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## Prenatal Exposure to Air Pollution, Maternal Diabetes and Preterm Birth

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### Abstract

Prenatal exposure to ambient air pollution has been associated with preterm birth in several studies. Associations between air pollution and gestational or pre-existing diabetes have been hypothesized but are not well established. We examined the association between air pollution exposure in pregnancy and gestational diabetes and whether the association between air pollution and preterm birth is modified by diabetes (gestational or pre-existing) in a highly polluted area of California.

Birth certificates and hospital discharge data from all singleton births from 2000-2006 to women living in four counties in the San Joaquin Valley of California were linked to criteria air pollution and traffic density measurements at the geocoded maternal residence. Air pollutants were dichotomized at the highest quartile and compared to the lower three quartiles.

Logistic regression models were adjusted for maternal race-ethnicity, age, education, payment of birth expenses, and prenatal care. There were consistent inverse associations between exposure to air pollution during the first two trimesters and gestational diabetes (statistically significant odds ratios (OR) less than 1). When stratified by any diabetes (gestational or pre-existing), associations between air pollution exposure during pregnancy and categories of preterm birth (20-27, 28-31, 32-33, 34-36 weeks) were generally similar with few exceptions of exposures to carbon monoxide (CO) and particulate matter <2.5 microns (PM<sub>2.5</sub>). Those with diabetes and exposure higher levels

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Conflicts of Interest:  
none

of CO (in first trimester or entire pregnancy) or PM<sub>2.5</sub> (in first trimester) had higher risk of extremely preterm birth (20-27 weeks) compared with those without diabetes.

The associations between traffic-related air pollution and gestational diabetes were in the unexpected (“protective”) direction. Among those with any diabetes, associations were stronger between CO and PM<sub>2.5</sub> and extremely preterm birth.

## Keywords

air pollution; preterm birth; pregnancy; diabetes

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## Introduction

Prenatal exposure to ambient air pollution has been associated with preterm birth in several studies [1–4]. In a previous investigation of the current cohort, preterm birth was associated with increased exposure to particulate matter <10 (PM<sub>10</sub>) and 2.5 microns (PM<sub>2.5</sub>) during pregnancy. The associations were strongest with exposure in the second trimester, particularly for early preterm births (<28 weeks gestation) [5].

It has been hypothesized that adult exposure to air pollution may be associated with Type 2 diabetes and both the experimental and epidemiological evidence in support of this hypothesis are robust [6, 7]. Long-term air pollution exposure may both decrease insulin-dependent glucose uptake leading to insulin resistance and impair β-cell function resulting in reduced insulin secretion [8]. Upstream mechanistic pathways linking air pollution exposure to insulin resistance and β-cell dysfunction that have been suggested by experimental animal data include oxidative stress and systemic inflammation [7]. A systematic review and meta-analysis of ambient air pollution in adults and diabetes studies in Europe and North America observed an 8-10% increase in odds of diabetes for a 10 μg/m<sup>3</sup> increase in PM<sub>2.5</sub> or nitrogen dioxide (NO<sub>2</sub>) [9].

Several studies have investigated the associations between air pollution and diabetes in pregnancy. One study in Taiwan found associations between PM<sub>2.5</sub> and oral glucose tolerance tests, a screening test for gestational diabetes, during pregnancy [10, 11]. Another study found preconception and early pregnancy nitrogen oxides (NO<sub>x</sub>) exposure were associated with gestational diabetes [12, 13]. Exposure to PM<sub>2.5</sub> and ozone (O<sub>3</sub>) during pregnancy was associated with gestational diabetes in a study in Florida. A prospective cohort in Boston, Massachusetts found an association between traffic-related air pollution and impaired glucose tolerance, but not gestational diabetes [14]. In a retrospective study also in Massachusetts, no consistent association between air pollution and gestational diabetes was observed except when stratified by maternal age <20 years, where they found a 1.36 higher odds of gestational diabetes for each IQR increase of second trimester PM<sub>2.5</sub> [15].

It is plausible that the association between air pollution and preterm birth may be stronger among those with gestational or pre-existing diabetes, given their common associations. There have been a few studies that have examined diabetes (either gestational or pre-

existing) as a potential effect modifier of the association between air pollution and preterm birth. A study in Ontario, Canada found associations between PM<sub>2.5</sub> and NO<sub>2</sub> and preterm birth among those with pre-existing diabetes [16, 17]. In a study of over 1 million births in Taiwan, associations between O<sub>3</sub> and preterm birth were stronger among those with gestational diabetes [18, 19]. We are also interested in the possibility that diabetes is on the pathway between air pollution and preterm birth – i.e., that diabetes mediates the air pollution – preterm birth effect.

We examine the association between air pollution exposure in pregnancy and gestational diabetes and whether the association between air pollution and preterm birth is modified and/or mediated by diabetes in a highly polluted area of California.

## Methods

### Study Population

Birth certificates from all 2000-2006 births to women living in the four most populated counties in the San Joaquin Valley of California (Fresno, Kern, Stanislaus and San Joaquin) were obtained from the California Department of Health. The four study counties included 329,650 births in 2000-2006. Exclusions were multiple births (n=8,373), those missing file numbers (n=262), those with gestational age missing or <20 weeks or >42 weeks (n=45,726), and those with birth weight missing or <500g or >5000g (n=762). Completeness of pollutant assignments was 80% for CO, 94% for NO<sub>2</sub>, 93% for PM<sub>10</sub>, 93% for PM<sub>2.5</sub>, and 96% for traffic density. The study population included 262,182 births with measurements for at least one of these pollutants. Furthermore, we linked the birth records with Office of Statewide Health and Planning (OSHPD) maternal and infant hospital discharge data, with 98.61% of successfully linked (n=258,522). We also removed 6317 births with any missing adjusted covariates. Therefore, we included 252,205 births for further analysis.

