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Air pollution exposure and risk of adverse obstetric and neonatal outcomes among women with type 1 diabetes

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Abstract

Aims/Hypothesis: Women with type 1 diabetes have increased risk for poor obstetric outcomes. Prenatal air pollution exposure is also associated with adverse outcomes for women and infants. We examined whether women with type 1 diabetes are more vulnerable than other women to pollution-associated risks during pregnancy.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods: In singleton deliveries from the Consortium on Safe Labor (2002-2008), obstetric and neonatal outcomes were compared for women with type 1 diabetes (n=507) and women without autoimmune disease (n=204,384). Preconception, trimester, and whole pregnancy average air pollutant exposure (ozone (O_3), carbon monoxide (CO), particulate matter >10 microns (PM_{10}), PM >2.5 microns ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen oxides (NO_x)) were estimated using modified Community Multiscale Air Quality models. Poisson regression models with diabetes*pollutant interaction terms estimated relative risks and 95% confidence intervals for adverse outcomes, adjusted for maternal characteristics and geographic region.

Results: For whole pregnancy exposure to SO_2, women with type 1 diabetes had 15% increased risk (RR:1.15 95%CI:1.01,1.31) and women without autoimmune disease had 5% increased risk (RR:1.05 95%CI:1.05,1.06) for small for gestational age birth ($p_{interaction}$=0.09). Additionally, whole pregnancy O_3 exposure was associated with 10% increased risk (RR:1.10 95%CI:1.02,1.17) among women with type 1 diabetes and 2% increased risk (RR:1.02 95%CI:1.00,1.04) among women without autoimmune disease for perinatal mortality ($p_{interaction}$=0.08). Similar patterns were observed between $PM_{2.5}$ exposure and spontaneous preterm birth.

Conclusions: Pregnant women with type 1 diabetes may be at greater risk for adverse outcomes when exposed to air pollution than women without autoimmune disease.

Keywords

Air pollution; Neonatal; Obstetrics; Type 1 diabetes; Pregnancy

1. Introduction

Women with type 1 diabetes and their infants are known to be at increased risk for a range of poor obstetric and neonatal outcomes including gestational hypertension, preeclampsia, fetal growth restriction, and preterm birth(Evers et al., 2004; Williams et al., 2019). Additionally, pregnant women and their infants exposed to high levels of ambient air pollution are known to be at increased risk for similar poor obstetric and neonatal outcomes(Männistö et al., 2015; Mendola et al., 2016a, 2016b; Nobles et al., 2018; Zhu et al., 2017). Evidence suggests inflammation may contribute to poor obstetric and neonatal outcomes among both women with type 1 diabetes (Groen et al., 2015; Hoch et al., 2019; Huynh et al., 2015) and women exposed to high levels of air pollution (Fiorito et al., 2018; Lawal, 2017; Li et al., 2016; Moudgil and Choubey, 2011; Reboul et al., 2017).

Poor outcomes among women with type 1 diabetes and their infants may in part be due to autoimmune inflammation (Groen et al., 2015; Hoch et al., 2019; Huynh et al., 2015). Exposure to high levels of air pollution may be related to systemic inflammation and oxidative stress, which may propagate autoimmune inflammation (Fiorito et al., 2018; Lawal, 2017; Li et al., 2016; Moudgil and Choubey, 2011; Reboul et al., 2017). Excessive inflammation during pregnancy may impair placental development.(Kim et al., 2015) In turn, impaired placental development may also contribute to poor obstetric outcomes among women with type 1 diabetes, including hypertensive disorders of pregnancy and small for gestational age birth (Germain et al., 1999; Gutaj and Wender-Ozegowska, 2016; Nijman et al., 2016; Redline, 2012; Wright et al., 2017). However, the relationship between ambient air

pollution and obstetric and neonatal outcomes among women with type 1 diabetes remains unexamined.

Current evidence suggests pregnant women with type 1 diabetes may be especially susceptible to high levels of air pollution. One prior study reported a stronger association between air pollution and preterm birth among women with pre-existing diabetes compared to women without diabetes, but this study did not differentiate between type 1 diabetes and other types of diabetes (Lavigne et al., 2016). Clinical evidence suggests animals with induced type 1 diabetes may have a greater inflammatory response to air pollution than animals without diabetes (Nemmar et al., 2013; Yan et al., 2014). For instance, diesel exhaust particle exposure was associated with airway resistance and lung inflammation among mice regardless of diabetes status, yet the presence of oxidative stress and inflammatory biomarkers was greater among mice with diabetes (Nemmar et al., 2013). Thus, we hypothesized that women with type 1 diabetes and their infants would have greater risk of poor outcomes when exposed to air pollution compared to women without autoimmune disorders and their infants.

