Environmental Research 170 (2019) 160–167

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Prenatal exposure to air pollution, maternal diabetes and preterm birth

Amy M. Padula[a,*], Wei Yang[b], Fredrick W. Lurmann[c], John Balmes[d,e], S. Katharine Hammond[d], Gary M. Shaw[b]

[a] Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA
[b] Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA
[c] Sonoma Technology, Inc., Petaluma, CA, USA
[d] Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, CA, USA
[e] Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

ARTICLE INFO

Keywords:
Air pollution
Preterm birth
Pregnancy
Diabetes

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 to 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 μm ($PM_{2.5}$). Those with diabetes and exposure higher levels of CO (in first trimester or entire pregnancy) or $PM_{2.5}$ (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 $PM_{2.5}$ and extremely preterm birth.

1. Introduction

Prenatal exposure to ambient air pollution has been associated with preterm birth in several studies (Stieb et al., 2012; Pereira et al., 2014; Schifano et al., 2013; Li et al., 2017). In a previous investigation of the current cohort, preterm birth was associated with increased exposure to particulate matter < 10 (PM_{10}) and 2.5 μm ($PM_{2.5}$) during pregnancy. The associations were strongest with exposure in the second trimester, particularly for early preterm births (< 28 weeks gestation) (Padula et al., 2014a).

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 (Eze et al., 2015a; Rajagopalan and Brook, 2012). 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 (Park, 2017). 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 (Rajagopalan and Brook, 2012). A systematic review and meta-analysis of ambient air pollution in adults and diabetes studies in Europe and North America observed an 8–10%

Abbreviations: Aor, adjusted odds ratio; CI, confidence interval; CO, carbon monoxide; PM_{10}, particulate matter less than 10 μm; $PM_{2.5}$, particulate matter less than 2.5 μm; NO_2, nitrogen dioxide

* Correspondence to: 550 16th Street, San Francisco, CA 94143, USA.
E-mail address: amy.padula@ucsf.edu (A.M. Padula).

https://doi.org/10.1016/j.envres.2018.12.031
Received 23 October 2018; Received in revised form 3 December 2018; Accepted 14 December 2018
Available online 15 December 2018
0013-9351/

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 (%)*					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†		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 1st 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						
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

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

* Percentages may not equal 100 owing to rounding.

† 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).

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

	CO (ppm)		**NO_2** (ppb)		**PM_{10}** ($\mu g/m^3$)		**$PM_{2.5}$** ($\mu g/m^3$)		**Traffic density**	
Entire pregnancy	0.49	0.18	17.26	4.14	35.93	11.55	17.05	6.39	16.51	45.23
1st trimester	0.49	0.28	17.42	6.43	34.86	16.37	15.18	13.45		
2nd trimester	0.47	0.29	17.01	6.63	34.75	16.59	14.41	12.77		
3rd trimester	0.45	0.29	16.88	6.68	34.81	17.47	13.91	12.4		
Last 6 weeks	0.45	0.29	16.63	6.94	34.05	17.38	13.34	12.2		

increase in odds of diabetes for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ or nitrogen dioxide (NO_2) (Eze et al., 2015b).

Several studies have investigated the associations between air pollution and diabetes in pregnancy. One study in Taiwan found associations between $PM_{2.5}$ and oral glucose tolerance tests, a screening test for gestational diabetes, during pregnancy (M.C. Lu et al., 2017; M.-C. Lu et al., 2017). Another study found preconception and early pregnancy nitrogen oxides (NO_X) exposure were associated with gestational diabetes (Robledo et al., 2015a, 2015b). Exposure to $PM_{2.5}$ and ozone (O_3) 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 (Fleisch et al., 2014). In a retrospective study also in Massachusetts, no consistent association between