Preterm birth was defined by gestational age at birth as determined from the last menstrual period on the birth certificate. The maternal residence at birth street address locations obtained from birth certificates were geocoded to X and Y coordinates with ArcGIS software (ESRI, Redlands, California). Addresses were corrected with ZP4 software (Semaphore Corporation, Aptos, California).

Ambient air quality data were acquired from U.S. Environmental Protection Agency's Air Quality System database ([www.epa.gov/ttn/airs/airsaqs](http://www.epa.gov/ttn/airs/airsaqs)). Daily metrics of the following pollutants were calculated: carbon monoxide (CO), nitrogen dioxide (NO<sub>2</sub>), particulate matter than 10 µm (PM<sub>10</sub>), and PM than 2.5 µm (PM<sub>2.5</sub>). These data were used to create averages for each trimester of pregnancy, entire pregnancy average, and the last 6 weeks of pregnancy. The station-specific daily air quality data were spatially interpolated using inverse distance-squared weighting [5]. Data from up to four air quality measurement stations were included in each interpolation. Traffic density was calculated from distance-decayed annual average daily traffic volumes within a 300m radius of geocoded maternal residences [20]. Further details on exposure assessment were published previously [5, 21].

Variables from birth certificates included in analyses were: maternal age (<20, 20-24, 25-29, 30-34, >35 years), maternal race (White, Hispanic, African-American, Asian, other), maternal education (no high school, some high school, some college, bachelors or other degree), parity (0, >1), prenatal care (initiated in first trimester), Medi-Cal (Medicaid) or other government program payment of birth costs, infant sex, year (2000-2006), season of conception, and maternal county of residence (Fresno, Kern, Stanislaus, San Joaquin).

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.

### Statistical Analysis

The pollutants for each exposure period were dichotomized at the highest quartile and compared to the lower three quartiles. A sensitivity analysis was also performed comparing the highest to the lowest quartile of each exposure. First, second, and third pregnancy trimesters were defined as gestational weeks 1-13, 14-26, and 27 to birth, respectively. Additionally, we calculated metrics for the last 6 weeks of pregnancy (birth minus 42 days). Exposure periods of the term births were truncated to match the same period as the comparison period-length of the preterm births and the last 6-week exposures were matched on gestational age between preterm and term births.

For the first main analysis, the outcome was diagnosis of gestational diabetes (ICD-9 code: 648.8), obtained from OSHPD - the hospital discharge records of the mother. Those with pre-existing diabetes were excluded.

In the second main analysis, preterm birth categories (20-27, 28-31, 32-33, 34-36 weeks) were compared to term births (37-42 weeks) and diabetes (either gestational or pre-existing diabetes; ICD-9 code: 648.0, 250) was considered as an effect modifier. We chose to combine these two conditions because we hypothesize that the potential susceptibility to air pollution among the two groups may be shared. Although age may be a factor (and is adjusted for in the model), women with gestational diabetes are at risk for diabetes later in life. Additionally, those with diabetes are no longer at risk of developing gestational diabetes, and our aim was to include them as a potentially susceptible group. We performed a stratified analysis to explore the association between the pollutant and preterm birth by diabetes and no diabetes. Secondly, we created an interaction term (exposure  $\times$  diabetes) to add into the model and used Wald's method to assess the multiplicative interaction.

Models for both analyses were adjusted for the covariates maternal race, age, education, payment of birth expenses/insurance type, and prenatal care. We performed a sensitivity analysis with additional adjustment for season of conception and limited preterm births to those that were spontaneous (preterm labor or premature rupture of membranes) as opposed to medically indicated. Additionally, we removed women from the analysis who had been diagnosed by either pre-existing or pregnancy-induced hypertension, or pre-eclampsia to disentangle any potential association attributable to hypertension.

To evaluate the question of whether diabetes mediates the relationship between PM<sub>2.5</sub> and extreme preterm birth (20-27 weeks gestation), we employed the four step method of Baron and Kenny [22]. It included the following regressions: (1) preterm birth ~ (B) PM<sub>2.5</sub> + covariates; (2) diabetes ~ PM<sub>2.5</sub> + covariates; (3) preterm birth ~ diabetes + covariates; (4) preterm birth ~ (B1) PM<sub>2.5</sub> + (B2) diabetes + covariates) and provides a calculation of an indirect effect by either B-B1 [23] or B\*B2 [24].

All analyses were performed with SAS 9.4 (Cary, NC).

## Results

The study population was majority Hispanic, followed by white, non-Hispanic (Table 1). More than half had birth expenses paid by Medi-Cal (public insurance) and 5% were diagnosed with gestational diabetes. The distribution of the pollutants (CO, NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub>) and traffic density by exposure periods (Table 2). The medians did not change considerably across pollutants and the distribution was wider for the shorter exposure periods (i.e., trimester averages compared to entire pregnancy). Air pollution was dichotomized at the highest quartile cut off: 0.60 ppm for CO, 19.47 ppb for NO<sub>2</sub>, 42.65 µg/m<sup>3</sup> for PM<sub>10</sub>, 20.72 µg/m<sup>3</sup> for PM<sub>2.5</sub>, and 45.85 for traffic density. The correlations between each of the pollutants and exposure periods are presented in the Appendix.