2. Methods

2.1 Data and sample.

The Consortium on Safe Labor (CSL) was a U.S. retrospective cohort study from 2002-2008 that abstracted labor and delivery information from electronic medical records from 19 U.S. hospitals. Data extracted for deliveries at 23 gestational weeks or later (n of pregnancies=228,438) included: maternal sociodemographic characteristics, medical, reproductive and prenatal history, labor and delivery summaries, postpartum and newborn data (Zhang et al., 2010). For these analyses, we excluded multifetal pregnancies (n=5,063; 2.2%), mothers with thyroid disease (n=3,772; 1.6%), systemic lupus erythematosus (n=202; 0.08%), multiple sclerosis (n=146; 0.08%), rheumatoid arthritis (n=123; 0.05%), Crohn's disease (n=169; 0.07%), as well as mothers with other autoimmune disease (n=1,764; 0.7%) such as unspecified diseases of connective tissue, thrombophilia, hemorrhagic conditions, ulcerative colitis, coeliac disease, Grave's disease and Hashimoto's thyroiditis. Participants from one site for which ICD-9 codes were not reported and no cases of type 1 diabetes were identified (n=12,308, 5.3%) were also excluded. Type 1 diabetes cases were identified using electronic medical records and discharge ICD-9 codes: 250.01, 250.03, 250.11, 250.13, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.81, 250.83, 250.91, 250.93. The reference population were women without diagnosed autoimmune disease. The analytic sample included 507 women with type 1 diabetes with no known other autoimmune disease, and 204,384 women without any identified autoimmune disease.

Outcome variables were based on our prior study of birth outcomes among women with type 1 diabetes in the CSL (Williams et al., 2019): cesarean delivery (overall, pre-labor, after induced labor, and after spontaneous labor), preeclampsia, preterm birth (PTB; < 37 weeks of gestation; overall, spontaneous preterm delivery, indicated preterm delivery), small for gestational age (SGA), NICU admission, neonatal respiratory distress syndrome, and perinatal mortality (pregnancy loss ≥ 23 weeks of gestation through neonatal mortality ≤ 7 days) as identified from medical records and ICD-9 codes.

2.2 Air pollution data.

The Air Quality and Reproductive Health study linked CSL data to air pollution exposures using a modified Community Multiscale Air Quality (CMAQ) model. CMAQ is a three-dimensional multipollutant air quality model used to predict ambient pollutant levels using emissions data from the National Emission Inventories and meteorological data from the Weather Research Forecasting Model. Maternal exposure was based on the predicted hourly ambient pollutant concentrations within hospital referral regions, weighted to reflect population concentration (Chen et al., 2014). For this study we examined average mean air pollution exposures for ozone (O_3), carbon monoxide (CO), particulate matter >10 microns (PM_{10}), particulate matter >2.5 microns ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen oxides (NO_x) during the 3-month preconception period, first trimester (gestational weeks 1-13), second trimester (gestational weeks 14-28), and whole pregnancy (conception to birth) exposure windows. Third trimester was not analyzed as preterm births (11% of CSL) would not have complete exposure estimates.

2.3 Statistical Analysis.

Descriptive statistics were summarized by type 1 diabetes status (present/absent). Binary Poisson regression models with the log link function and robust standard errors to account for repeat pregnancies with interaction terms for type 1 diabetes*pollutant estimated relative risks (RR) and 95% confidence intervals (95% CI) for adverse outcomes. Risks associated with air pollution exposure are estimated based on each interquartile range (IQR; the difference between the 25–75 percentiles based on the distribution among the overall sample) increase. If the coefficient for the interaction term was >0 and p-value was <0.10, this supports the hypothesized interaction that the effect of an IQR increase of air pollution is stronger among women with type 1 diabetes than among women without autoimmune disease. Models include type 1 diabetes status, air pollution, and the interaction term; thus, the RR represents the additional risk attributable to the interaction between type 1 diabetes and air pollution, independent of the risks attributable to type 1 diabetes and air pollution. In separate models, we examined exposure to air pollution in 4 windows: the 3-month preconception period, first trimester, second trimester, and whole pregnancy exposure windows.