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	1st Trimester	**0.87 (0.83–0.91)**	**0.91 (0.87–0.96)**
CO	2nd Trimester	**0.90 (0.86–0.94)**	**0.92 (0.88–0.96)**
NO_2	1st Trimester	**0.87 (0.83–0.91)**	**0.91 (0.87–0.95)**
NO_2	2nd Trimester	**0.87 (0.83–0.91)**	**0.94 (0.90–0.98)**
PM_{10}	1st Trimester	**0.90 (0.86–0.93)**	**0.94 (0.90–0.97)**
PM_{10}	2nd Trimester	**0.87 (0.84–0.90)**	**0.92 (0.89–0.96)**
$PM_{2.5}$	1st Trimester	0.98 (0.94–1.02)	1.01 (0.97–1.06)
$PM_{2.5}$	2nd Trimester	**0.94 (0.90–0.98)**	0.96 (0.92–1.00)
Traffic Density	Entire pregnancy	0.97 (0.93–1.01)	0.99 (0.95–1.03)

Highest quartile cut offs: 0.60 ppm for CO, 19.47 ppb for NO_2, 42.65 μg/m^3 for PM_{10}, 20.72 μg/m^3 for $PM_{2.5}$, and 45.85 for traffic density.

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

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 $PM_{2.5}$ (Fleisch et al., 2016).

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 $PM_{2.5}$ and NO_2 and preterm birth among those with pre-existing diabetes (Lavigne et al., 2016a, 2016b). In a study of over 1 million births in Taiwan, associations between O_3 and preterm birth were stronger among those with gestational diabetes (Lin et al., 2015). 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.

2. Methods

2.1. 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 = 8373), 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 < 500 g or > 5000 g (n = 762). Completeness of pollutant assignments was 80% for CO, 94% for NO_2, 93% for PM_{10}, 93% for $PM_{2.5}$, 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). Daily metrics of the following pollutants were calculated: carbon monoxide (CO), nitrogen dioxide (NO_2), particulate matter ≤ than 10 μm (PM_{10}), and PM ≤ than 2.5 μm ($PM_{2.5}$). 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 (Padula et al., 2014a). 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 300 m radius of geocoded maternal residences (Kan et al., 2008). Further details on exposure assessment were published previously (Padula et al., 2014a, 2014b).

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.