### Air pollution and gestational diabetes

There was a consistent inverse association between exposure to traffic-related air pollution during pregnancy and gestational diabetes, excluding those with pre-existing diabetes (Table 3). In general, there was approximately a 5-10% decrease in risk of gestational diabetes comparing above to below highest quartile of exposure to CO, NO<sub>2</sub> and PM<sub>2.5</sub>. Pollutant exposures were limited to the first two trimesters, prior to diabetes screening and diagnosis, which generally occurs in weeks 24-28. When comparing the highest to the lowest quartile of exposure, the results were similar and in some cases the associations were slightly larger (data not shown).

### Air pollution and preterm birth among those with pre-existing and gestational diabetes

When stratified by diabetes status (preexisting or gestational versus neither), the associations between air pollution and preterm birth were generally very similar across strata with few notable exceptions (Table 4). Five estimates were statistically different with cut-off of p<0.05 for the Mantel Hanzel chi-square. The association between PM<sub>2.5</sub> during the first trimester of pregnancy and very early preterm birth (20-27 weeks) was considerably stronger among those with diabetes (aOR=2.15; 95% CI: 1.24, 3.73) compared with those without diabetes (aOR=1.07; 95% CI: 0.95, 1.20). A similar pattern was observed for CO during the entire pregnancy and first trimester and very early preterm birth. The association between PM<sub>10</sub> and late preterm birth (34-36 weeks) was observed among those without diabetes (aOR= 1.11; 95% CI: 1.07, 1.14) and not among those with diabetes. Mantel Hanzel chi-square p-values were noted for those with p<0.02 (Table 4).

### Mediation of diabetes in the association between PM<sub>2.5</sub> and extreme preterm birth

The results of the mediation analysis did not show that diabetes mediated the relationship between PM<sub>2.5</sub> and extreme preterm birth. The third regression of preterm birth on diabetes was not significant and the calculation of the indirect effect was near zero (0.0009).

### Sensitivity Analyses

When analyses were conducted comparing the highest quartile to the lowest quartile (rather than the lower three quartiles) of pollutant measures, the observed results were not meaningfully different. Similarly, results did not differ when we restricted the outcome to include only spontaneous preterm births nor when we removed women with hypertension or pre-eclampsia from the analysis.

### Discussion

Our large population-based study observed inverse associations (in the unexpected direction) between air pollution exposures during pregnancy and gestational diabetes. One explanation might be that a subset of the population at risk for gestational diabetes and exposed to high levels of air pollution resulted in miscarriage – and therefore removed from study observation. These results add to the existing inconsistency across studies examining air pollution exposures during pregnancy and gestational diabetes [10, 12, 14, 15].

We did find evidence of effect modification by diabetes in the relationship between CO and PM<sub>2.5</sub> and very early preterm birth. This finding is consistent with the few previous studies [16, 18]. though our results were not consistent across multiple pollutants (PM<sub>10</sub>, NO<sub>2</sub>) nor multiple categories of preterm birth (32-33 and 34-36 weeks). Furthermore, the first trimester and the entire pregnancy period were more often statistically significant for these associations.

Births on the early end of the very early preterm birth category (20-27 weeks) may have not had the opportunity to receive gestational diabetes testing, therefore leading to possible misclassification of the modifier. However, most women have the test between 24-28 weeks and even earlier if there is high glucose in the urine earlier in pregnancy to capture those at risk of GDM. The confidence intervals surrounding estimates of odds of preterm birth given air pollution exposure among those with diabetes (~5%) are less precise than the those among those without diabetes owing to the sample size. This may have decreased our ability to discern a difference in the associations between other air pollutants and preterm birth by diabetes status.

Our previous analyses of these data excluded women with diabetes to determine the effect of air pollution on preterm birth. The current analysis provides a potential pathway by which air pollution may affect some proportion of preterm birth. Several mechanisms of action have been hypothesized to explain the pathway by which toxicants may affect adverse reproductive outcomes including preterm birth and gestational diabetes [25]. Oxidative stress has been identified as the most relevant with evidence from increased levels of lipid peroxidation products and inflammatory cytokines in response to air pollution exposure [26, 27].

Although our study sample was large and population-based, it was not designed specifically to investigate diabetes and identification of diabetes was ascertained via the medical discharge record; however, we do not expect that any errors in identification of diabetes were likely related to air pollution levels, thus, resulting in non-differential misclassification. We did not have access to additional relevant clinical data such as oral glucose tolerance test glucose levels or treatment of diabetes during pregnancy. Regardless, our study included detailed air pollution exposure assessment at the precise geocoded residence over a wide geography and across several years. The levels of several pollutants (PM<sub>2.5</sub>, PM<sub>10</sub> and ozone) caused the San Joaquin Valley to be in nonattainment during this period. In other words, the levels of these pollutants are higher than acceptable according to the Clean Air Act.

In conclusion, our study observed an inverse association between air pollution exposure and risk of gestational diabetes and a stronger effect of CO and PM<sub>2.5</sub> and CO on very early preterm birth among those with diabetes, compared to those without. This may help identify populations that are particularly vulnerable to the detrimental effects of air pollution. Future research could examine this relationship in additional studies and examine additional maternal morbidities, such as pre-eclampsia, to explore potential mechanisms by which air pollution affects preterm birth.