Covariates were identified based on previous literature (Evers et al., 2004; Williams et al., 2019). Regression models were adjusted for maternal characteristics including age (continuous), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), preconception Body Mass Index (BMI, <18.5, 18.5-<224.9, 25-<29.9, ≥30 kg/m^2), health insurance (public, private, other), marital status (married, divorced/widowed, single, unknown), smoking during pregnancy (yes/no), alcohol use during pregnancy (yes/no), any other chronic diseases (yes/no: asthma, depression, heart disease, hypertension, renal disease) and area-level factors including hospital type (University Teaching Hospital, Community Teaching Hospital, Non-teaching Community Hospital) and census region (Northeast, West, South, Midwest). BMI was imputed using multiple imputations (10 iterations) due to a high degree of missingness (34.1%). All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). As this is a novel examination of these relationships, we did not adjust for multiple comparisons (Rothman,

1990). Institutional Review Boards approval was obtained at all participating sites and data are de-identified.

3. Results

Women with type 1 diabetes and women without autoimmune disease were similar in regard to race/ethnicity, age, insurance status and marital status (Table 1). Women with type 1 diabetes had higher prevalence of other chronic diseases (i.e., asthma, depression, heart disease, hypertension, renal disease) and higher preconception BMI than women without autoimmune disease (Table 1). A higher percentage of women with type 1 diabetes lived in the South and gave birth at University Teaching Hospitals compared to women without autoimmune disease (Table 1). Mean values and IQR of criteria air pollutants did not meaningfully differ between exposure windows (Table 2) or between women with type 1 diabetes and those without autoimmune disease (Supplemental Table 1). Women with type 1 diabetes and their infants experienced higher rates of all adverse outcomes compared to women without autoimmune disease, except for small for gestational age births (Table 3).

Adjusted results for the association between O_3, $PM_{2.5}$, and SO_2, and poor obstetric and neonatal outcomes among women with type 1 diabetes and women without autoimmune disease are in Table 4. Few increases in risk were observed for CO, PM_{10}, and NO_x (Supplemental Table 2). We observed some consistent increased risks with exposure to air pollution among women with type 1 diabetes compared to women without autoimmune disease for spontaneous PTB, indicated PTB, and SGA. Specifically, for spontaneous PTB, women with type 1 diabetes had an increased risk when exposed to similar levels of $PM_{2.5}$ as women without autoimmune disease ($p_{interaction}<0.10$). First trimester exposure to PM2.5 was associated with a 5% increase in risk among women with type 1 diabetes (RR: 1.05 95% CI: 1.00, 1.10) and an approximate 4% decrease in risk among women without autoimmune disease (RR: 0.96 95% CI: 0.96, 0.97, $p_{interaction} = 0.07$) with similar associations observed for second trimester and whole pregnancy exposures: 7% increased versus 4% decreased risk for second trimester and 6% increased risk versus 6% decreased risk for whole pregnancy, for type 1 diabetes versus no autoimmune disorder, respectively. Additionally, SO_2 exposure in the first and second trimesters was associated with higher risk of spontaneous PTB among women with type 1 diabetes compared to women without autoimmune disease (Table 4).

For indicated PTB, exposure to high levels of O_3 was associated with increases in risk among women with type 1 diabetes but not women without autoimmune disease in the first trimester and second trimester exposure windows (Table 4). Exposure to PM_{10} in the first trimester was also associated with increased risk of indicated PTB (RR: 1.07 95% CI: 1.02, 1.12) among women with type 1 diabetes but not women without autoimmune disease (RR: 1.01 95% CI:1.00, 1.02), ($p_{interaction} = 0.09$) and similar associations were observed for whole pregnancy exposure to PM_{10} (Table 4).

For SGA, exposure to SO_2 in all 4 exposure windows was associated with increases in risk among women with type 1 diabetes but not women without autoimmune disease ($p_{interaction}$ all < 0.10). Similarly, exposure to $PM_{2.5}$ in the second trimester ($p_{interaction} = 0.09$) and

whole pregnancy ($p_{interaction}$ = 0.06) exposure windows was associated with higher risk of SGA among women with type 1 diabetes than among women without autoimmune disease (Table 4).

For perinatal mortality, whole pregnancy O_3 exposure was associated with increased risk among women with type 1 diabetes (RR: 1.10 95% CI: 1.02, 1.17) compared to women without autoimmune disease (RR: 1.02 95%CI: 1.00, 1.04) ($p_{interaction}$ = 0.08). Exposure to SO_2 during all 4 exposure windows were associated with an approximate 15% increased risk of perinatal mortality among women with type 1 diabetes with observed decreased risk among women without autoimmune disease, yet these observations were not statistically significant, nor were the interaction terms statistically significant.