2.2. 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

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‡
			With diabetes† (N = 14,493)	Without diabetes (N = 237,712)	
34–36 weeks	CO	Entire pregnancy	1.12 (0.98–1.28)	**1.12 (1.08–1.16)**	
		1st trimester	1.06 (0.93–1.19)	**1.05 (1.01–1.08)**	
		2nd trimester	0.98 (0.87–1.12)	1.02 (0.98–1.05)	
		3rd trimester	0.88 (0.77–1.00)	0.98 (0.94–1.01)	0.123
		Last 6 weeks	0.84 (0.74–0.95)	0.96 (0.93–1.00)	0.042
	NO_2	Entire pregnancy	0.99 (0.87–1.12)	1.07 (1.04–1.11)	
		1st trimester	0.96 (0.86–1.08)	1.03 (1.00–1.06)	
		2nd trimester	0.97 (0.86–1.09)	1.03 (0.99–1.06)	
		3rd 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)	0.154
	PM_{10}	Entire pregnancy	1.01 (0.90–1.15)	**1.09 (1.05–1.12)**	
		1st trimester	0.96 (0.85–1.08)	**1.11 (1.07–1.14)**	0.029
		2nd trimester	1.01 (0.90–1.14)	1.09 (1.05–1.12)	
		3rd 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)	
	$PM_{2.5}$	Entire pregnancy	**1.19 (1.05–1.34)**	**1.23 (1.19–1.27)**	
		1st trimester	1.04 (0.93–1.16)	**1.05 (1.01–1.08)**	
		2nd trimester	1.05 (0.94–1.18)	**1.05 (1.01–1.08)**	
		3rd trimester	**0.86 (0.76–0.97)**	**0.94 (0.91–0.97)**	
		Last 6 weeks	0.89 (0.79–1.00)	0.99 (0.96–1.02)	0.114
	Traffic density	Entire pregnancy	0.96 (0.85–1.09)	**1.05 (1.01–1.08)**	
32–33 weeks	CO	Entire pregnancy	1.07 (0.79–1.44)	**1.17 (1.08–1.27)**	
		1st trimester	0.99 (0.75–1.30)	0.95 (0.88–1.03)	
		2nd trimester	0.99 (0.75–1.31)	0.98 (0.90–1.06)	
		3rd 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)	0.136
	NO_2	Entire pregnancy	1.04 (0.79–1.37)	1.12 (1.03–1.21)	
		1st trimester	1.12 (0.87–1.44)	1.00 (0.93–1.07)	
		2nd trimester	1.01 (0.78–1.31)	1.03 (0.96–1.11)	
		3rd 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)	
	PM_{10}	Entire pregnancy	0.95 (0.71–1.26)	**1.13 (1.04–1.22)**	
		1st trimester	1.01 (0.77–1.33)	**1.19 (1.11–1.29)**	
		2nd trimester	1.16 (0.89–1.51)	**1.10 (1.02–1.19)**	
		3rd trimester	1.02 (0.78–1.32)	**1.09 (1.01–1.17)**	
		Last 6 weeks	0.98 (0.75–1.28)	1.01 (0.94–1.09)	
	$PM_{2.5}$	Entire pregnancy	**1.35 (1.03–1.76)**	**1.46 (1.36–1.58)**	
		1st trimester	0.97 (0.75–1.25)	1.03 (0.96–1.10)	
		2nd trimester	1.09 (0.84–1.41)	1.08 (1.00–1.16)	
		3rd 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)	**1.09 (1.01–1.18)**	
28–31 weeks	CO	Entire pregnancy	0.96 (0.63–1.44)	**1.16 (1.05–1.28)**	
		1st trimester	0.75 (0.51–1.12)	1.01 (0.92–1.11)	0.140
		2nd trimester	0.93 (0.63–1.36)	0.98 (0.89–1.08)	
		3rd 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)	
	NO_2	Entire pregnancy	0.92 (0.64–1.33)	**1.12 (1.02–1.23)**	
		1st trimester	0.88 (0.63–1.23)	**1.13 (1.04–1.23)**	0.168
		2nd trimester	1.13 (0.82–1.57)	0.98 (0.90–1.07)	
		3rd 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)	
	PM_{10}	Entire pregnancy	0.96 (0.66–1.41)	1.01 (0.91–1.11)	
		1st trimester	1.26 (0.89–1.78)	**1.11 (1.01–1.22)**	
		2nd trimester	1.17 (0.82–1.66)	1.02 (0.93–1.13)	
		3rd 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)	
	$PM_{2.5}$	Entire pregnancy	1.27 (0.89–1.81)	**1.37 (1.25–1.50)**	
		1st trimester	0.89 (0.63–1.25)	1.09 (1.00–1.19)	
		2nd trimester	1.22 (0.88–1.70)	1.06 (0.97–1.16)	
		3rd trimester	1.13 (0.80–1.60)	0.89 (0.81–0.98)	0.166
		Last 6 weeks	1.17 (0.83–1.63)	1.04 (0.95–1.14)	
	Traffic Density	Entire pregnancy	0.82 (0.57–1.19)	1.02 (0.93–1.12)	
20–27 weeks	CO	Entire pregnancy	**2.21 (1.20–4.08)**	1.07 (0.93–1.23)	0.026
		1st trimester	**1.89 (1.04–3.44)**	0.99 (0.87–1.13)	0.038
		2nd trimester	0.76 (0.37–1.53)	1.01 (0.89–1.15)	
		3rd trimester	NC	NC	
		Last 6 weeks	0.83 (0.42–1.65)	1.04 (0.91–1.18)	
	NO_2	Entire pregnancy	1.56 (0.87–2.80)	**1.21 (1.07–1.37)**	
		1st trimester	1.39 (0.80–2.42)	1.04 (0.93–1.17)	
		2nd trimester	0.77 (0.41–1.44)	1.02 (0.90–1.15)	
		3rd trimester	NC	NC	

(*continued on next page*)

Table 4 (*continued*)