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### **Appendix**



**Appendix Table 1.**

Pearson Correlation of pollutant averages across entire pregnancy (EP), each trimester (T1, T2, T3) and the last 6 weeks of pregnancy (L6W).

	CO						NO <sub>2</sub>						PM <sub>10</sub>						PM <sub>2.5</sub>								
	EP	T1	T2	T3	L6W	EP	T1	T2	T3	L6W	EP	T1	T2	T3	L6W	EP	T1	T2	T3	L6W	EP	T1	T2	T3	L6W		
CO EP																											
CO T1	<b>0.46</b>																										
CO T2	<b>0.84</b>	<b>0.17</b>																									
CO T3	<b>0.46</b>	<b>-0.43</b>	<b>0.32</b>																								
CO L6W	<b>0.31</b>	<b>-0.41</b>	<b>0.11</b>	<b>0.93</b>																							
NO <sub>2</sub> EP	<b>0.75</b>	<b>0.25</b>	<b>0.67</b>	<b>0.42</b>	<b>0.31</b>																						
NO <sub>2</sub> T1	<b>0.47</b>	<b>0.82</b>	<b>0.34</b>	<b>-0.38</b>	<b>-0.41</b>	<b>0.59</b>																					
NO <sub>2</sub> T2	<b>0.74</b>	<b>0.02</b>	<b>0.83</b>	<b>0.47</b>	<b>0.29</b>	<b>0.87</b>	<b>0.34</b>																				
NO <sub>2</sub> T3	<b>0.27</b>	<b>-0.42</b>	<b>0.15</b>	<b>0.81</b>	<b>0.80</b>	<b>0.57</b>	<b>-0.20</b>	<b>0.45</b>																			
NO <sub>2</sub> L6W	<b>0.14</b>	<b>-0.37</b>	<b>-0.02</b>	<b>0.71</b>	<b>0.79</b>	<b>0.45</b>	<b>-0.21</b>	<b>0.26</b>	<b>0.93</b>																		
PM <sub>10</sub> EP	<b>0.57</b>	<b>0.07</b>	<b>0.46</b>	<b>0.49</b>	<b>0.43</b>	<b>0.48</b>	<b>0.12</b>	<b>0.47</b>	<b>0.42</b>	<b>0.38</b>																	
PM <sub>10</sub> T1	<b>0.57</b>	<b>0.59</b>	<b>0.52</b>	<b>-0.13</b>	<b>-0.21</b>	<b>0.42</b>	<b>0.63</b>	<b>0.39</b>	<b>-0.20</b>	<b>0.59</b>																	
PM <sub>10</sub> T2	<b>0.50</b>	<b>-0.26</b>	<b>0.58</b>	<b>0.60</b>	<b>0.48</b>	<b>0.46</b>	<b>-0.13</b>	<b>0.61</b>	<b>0.49</b>	<b>0.82</b>	<b>0.28</b>																
PM <sub>10</sub> T3	<b>0.04</b>	<b>-0.21</b>	<b>-0.20</b>	<b>0.52</b>	<b>0.61</b>	<b>0.07</b>	<b>-0.28</b>	<b>-0.08</b>	<b>0.57</b>	<b>0.60</b>	<b>-0.13</b>	<b>0.38</b>															
PM <sub>10</sub> L6W	<b>0.00</b>	<b>-0.04</b>	<b>-0.26</b>	<b>0.34</b>	<b>0.51</b>	<b>0.03</b>	<b>-0.13</b>	<b>-0.18</b>	<b>0.43</b>	<b>0.59</b>	<b>0.46</b>	<b>-0.11</b>	<b>0.21</b>	<b>0.86</b>													
PM <sub>2.5</sub> EP	<b>0.76</b>	<b>0.34</b>	<b>0.70</b>	<b>0.30</b>	<b>0.17</b>	<b>0.59</b>	<b>0.41</b>	<b>0.64</b>	<b>0.11</b>	<b>0.01</b>	<b>0.70</b>	<b>0.57</b>	<b>0.08</b>	<b>0.01</b>													
PM <sub>2.5</sub> T1	<b>0.26</b>	<b>0.87</b>	<b>0.04</b>	<b>-0.50</b>	<b>-0.47</b>	<b>0.10</b>	<b>0.71</b>	<b>-0.08</b>	<b>-0.50</b>	<b>-0.42</b>	<b>0.10</b>	<b>0.62</b>	<b>-0.27</b>	<b>-0.18</b>	<b>0.42</b>												
PM <sub>2.5</sub> T2 <sup>nd</sup>	<b>0.65</b>	<b>0.08</b>	<b>0.87</b>	<b>0.19</b>	<b>0.01</b>	<b>0.54</b>	<b>0.30</b>	<b>0.73</b>	<b>0.05</b>	<b>-0.10</b>	<b>0.50</b>	<b>0.58</b>	<b>0.61</b>	<b>-0.21</b>	<b>0.77</b>	<b>0.05</b>											
PM <sub>2.5</sub> T3 <sup>rd</sup>	<b>0.28</b>	<b>-0.50</b>	<b>0.20</b>	<b>0.86</b>	<b>0.81</b>	<b>0.29</b>	<b>-0.45</b>	<b>0.40</b>	<b>0.69</b>	<b>0.61</b>	<b>0.53</b>	<b>-0.11</b>	<b>0.62</b>	<b>0.56</b>	<b>0.36</b>	<b>0.37</b>	<b>-0.49</b>	<b>0.17</b>									
PM <sub>2.5</sub> L6W	<b>0.15</b>	<b>-0.46</b>	<b>0.00</b>	<b>0.79</b>	<b>0.86</b>	<b>0.18</b>	<b>-0.47</b>	<b>0.21</b>	<b>0.67</b>	<b>0.66</b>	<b>0.44</b>	<b>-0.20</b>	<b>0.47</b>	<b>0.62</b>	<b>0.52</b>	<b>0.21</b>	<b>-0.45</b>	<b>-0.03</b>	<b>0.90</b>								
<b>Traffic Density</b>	<b>0.00</b>	<b>0.01</b>	<b>-0.01</b>	<b>0.00</b>	<b>0.00</b>	<b>0.15</b>	<b>0.10</b>	<b>0.10</b>	<b>0.10</b>	<b>0.09</b>	<b>-0.03</b>	<b>-0.02</b>	<b>-0.02</b>	<b>-0.02</b>	<b>-0.02</b>	<b>0.01</b>	<b>0.01</b>	<b>0.00</b>	<b>0.01</b>	<b>0.01</b>	<b>0.01</b>	<b>0.00</b>	<b>0.00</b>	<b>0.01</b>	<b>0.01</b>	<b>0.01</b>	<b>0.01</b>