4. Conclusions

This study is the first report of the association between criteria air pollutants and poor obstetric and neonatal outcomes among women with type 1 diabetes and their infants. We found modest evidence of increased risk for spontaneous and indicated preterm birth, small for gestational age births and perinatal mortality indicating that women with type 1 diabetes and their infants had greater risk of poor outcomes when exposed to high levels of air pollution compared to women without autoimmune disorders and their infants. Exposures during three months preconception, first trimester, and second trimester were consistently associated with increased risks among women with type 1 diabetes suggesting chronic exposure to air pollution increases risk of poor obstetric and neonatal outcomes. The observed risks represent a marginal increase in risk above the average obstetric and neonatal risks associated with type 1 diabetes. As women with type 1 diabetes and their infants are at increased risk for a range of poor outcomes, understanding exposures that may further increase risk is important.

In addition to hyperglycemia and potential vascular disease, autoimmune inflammation may contribute to poor outcomes among pregnant women with type 1 diabetes and their infants (Groen et al., 2015; Huynh et al., 2015). For instance, placental tissue from women with type 1 diabetes has increased levels of inflammatory biomarkers (Hoch et al., 2019; Huynh et al., 2015), and evidence suggests this inflammation may occur early in pregnancy (Groen et al., 2015; Hoch et al., 2019), which in turn increases risk of maternal vascular malperfusion and distal villous hypoplasia in the placenta (Desoye and Shafrir, 1994; Gutaj and Wender-Ozegowska, 2016; Maahs et al., 2010). Maternal vascular malperfusion is associated with an increased risk for preterm birth (Germain et al., 1999; Nijman et al., 2016), small for gestational age birth (Gutaj and Wender-Ozegowska, 2016; Wright et al., 2017), and other maternal complications like preeclampsia (Wright et al., 2017). Evidence suggests distal villous hypoplasia may be associated with poor fetal growth and stillbirth (Gutaj and Wender-Ozegowska, 2016; Redline, 2012).

Poor obstetric outcomes associated with high levels of air pollution may be related to systemic inflammation and oxidative stress. For example, exposure to high levels of $PM_{2.5}$ is associated with the generation of reactive oxygen species (Li et al., 2016; Reboul et al., 2017), which interfere with inflammatory kinases that regulate transcription factors and

increase circulation of proinflammatory cytokines (Lawal, 2017). These proinflammatory cytokines may then propagate autoimmune inflammation leading to vascular complications (Fiorito et al., 2018; Hettfleisch et al., 2017; Männistö et al., 2015; Mendola et al., 2016b; Moudgil and Choubey, 2011; Zhu et al., 2017) and less than optimal conditions for placentation (Kim et al., 2015). Furthermore, women exposed to high levels of air pollution have increased risk for impaired placental vasculature (Hettfleisch et al., 2017) and lower placental weight (van den Hooven et al., 2012), thus increasing risk for poor obstetric and neonatal outcomes (Germain et al., 1999; Gutaj and Wender-Ozegowska, 2016; Nijman et al., 2016; Redline, 2012; Wright et al., 2017).

These two lines of evidence taken together suggest women with type 1 diabetes, a population predisposed for poor placental vascularization, experience excessive autoimmune inflammation when exposed to higher levels of air pollution, thus further increasing risk for poor placental vascularization and resulting poor obstetric and neonatal outcomes. We did have some observations to support our hypothesis, as air pollution exposure during three months preconception, first trimester, and second trimester were consistently associated with increased risks of some adverse outcomes (PTB, SGA, and perinatal mortality) among women with type 1 diabetes. The preconception and early pregnancy observations align with evidence that air pollution exposure early in pregnancy is associated with impaired placental vasculature (Hettfleisch et al., 2017).