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)	
		Last 6 weeks	0.60 (0.31–1.16)	1.06 (0.94–1.19)	0.099
	PM_{10}	Entire pregnancy	1.32 (0.72–2.42)	**1.15 (1.01–1.30)**	
		1st trimester	1.73 (0.98–3.06)	**1.18 (1.04–1.33)**	0.175
		2nd trimester	0.83 (0.43–1.59)	1.04 (0.92–1.18)	
		3rd trimester	NC	NC	
		Last 6 weeks	0.54 (0.26–1.11)	0.89 (0.79–1.02)	0.197
	$PM_{2.5}$	Entire pregnancy	**2.44 (1.39–4.29)**	**1.58 (1.40–1.78)**	0.119
		1st trimester	**2.15 (1.24–3.73)**	1.07 (0.95–1.20)	0.014
		2nd trimester	1.32 (0.74–2.36)	1.07 (0.94–1.20)	
		3rd trimester	NC	NC	
		Last 6 weeks	**2.56 (1.60–4.09)**	**1.75 (1.57–1.94)**	
	Traffic Density	Entire pregnancy	1.54 (0.95–2.50)	**1.19 (1.06–1.33)**	

NC, not calculated

Highest quartile cut offs: 0.60 ppm for CO, 19.47 ppb for NO_2, 42.65 μg/m^3 for PM_{10}, 20.72 μg/m^3 for $PM_{2.5}$, and 45.85 for traffic density

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

† Gestational and pre-existing diabetes.

‡ P-value < 0.2 for Wald's Chi-squared test for interaction.

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 × 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 $PM_{2.5}$ and extreme preterm birth (20–27 weeks gestation), we employed the four step method of Baron and Kenny (Baron and Kenny, 1986). It included the following regressions: (1) preterm birth ~ (B) $PM_{2.5}$ + covariates; (2) diabetes ~ $PM_{2.5}$ + covariates; (3) preterm birth ~ diabetes + covariates; (4) preterm birth ~ (B1) $PM_{2.5}$ + (B2) diabetes + covariates) and provides a calculation of an indirect effect by either B-B1 (Judd and Kenny, 1981) or B*B2 (Sobel, 1982).

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

3. 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_2, PM_{10} and $PM_{2.5}$) 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_2, 42.65 μg/m^3 for PM_{10}, 20.72 μg/m^3 for $PM_{2.5}$, and 45.85 for traffic density. The correlations between each of the pollutants and exposure periods are presented in the Appendix.

3.1. 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_2 and $PM_{2.5}$. 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).

3.2. 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 $PM_{2.5}$ 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_{10} 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).

3.3. Mediation of diabetes in the association between $PM_{2.5}$ and extreme preterm birth

The results of the mediation analysis did not show that diabetes mediated the relationship between $PM_{2.5}$ 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).

3.4. 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.

4. 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 (M.-C. Lu et al., 2017; M.C. Lu et al., 2017; Robledo et al., 2015a; Fleisch et al., 2014, 2016).

We did find evidence of effect modification by diabetes in the relationship between CO and $PM_{2.5}$ and very early preterm birth. This finding is consistent with the few previous studies (Lavigne et al., 2016a; Lin et al., 2015), though our results were not consistent across multiple pollutants (PM_{10}, NO_2) 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 and 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 (Ferguson and Chin, 2017). 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 (Ferguson et al., 2013; Vadillo-Ortega et al., 2014).

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 ($PM_{2.5}$, PM_{10} 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 $PM_{2.5}$ 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.

Appendix

See Table 1

Acknowledgements

Support for this study came from NIEHS (R21 ESO14891, P20 ES018173, P01ES022849, R00ES021470), and the March of Dimes Prematurity Research Center at Stanford University. This publication was made possible by US EPA STAR Grant RD83459601 and RD83543501. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the US EPA. Further, the US EPA does not endorse the purchase of any commercial products or services mentioned in the publication. We thank Bryan Penfold of Sonoma Technology, Inc. for traffic data processing and traffic density estimation.

Conflicts of interest

None.