Bolded correlation coefficients were statistically significant (p<0.05)

## Abbreviations:

<b>AOR</b>	adjusted odds ratio
<b>CI</b>	confidence interval
<b>CO</b>	carbon monoxide
<b>PM<sub>10</sub></b>	particulate matter less than 10 µm
<b>PM<sub>2.5</sub></b>	particulate matter less than 2.5 µm
<b>NO<sub>2</sub></b>	nitrogen dioxide

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**Highlights**

- Prenatal air pollution may be associated with diabetes
- Prenatal air pollution may be more critical for certain at-risk populations
- Prenatal air pollution among those with diabetes may increase risk of preterm birth
- Research is needed to identify vulnerable populations for air pollution exposure

**Table 1.**

Distribution of covariates by gestational age in births in the four most populous counties in San Joaquin Valley, California, 2000-2006.

Covariate	Gestational age in weeks (%) <sup>*</sup>					Total N=252,205
	37-42 n=223,417	34-36 n=21,225	32-33 n=3702	28-31 n=2550	20-27 n=1311	
Spontaneous preterm birth <sup>†</sup>		35.8	47.9	59.1	69.3	41.0
Maternal age (years)						
<20	13.3	15.2	16.9	20.3	20.8	13.6
20-24	28.9	28.7	28.5	28.3	26.4	28.9
25-29	27.7	25.6	23.3	22.9	21.4	27.3
30-34	19.4	18.2	18.1	15.3	18.7	19.2
>35	10.8	12.3	13.2	13.2	12.7	11.0
Race/ethnicity						
White, non-Hispanic	30.6	26.0	23.2	24.1	23.0	30.0
Asian	7.4	8.7	8.3	9.4	7.9	7.6
African-American	4.9	6.7	8.0	9.1	9.2	5.1
Hispanic	55.7	57.3	59.2	56.1	58.4	55.9
Other	1.3	1.3	1.3	1.3	1.5	1.31.5
Education						
<High school	12.1	12.5	13.9	11.7	11.1	12.1
High school	53.2	57.6	59.2	62.8	60.8	53.8
Some college	21.5	19.9	18.6	17.7	19.8	21.3
College degree	13.2	10.0	8.3	7.8	8.4	12.8
Medi-Cal	53.4	60.2	64.5	64.0	60.2	54.3
Prenatal care in 1 <sup>st</sup> trimester	82.1	78.3	73.9	68.4	67.3	81.4
Low SES	17.3	20.2	23.5	22.6	21.5	17.7
Diabetes diagnoses						
Gestational diabetes	4.9	6.2	6.1	5.3	3.1	5.0
Pre-existing diabetes	0.7	1.4	1.6	1.5	1.1	0.8
Hypertension diagnoses						
Pregnancy-induced	3.9	8.5	12.3	11.8	6.4	4.5
Pre-existing	1.0	1.9	3.1	3.0	2.5	1.1
Cesarean section	25.4	29.1	35.6	43.9	41.0	26.1
First born	35.3	33.0	34.3	35.8	41.0	35.2
County						
Fresno	32.7	35.2	35.0	33.1	37.0	32.9
Stanislaus	23.2	24.8	26.7	25.2	23.8	23.4
Kern	25.5	23.0	21.1	23.1	22.1	25.1
San Joaquin	18.7	17.0	17.2	18.6	17.1	18.5
Year						

Covariate	Gestational age in weeks (%) <sup>*</sup>					Total N=252,205
	37-42 n=223,417	34-36 n=21,225	32-33 n=3702	28-31 n=2550	20-27 n=1311	
2000	13.2	12.5	12.5	12.8	15.7	13.1
2001	13.4	12.6	11.8	13.2	12.5	13.3
2002	13.7	13.0	13.3	12.3	12.4	13.6
2003	13.9	13.9	13.8	13.3	13.4	13.9
2004	14.4	14.5	14.7	14.2	15.0	14.4
2005	15.1	16.0	15.3	16.8	15.0	15.2
2006	16.5	17.6	18.6	17.4	16.1	16.6

<sup>\*</sup> Percentages may not equal 100 owing to rounding.