Among general populations of pregnant women, several studies have reported increased preterm delivery risks associated with air pollution exposure across pregnancy, yet evidence is mixed (Estarlich et al., 2016; Johnson et al., 2016; Kingsley et al., 2017; Mendola et al., 2016a). Our observations suggest a potentially different risk profile for preterm birth among women with type 1 diabetes than women without autoimmune disease when exposed to criteria air pollutants. When exposed to $PM_{2.5}$ or SO_2 in preconception and first and second trimester exposure windows, women with type 1 diabetes had a higher risk for spontaneous preterm delivery than women without autoimmune disease. A similar difference in risk was observed for prenatal O_3 or PM_{10} exposure associated with indicated preterm birth. The observed differences in risk for women with type 1 diabetes compared to women without autoimmune is in line with prior data. One study examined the association between whole pregnancy criteria air pollution exposure and birth outcomes among women with various comorbidities found some evidence of an increased risk for preterm birth among women with pre-existing diabetes (Lavigne et al., 2016). However, women with type 1 diabetes were grouped with women with type 2 diabetes, and the prevalence of the specific type of diabetes within the larger pre-existing diabetes group was not reported.

We found an increased risk for SGA among women with type 1 diabetes and women without autoimmune disease when exposed to SO_2. This increase in risk was observed for preconception exposures, and across pregnancy exposure windows, suggesting chronic exposure to SO_2 is associated with SGA. However, risk estimates among women with type 1 diabetes were 7-10% higher than among women without autoimmune disease. While a lower risk for SGA has been observed among women with type 1 diabetes (Evers et al., 2004; Williams et al., 2019), women with long-standing type 1 diabetes (diagnosed at age 0-4 years) may be at increased risk of SGA due to complications of vasculopathy and placental

insufficiency (Gutaj and Wender-Ozegowska, 2016). The sample of women with type 1 diabetes in the CSL may be especially susceptible to exposure to air pollution during pregnancy and may be driving the observed increase in risk for SGA.

For perinatal mortality, the most severe outcome we examined, we observed a higher risk among women with type 1 diabetes compared to women without autoimmune disease for whole pregnancy exposure to O_3. Similar risk differences were observed for SO_2 exposure, yet observations were not statistically significant. These observed increases in risk may indicate a poor environment for fetal development, thus increasing risk of both stillbirth and neonatal mortality. In contrast, whole pregnancy exposure to NO_x was associated with a decrease in risk of perinatal mortality. Although our findings are more suggestive than conclusive, the severity of this perinatal mortality warrants further examination of these potential relationships among this high-risk population of pregnant women.

We observed several inverse associations, suggesting women exposed to high levels of air pollution may have low risk for adverse outcomes. Replication of our findings among other samples is needed to better understand these inverse associations. One potential explanation for the observed inverse associations is the healthy survivor effect. Exposure to higher levels of air pollution during preconception and early pregnancy is associated with increased risk of pregnancy loss early in pregnancy (prior to 20 weeks)(Enkhmaa et al., 2014; Green et al., 2009; Zhang et al., 2019). The healthy survivor effect suggests the prevalence of pregnant women and fetuses more susceptible to air pollution may be lower in these data, as the CSL only contains births after 23 gestational weeks or later (Smith et al., 2020). Despite the potentially low prevalence of highly susceptible pregnancies we still observed increases in risk among women with type 1 diabetes, suggesting that even among healthy survivors, women with type 1 diabetes are more susceptible to negative consequences of air pollution exposure. Among women without autoimmune disease, the protective effects may be evidence of the healthy survivor effect among a non-immunocompromised population. Additional research on air pollution and pregnancy loss is warranted to better understand the healthy survivor phenomenon.

Our findings are notable for several reasons. This first examination of the association between ambient air pollution and obstetric outcomes among women with type 1 diabetes suggests women with type 1 diabetes are a high-risk population that may be more susceptible to air pollution exposure. The large amount of clinical data allowed us to examine a range of maternal and neonatal outcomes during and after pregnancy. Additionally, the richness of the data allowed us to account for maternal complications like cardiovascular disease and renal disease. The air pollution exposure models account for population density, weather, and temporal and spatial variability, which may better predict exposure levels than other methods(Chen et al., 2014). As we observed several increases in risk for key obstetric and neonatal outcomes, further research is warranted to better understand the physiologic mechanisms underlying these associations.

Limitations of this study should be taking into consideration. The CSL did not collect information on placental pathology. However, given the current evidence regarding vasculopathy among women with type 1 diabetes and vascular effects of air pollution

exposure, these results can inform future work regarding the proposed pathway regarding placental vascularization. As the CSL lacks data on serum glucose levels and disease management data, we were unable to assess whether exposure to higher levels of air pollution effects metabolic control among women with type 1 diabetes. Therefore, our observed risks are average for women with type 1 diabetes, and poorly controlled type 1 diabetes may increase the risks for poor outcomes.