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_2**					**PM_{10}**					**$PM_{2.5}$**				
	EP	T1	T2	T3	L6W	EP	T1	T2	T3	L6W	EP	T1	T2	T3	L6W	EP	T1	T2	T3	L6W
CO EP																				
CO T1	**0.46**																			
CO T2	**0.84**	**0.17**																		
CO T3	**0.46**	**− 0.43**	**0.32**																	
CO L6W	**0.31**	**− 0.41**	**0.11**	**0.93**																
NO_2 EP	**0.75**	**0.25**	**0.67**	**0.42**	**0.31**															
NO_2 T1	**0.47**	**0.82**	**0.34**	**− 0.38**	**− 0.41**	**0.59**														
NO_2 T2	**0.74**	**0.02**	**0.83**	**0.47**	**0.29**	**0.87**	**0.34**													
NO_2 T3	**0.27**	**− 0.42**	**0.15**	**0.81**	**0.80**	**0.57**	**− 0.20**	**0.45**												
NO_2 L6W	**0.14**	**− 0.37**	**− 0.02**	**0.71**	**0.79**	**0.45**	**− 0.21**	**0.26**	**0.93**											
PM_{10} EP	**0.57**	**0.07**	**0.46**	**0.49**	**0.43**	**0.48**	**0.12**	**0.47**	**0.42**	**0.38**										
PM_{10} T1	**0.57**	**0.59**	**0.52**	**− 0.13**	**− 0.21**	**0.42**	**0.63**	**0.39**	**− 0.20**	**− 0.25**	**0.59**									
PM_{10} T2	**0.50**	**− 0.26**	**0.58**	**0.60**	**0.48**	**0.46**	**− 0.13**	**0.61**	**0.49**	**0.39**	**0.82**	**0.28**								
PM_{10} T3	**0.04**	**− 0.21**	**− 0.20**	**0.52**	**0.61**	**0.07**	**− 0.28**	**− 0.08**	**0.57**	**0.64**	**0.60**	**− 0.13**	**0.38**							
PM_{10} L6W	0.00	**− 0.04**	**− 0.26**	**0.34**	**0.51**	**0.03**	**− 0.13**	**− 0.18**	**0.43**	**0.59**	**0.46**	**− 0.11**	**0.21**	**0.86**						
$PM_{2.5}$ EP	**0.76**	**0.34**	**0.70**	**0.30**	**0.17**	**0.59**	**0.41**	**0.64**	**0.11**	**0.01**	**0.70**	**0.72**	**0.57**	**0.08**	**0.01**					
$PM_{2.5}$ T1	**0.26**	**0.87**	**0.04**	**− 0.50**	**− 0.47**	**0.10**	**0.71**	**− 0.08**	**− 0.50**	**− 0.42**	**0.10**	**0.62**	**− 0.27**	**− 0.18**	**− 0.03**	**0.42**				
$PM_{2.5}$ T2nd	**0.65**	**0.08**	**0.87**	**0.19**	**0.01**	**0.54**	**0.30**	**0.73**	**0.05**	**− 0.10**	**0.50**	**0.58**	**0.61**	**− 0.21**	**− 0.27**	**0.77**	**0.05**			
$PM_{2.5}$ T3rd	**0.28**	**− 0.50**	**0.20**	**0.86**	**0.81**	**0.29**	**− 0.45**	**0.40**	**0.69**	**0.61**	**0.53**	**− 0.11**	**0.62**	**0.56**	**0.36**	**0.37**	**− 0.49**	**0.17**		
$PM_{2.5}$ L6W	**0.15**	**− 0.46**	0.00	**0.79**	**0.86**	**0.18**	**− 0.47**	**0.21**	**0.67**	**0.66**	**0.44**	**− 0.20**	**0.47**	**0.62**	**0.52**	**0.21**	**− 0.45**	**− 0.03**	**0.90**	
Traffic Density	0.00	**0.01**	**− 0.01**	0.00	0.00	**0.15**	**0.10**	**0.10**	**0.10**	**0.09**	**− 0.03**	**− 0.02**	**− 0.02**	**− 0.02**	**− 0.02**	**0.01**	**0.01**	**0.00**	**0.01**	**0.01**

Bolded correlation coefficients were statistically significant ($p < 0.05$).