<sup>†</sup> Spontaneous preterm birth identified as those births <37 weeks with preterm premature rupture of membranes (ICD-9-CM code 658.1 or birth certificate complication of labor/delivery code 10), those with premature labor (ICD-9-CM code 644), or the use of tocolytics (birth certificate complication/procedure of pregnancy code 28).

Percentage of total was calculated among preterm, i.e.  $11791/28788 \times 100 = 41.0\%$

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**Table 2.** Distribution of pollutant averages across each exposure period - median (interquartile range)

	CO (ppm)	NO <sub>2</sub> (ppb)	PM <sub>10</sub> (µg/m <sup>3</sup> )	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	Traffic Density		
<b>Entire Pregnancy</b>	0.49	17.26	35.93	17.05	6.39	16.51	45.23
<b>1<sup>st</sup> trimester</b>	0.49	17.42	34.86	16.37	15.18	13.45	
<b>2<sup>nd</sup> trimester</b>	0.47	17.01	34.75	16.59	14.41	12.77	
<b>3<sup>rd</sup> trimester</b>	0.45	16.88	34.81	17.47	13.91	12.4	
<b>Last 6 weeks</b>	0.45	16.63	34.05	17.38	13.34	12.2	

**Table 3.**

Association between air pollution and gestational diabetes comparing above versus below highest quartile of exposure (N=252,205)

Pollutant	Exposure Period	Odds Ratio (95% Confidence Interval)	
		Unadjusted	Adjusted*
CO	1 <sup>st</sup> Trimester	<b>0.87 (0.83-0.91)</b>	<b>0.91 (0.87-0.96)</b>
CO	2 <sup>nd</sup> Trimester	<b>0.90 (0.86-0.94)</b>	<b>0.92 (0.88-0.96)</b>
NO <sub>2</sub>	1 <sup>st</sup> Trimester	<b>0.87 (0.83-0.91)</b>	<b>0.91 (0.87-0.95)</b>
NO <sub>2</sub>	2 <sup>nd</sup> Trimester	<b>0.87 (0.83-0.91)</b>	<b>0.94 (0.90-0.98)</b>
PM <sub>10</sub>	1 <sup>st</sup> Trimester	<b>0.90 (0.86-0.93)</b>	<b>0.94 (0.90-0.97)</b>
PM <sub>10</sub>	2 <sup>nd</sup> Trimester	<b>0.87 (0.84-0.90)</b>	<b>0.92 (0.89-0.96)</b>
PM <sub>2.5</sub>	1 <sup>st</sup> Trimester	0.98 (0.94-1.02)	1.01 (0.97-1.06)
PM <sub>2.5</sub>	2 <sup>nd</sup> Trimester	<b>0.94 (0.90-0.98)</b>	0.96 (0.92-1.00)
Traffic Density	Entire pregnancy	0.97 (0.93-1.01)	0.99 (0.95-1.03)

\* Adjusted for maternal race, age, education, payment of birth expenses/insurance type, prenatal care (and for pollutants, the alternative trimester of exposure)

Highest quartile cut offs: 0.60 ppm for CO, 19.47 ppb for NO<sub>2</sub>, 42.65 µg/m<sup>3</sup> for PM<sub>10</sub>, 20.72 µg/m<sup>3</sup> for PM<sub>2.5</sub>, and 45.85 for traffic density



**Table 4.**

Association between air pollution and preterm birth, stratified by diabetes (N=N=252,205)

