly higher among males for CO and $NO_2$ but not $PM_{10}$ or ozone (9,17). Malmqvist et al. (18) did not observe sex differences in preterm births for women exposed to nitrogen oxides.

Several studies have demonstrated a disproportionate number of males among preterm births. One can speculate that the underlying mechanism for this could be the sex difference in the inflammation and/or infection response (4–7). In addition, studies suggest that ambient air pollution could contribute to the inflammatory process in pregnant women, leading to adverse birth outcomes, such as preterm birth (15,16). The combination of these two explanations and/or theories could in part explain our results, that exposure to certain types of air pollution, in particular $PM_{10}$ and $NO_2$, could have a sex-specific effect on the risk of preterm birth, in different times of gestation. However, the question of whether air pollution altered the primary sex ratio was not addressed in this study.

Our study included many births over several years in a highly exposed region of the United States. By geocoding the maternal residence, we did have precise estimates for exposure; however, there could be misclassification of exposure because we were able to account for neither mothers' change in residence nor mobility during pregnancy.

Much remains to be learned about preterm birth etiologies. The observation that males are far more likely among preterm births, particularly very early gestational age deliveries, may offer an interesting clue to pursue. Our goal was to investigate a previously observed association between ambient air pollution and preterm birth found that it was not generally modified by infant sex. Our finding of a higher risk of very early preterm birth among males among those exposed to a higher level of $NO_2$ during the second trimester should be revisited in future studies.

## Acknowledgments

Partial support for this study came from the March of Dimes Prematurity Research Center at Stanford University, the NIH-NCATS-CTSA (UL1 TR001085), the Stanford Child Health Research Institute, the NIH-NIEHS (K99

ES021470, P20 ES018173, R21 ESO14891), and the US EPA (R834596). We thank Frederick Lur-mann of Sonoma Technology, Inc., for pollutant estimation.

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### Table 1

Adjusted odds ratios and 95% confidence interval (CI), comparing the highest to the lower three quartiles of exposure of the different pollutants, divided by infant sex across gestational age categories

| Exposure during second trimester | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gestational age (wk) | Males | | | Females | | | *P* |
| | OR | 95% CI | | OR | 95% CI | | |
| $PM_{2.5}$ | | | | | | | |
| 37–42 | 1.00 | | | 1.00 | | | |
| <37 | 1.21 | 1.16 | 1.26 | 1.16 | 1.11 | 1.21 | .11 |
| 34–36 | 1.12 | 1.07 | 1.17 | 1.06 | 1.01 | 1.11 | .09 |
| 32–33 | 1.15 | 1.04 | 1.27 | 1.28 | 1.15 | 1.43 | .18 |
| 28–31 | 1.54 | 1.36 | 1.74 | 1.57 | 1.37 | 1.80 | .87 |
| 20–27 | 2.60 | 2.19 | 3.09 | 2.27 | 1.87 | 2.75 | .25 |
| $PM_{10}$ | | | | | | | |
| 37–42 | 1.00 | | | 1.00 | | | |
| <37 | 1.19 | 1.14 | 1.24 | 1.15 | 1.11 | 1.21 | .41 |
| 34–36 | 1.12 | 1.07 | 1.17 | 1.11 | 1.06 | 1.16 | .83 |
| 32–33 | 1.21 | 1.09 | 1.35 | 1.13 | 1.01 | 1.27 | .38 |
| 28–31 | 1.30 | 1.14 | 1.48 | 1.25 | 1.08 | 1.45 | .67 |
| 20–27 | 2.19 | 1.83 | 2.60 | 2.09 | 1.73 | 2.54 | .75 |
| CO | | | | | | | |
| 37–42 | 1.00 | | | 1.00 | | | |
| <37 | 1.10 | 1.06 | 1.15 | 1.09 | 1.04 | 1.14 | .67 |
| 34–36 | 1.06 | 1.01 | 1.11 | 1.04 | 0.99 | 1.10 | .65 |
| 32–33 | 0.99 | 0.88 | 1.11 | 1.09 | 0.96 | 1.23 | .23 |
| 28–31 | 1.19 | 1.04 | 1.37 | 1.20 | 1.03 | 1.39 | .99 |
| 20–27 | 1.82 | 1.51 | 2.18 | 1.71 | 1.40 | 2.10 | .64 |
| $NO_2$ | | | | | | | |
| 37–42 | 1.00 | | | 1.00 | | | |
| <37 | 1.11 | 1.07 | 1.16 | 1.08 | 1.03 | 1.12 | .29 |
| 34–36 | 1.07 | 1.03 | 1.12 | 1.06 | 1.01 | 1.11 | .69 |
| 32–33 | 1.07 | 0.96 | 1.18 | 1.07 | 0.96 | 1.19 | .92 |
| 28–31 | 1.10 | 0.97 | 1.25 | 1.13 | 0.99 | 1.30 | .84 |
| 20–27 | 1.82 | 1.52 | 2.17 | 1.31 | 1.07 | 1.61 | .01 |

Adjusted for maternal age, education, race, infant birth weight, prenatal care in first trimester, Medi-Cal payment for birth expenses/insurance type.