References

Baron, R.M., Kenny, D.A., 1986. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J. Pers. Soc. Psychol. 51 (6), 1173–1182.

Eze, I.C., et al., 2015a. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ. Health Perspect. 123 (5), 381–389.

Eze, I.C., et al., 2015b. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ. Health Perspect.

Ferguson, K.K., Chin, H.B., 2017. Environmental chemicals and preterm birth: biological mechanisms and the state of the science. Curr. Epidemiol. Rep. 4 (1), 56–71.

Ferguson, K.K., O'Neill, M.S., Meeker, J.D., 2013. Environmental contaminant exposures and preterm birth: a comprehensive review. J. Toxicol. Environ. Health B Crit. Rev. 16 (2), 69–113.

Fleisch, A.F., et al., 2014. Air pollution exposure and abnormal glucose tolerance during pregnancy: the project Viva cohort. Environ. Health Perspect. 122 (4), 378–383.

Fleisch, A.F., et al., 2016. Air pollution exposure and gestational diabetes mellitus among pregnant women in Massachusetts: a cohort study. Environ. Health 15, 40.

Judd, C.M., Kenny, D.A., 1981. Process analysis: estimating mediation in treatment evaluations. Eval. Rev. 5 (5), 602–619.

Kan, H., et al., 2008. Prospective analysis of traffic exposure as a risk factor for incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. Environ. Health Perspect. 116 (11), 1463–1468.

Lavigne, E., et al., 2016a. Ambient air pollution and adverse birth outcomes: differences by maternal comorbidities. Environ. Res. 148, 457–466.

Lavigne, E., et al., 2016b. Ambient air pollution and adverse birth outcomes: differences by maternal comorbidities. Environ. Res. 148 (C), 457–466.

Li, X., et al., 2017. Association between ambient fine particulate matter and preterm birth or term low birth weight: an updated systematic review and meta-analysis. Environ. Pollut. 227, 596–605.

Lin, Y.T., et al., 2015. Associations between ozone and preterm birth in women who develop gestational diabetes. Am. J. Epidemiol. 181 (4), 280–287.

Lu, M.C., et al., 2017. Association of temporal distribution of fine particulate matter with glucose homeostasis during pregnancy in women of Chiayi City, Taiwan. Environ. Res. 152, 81–87.

Lu, M.-C., et al., 2017. Association of temporal distribution of fine particulate matter with glucose homeostasis during pregnancy in women of Chiayi City, Taiwan. Environ. Res. 152 (C), 81–87.

Padula, A.M., et al., 2014a. Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California. Ann. Epidemiol. 24 (12), 888–95e4.

Padula, A.M., et al., 2014b. Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California. Ann. Epidemiol. 24 (12), 888–895 (e4).

Park, S.K., 2017. Ambient air pollution and type 2 diabetes: do the metabolic effects of air pollution start early in life? Diabetes 66 (7), 1755–1757.

Pereira, G., et al., 2014. Fine particulate matter and risk of preterm birth in Connecticut in 2000–2006: a longitudinal study. Am. J. Epidemiol. 179 (1), 67–74.

Rajagopalan, S., Brook, R.D., 2012. Air pollution and type 2 diabetes: mechanistic insights. Diabetes 61 (12), 3037–3045.

Robledo, C.A., et al., 2015a. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. Environ. Res. 137, 316–322.

Robledo, C.A., et al., 2015b. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. Environ. Res. 137 (c), 316–322.

Schifano, P., et al., 2013. Effect of ambient temperature and air pollutants on the risk of preterm birth, Rome 2001–2010. Environ. Int. 61, 77–87.

Sobel, M.E., 1982. Asymptotic confidence intervals for indirect effects in structural equation models. In: Leinhardt, S. (Ed.), Sociological Methodology. American Sociological Association, Washington D.C, pp. 290–312.

Stieb, D.M., et al., 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ. Res. 117, 100–111.

Vadillo-Ortega, F., et al., 2014. Air pollution, inflammation and preterm birth: a potential mechanistic link. Med. Hypotheses 82 (2), 219–224.