Gestational Age	Pollutant Exposure	Exposure period	Adjusted* Odds Ratio (95% Confidence Intervals)		P-value <0.2 <sup>‡</sup>
			With Diabetes <sup>†</sup> (N=14,493)	Without Diabetes (N=237,712)	
34-36 weeks	CO	Entire pregnancy	1.12(0.98-1.28)	<b>1.12 (1.08-1.16)</b>	0.123
		1 <sup>st</sup> trimester	1.06 (0.93-1.19)	<b>1.05 (1.01-1.08)</b>	
		2 <sup>nd</sup> trimester	0.98 (0.87-1.12)	1.02 (0.98-1.05)	
		3 <sup>rd</sup> trimester	0.88 (0.77-1.00)	0.98 (0.94-1.01)	
		Last 6 weeks	0.84 (0.74-0.95)	0.96 (0.93-1.00)	
		Entire pregnancy	0.99 (0.87-1.12)	1.07 (1.04-1.11)	
	NO <sub>2</sub>	1 <sup>st</sup> trimester	0.96 (0.86-1.08)	1.03 (1.00-1.06)	0.154
		2 <sup>nd</sup> trimester	0.97 (0.86-1.09)	1.03 (0.99-1.06)	
		3 <sup>rd</sup> trimester	0.92 (0.82-1.04)	0.99 (0.96-1.02)	
		Last 6 weeks	0.90 (0.80-1.02)	0.99 (0.96-1.02)	
		Entire pregnancy	1.01 (0.90-1.15)	<b>1.09 (1.05-1.12)</b>	
		Entire pregnancy	1.01 (0.90-1.15)	<b>1.09 (1.05-1.12)</b>	
32-33 weeks	PM <sub>10</sub>	1 <sup>st</sup> trimester	0.96 (0.85-1.08)	<b>1.11 (1.07-1.14)</b>	0.029
		2 <sup>nd</sup> trimester	1.01 (0.90-1.14)	1.09 (1.05-1.12)	
		3 <sup>rd</sup> trimester	1.00 (0.89-1.12)	1.04 (1.01-1.07)	
		Last 6 weeks	0.93 (0.82-1.04)	0.98 (0.95-1.01)	
		Entire pregnancy	<b>1.19 (1.05-1.34)</b>	<b>1.23 (1.19-1.27)</b>	
		Entire pregnancy	<b>1.19 (1.05-1.34)</b>	<b>1.23 (1.19-1.27)</b>	
	PM <sub>2.5</sub>	1 <sup>st</sup> trimester	1.04 (0.93-1.16)	<b>1.05 (1.01-1.08)</b>	0.114
		2 <sup>nd</sup> trimester	1.05 (0.94-1.18)	<b>1.05 (1.01-1.08)</b>	
		3 <sup>rd</sup> trimester	<b>0.86 (0.76-0.97)</b>	<b>0.94 (0.91-0.97)</b>	
		Last 6 weeks	0.89 (0.79-1.00)	0.99 (0.96-1.02)	
		Entire pregnancy	0.96 (0.85-1.09)	<b>1.05 (1.01-1.08)</b>	
		Entire pregnancy	1.07 (0.79-1.44)	<b>1.17 (1.08-1.27)</b>	
32-33 weeks	CO	1 <sup>st</sup> trimester	0.99 (0.75-1.30)	0.95 (0.88-1.03)	0.136
		2 <sup>nd</sup> trimester	0.99 (0.75-1.31)	0.98 (0.90-1.06)	
		3 <sup>rd</sup> trimester	0.89 (0.67-1.18)	1.03 (0.95-1.12)	
		Last 6 weeks	0.82 (0.62-1.10)	1.03 (0.95-1.12)	
		Entire pregnancy	1.04 (0.79-1.37)	1.12 (1.03-1.21)	
		Entire pregnancy	1.04 (0.79-1.37)	1.12 (1.03-1.21)	
	NO <sub>2</sub>	1 <sup>st</sup> trimester	1.12 (0.87-1.44)	1.00 (0.93-1.07)	0.136
		2 <sup>nd</sup> trimester	1.01 (0.78-1.31)	1.03 (0.96-1.11)	
		3 <sup>rd</sup> trimester	0.91 (0.70-1.18)	1.03 (0.96-1.11)	
		Last 6 weeks	0.88 (0.68-1.15)	1.00 (0.93-1.08)	
		Entire pregnancy	0.95 (0.71-1.26)	<b>1.13 (1.04-1.22)</b>	
		Entire pregnancy	0.95 (0.71-1.26)	<b>1.13 (1.04-1.22)</b>	
PM <sub>10</sub>	1 <sup>st</sup> trimester	1.01 (0.77-1.33)	<b>1.19 (1.11-1.29)</b>	0.136	
	2 <sup>nd</sup> trimester	1.16 (0.89-1.51)	<b>1.10 (1.02-1.19)</b>		
	3 <sup>rd</sup> trimester	1.02 (0.78-1.32)	<b>1.09 (1.01-1.17)</b>		
	Last 6 weeks	0.98 (0.75-1.28)	1.01 (0.94-1.09)		
	Entire pregnancy	1.04 (0.79-1.37)	1.12 (1.03-1.21)		
	Entire pregnancy	1.04 (0.79-1.37)	1.12 (1.03-1.21)		

Gestational Age	Pollutant Exposure	Exposure period	Adjusted* Odds Ratio (95% Confidence Intervals)		P-value <0.2‡
			With Diabetes† (N=14,493)	Without Diabetes (N=237,712)	
28-31 weeks	PM <sub>2.5</sub>	Entire pregnancy	<b>1.35 (1.03-1.76)</b>	<b>1.46 (1.36-1.58)</b>	0.140
		1 <sup>st</sup> trimester	0.97 (0.75-1.25)	1.03 (0.96-1.10)	
		2 <sup>nd</sup> trimester	1.09 (0.84-1.41)	1.08 (1.00-1.16)	
		3 <sup>rd</sup> trimester	0.90 (0.69-1.17)	0.93 (0.86-1.01)	
		Last 6 weeks	1.04 (0.80-1.35)	1.05 (0.98-1.14)	
	Traffic Density	Entire pregnancy	1.19 (0.92-1.56)	<b>1.09 (1.01-1.18)</b>	
		Entire pregnancy	0.96 (0.63-1.44)	<b>1.16 (1.05-1.28)</b>	
		1 <sup>st</sup> trimester	0.75 (0.51-1.12)	1.01 (0.92-1.11)	
		2 <sup>nd</sup> trimester	0.93 (0.63-1.36)	0.98 (0.89-1.08)	
		3 <sup>rd</sup> trimester	0.79 (0.52-1.19)	0.98 (0.88-1.08)	
	CO	2 <sup>nd</sup> trimester	0.93 (0.63-1.36)	0.98 (0.89-1.08)	
		3 <sup>rd</sup> trimester	0.79 (0.52-1.19)	0.98 (0.88-1.08)	
		Last 6 weeks	0.94 (0.64-1.36)	0.98 (0.89-1.08)	
		Entire pregnancy	0.92 (0.64-1.33)	<b>1.12 (1.02-1.23)</b>	
		1 <sup>st</sup> trimester	0.88 (0.63-1.23)	<b>1.13 (1.04-1.23)</b>	
NO <sub>2</sub>	2 <sup>nd</sup> trimester	1.13 (0.82-1.57)	0.98 (0.90-1.07)		
	3 <sup>rd</sup> trimester	0.79 (0.56-1.14)	0.94 (0.86-1.03)		
	Last 6 weeks	0.97 (0.69-1.36)	0.96 (0.88-1.05)		
	Entire pregnancy	0.96 (0.66-1.41)	1.01 (0.91-1.11)		
	1 <sup>st</sup> trimester	1.26 (0.89-1.78)	<b>1.11 (1.01-1.22)</b>		
PM <sub>10</sub>	2 <sup>nd</sup> trimester	1.17 (0.82-1.66)	1.02 (0.93-1.13)		
	3 <sup>rd</sup> trimester	0.78 (0.53-1.14)	0.96 (0.87-1.06)		
	Last 6 weeks	0.91 (0.64-1.30)	0.94 (0.86-1.04)		
	Entire pregnancy	1.27 (0.89-1.81)	<b>1.37 (1.25-1.50)</b>		
	1 <sup>st</sup> trimester	0.89 (0.63-1.25)	1.09 (1.00-1.19)		
PM <sub>2.5</sub>	2 <sup>nd</sup> trimester	1.22 (0.88-1.70)	1.06 (0.97-1.16)		
	3 <sup>rd</sup> trimester	1.13 (0.80-1.60)	0.89 (0.81-0.98)		
	Last 6 weeks	1.17 (0.83-1.63)	1.04 (0.95-1.14)		
	Entire pregnancy	0.82 (0.57-1.19)	1.02 (0.93-1.12)		
	1 <sup>st</sup> trimester	<b>1.89 (1.04-3.44)</b>	0.99 (0.87-1.13)		
CO	2 <sup>nd</sup> trimester	0.76 (0.37-1.53)	1.01 (0.89-1.15)		
	3 <sup>rd</sup> trimester	NC	NC		
	Last 6 weeks	0.83 (0.42-1.65)	1.04 (0.91-1.18)		
	Entire pregnancy	1.56 (0.87-2.80)	<b>1.21 (1.07-1.37)</b>		
	1 <sup>st</sup> trimester	1.39 (0.80-2.42)	1.04 (0.93-1.17)		
NO <sub>2</sub>	2 <sup>nd</sup> trimester	0.77 (0.41-1.44)	1.02 (0.90-1.15)		
	3 <sup>rd</sup> trimester	NC	NC		
	Last 6 weeks	0.60 (0.31-1.16)	1.06 (0.94-1.19)		
	Entire pregnancy	1.32 (0.72-2.42)	<b>1.15 (1.01-1.30)</b>		
	1 <sup>st</sup> trimester	1.73 (0.98-3.06)	<b>1.18 (1.04-1.33)</b>		
20-27 weeks	PM <sub>10</sub>	1 <sup>st</sup> trimester	1.73 (0.98-3.06)	<b>1.18 (1.04-1.33)</b>	
		1 <sup>st</sup> trimester	1.73 (0.98-3.06)	<b>1.18 (1.04-1.33)</b>	
		1 <sup>st</sup> trimester	1.73 (0.98-3.06)	<b>1.18 (1.04-1.33)</b>	
		1 <sup>st</sup> trimester	1.73 (0.98-3.06)	<b>1.18 (1.04-1.33)</b>	
		1 <sup>st</sup> trimester	1.73 (0.98-3.06)	<b>1.18 (1.04-1.33)</b>	

Gestational Age	Pollutant Exposure	Exposure period	Adjusted* Odds Ratio (95% Confidence Intervals)		P-value <0.2 <sup>‡</sup>
			With Diabetes <sup>†</sup> (N=14,493)	Without Diabetes (N=237,712)	
		2 <sup>nd</sup> trimester	0.83 (0.43-1.59)	1.04 (0.92-1.18)	
		3 <sup>rd</sup> trimester	NC	NC	
		Last 6 weeks	0.54 (0.26-1.11)	0.89 (0.79-1.02)	0.197
		Entire pregnancy	<b>2.44 (1.39-4.29)</b>	<b>1.58 (1.40-1.78)</b>	0.119
		1 <sup>st</sup> trimester	<b>2.15 (1.24-3.73)</b>	1.07 (0.95-1.20)	0.014
	PM <sub>2.5</sub>	2 <sup>nd</sup> trimester	1.32 (0.74-2.36)	1.07 (0.94-1.20)	
		3 <sup>rd</sup> trimester	NC	NC	
		Last 6 weeks	<b>2.56 (1.60-4.09)</b>	<b>1.75 (1.57-1.94)</b>	
	Traffic Density	Entire pregnancy	/1.54 (0.95-2.50)	<b>/1.19 (1.06-1.33)</b>	

NC, not calculated

\* Adjusted for maternal race, age, education, payment of birth expenses/insurance type, prenatal care

<sup>†</sup> Gestational and pre-existing diabetes

<sup>‡</sup> P-value <0.2 for Wald's Chi-squared test for interaction

Highest quartile cut offs: 0.60 ppm for CO, 19.47 ppb for NO<sub>2</sub>, 42.65 µg/m<sup>3</sup> for PM<sub>10</sub>, 20.72 µg/m<sup>3</sup> for PM<sub>2.5</sub>, and 45.85 for traffic density