We also do not have access to inflammatory biomarker data within the CSL, thus our confidence in the specific role of inflammation is modest. However, this study is the first to consider the interaction between type 1 diabetes and air pollution among pregnant women, and results suggest exposure to high levels of air pollution may increase risk for some poor obstetric and neonatal outcomes among women with type 1 diabetes. Given these initial findings and the suggestive evidence regarding the role of inflammation, additional research is warranted to better understand the potential biologic mechanisms.

While the sensitivity of ICD-codes for obstetric conditions is good,(Goff et al., 2012; Yasmeen et al., 2006; Zhang et al., 2010) it is possible this approach missed several cases. However, we expect that these conditions would be recorded in the medical records as autoimmune conditions are known to increase risk of pregnancy complications and are relevant for labor and delivery.

The criteria air pollution estimates are averaged over the hospital referral region in which the birth occurred and were not based on participant address. Misclassification may occur depending on length of time mothers spend inside the hospital referral region, although it does account for some local mobility. Approximately 10-30% of pregnant women move during pregnancy, yet most pregnant women move within the region to areas with similar levels of air pollution (Bell and Belanger, 2012). We also lack data on daily activity patterns. Pregnant women in their first trimester, compared to a general population sample, spend a similar amount of time indoors (Nethery et al., 2009). Thus, concerns regarding misclassification due to daily activity patterns are diminished.

In conclusion, women with type 1 diabetes appear to have higher risks for some obstetric and neonatal outcomes when exposed to similar levels of air pollution, compared to women without autoimmune disease. Chronic exposure may be important, suggesting a unique risk profile among women with type 1 diabetes compared to a general population of pregnant women. Given exposure to air pollution is difficult to manage across pregnancy, a better understanding of the role of disease management may be important to reduce these observed risks. These marginal increases in risk among women with type 1 diabetes merit additional attention given the severity of these poor obstetric and neonatal outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability:

Consortium on Safe Labor data is publicly available at https://dash.nichd.nih.gov/. Geographic identifying information is not publicly available, please see http://grants.nih.gov/grants/policy/data_sharing/ for National Institutes of Health data sharing policy.

Abbreviations

95% CI	95 percent confidence intervals
CMAQ	Community Multiscale Air Quality
CO	carbon monoxide
CSL	Consortium on Safe Labor
IQR	interquartile range
NO_x	nitrogen oxides
O_3	ozone carbon monoxide
PM_{10}	particulate matter >10 microns
$PM_{2.5}$	PM >2.5 microns
PTB	preterm birth
RR	risk ratio
SGA	small for gestational age birth
SO_2	sulfur dioxide

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Highlights

- First study of air pollution and obstetric events among women with type 1 diabetes
- Women with type 1 diabetes may be more susceptible to air pollution than controls
- Clinicians may better counsel women with type 1 diabetes about pregnancy intentions
- Increases in risk merit additional attention given severity of the outcomes

Table 1.

Percent of demographic characteristics for women with type 1 diabetes and women without autoimmune disease by demographic variables from the Consortium of Safe Labor, 2002-2008

	Women without autoimmune disease (N=204384)	Type I Diabetes (N=507)	*p-value*[a]
Race			
White	51.4	55.2	*<.01*
Black	20.8	24.5	
Hispanic	16.9	13.8	
Other	10.9	6.5	
Age (years)			
<20	9.3	9.3	*0.63*
20-24	25.3	25.0	
25-29	28.0	26.8	
30-34	22.4	23.9	
≥35	15.0	15.0	
Insurance			*<.01*
Private	57.1	59.0	
Public	30.3	35.7	
Other	12.6	5.3	
Marital Status			*<.05*
Married	60.3	55.4	
Widowed/Divorced	1.6	1.3	
Single	35.2	38.6	
Unknown	2.8	4.5	
Smoking			*0.85*
Yes	6.3	6.5	
No	93.7	93.5	
Alcohol			*0.46*
Yes	1.7	2.1	
No	98.3	97.9	
Other chronic diseases[b]			*<.01*
Yes	14.5	25.6	
No	85.5	74.3	
Preconception Body Mass Index (kg/m^2)			*<.01*
Underweight (<18.5)	3.6	1.3	
Normal (18.5-<25)	25.2	17.5	
Overweight (25-<30)	19.7	22.4	
Obese (≥30)	17.2	23.0	
Missing	34.1	35.5	
Hospital Type			*<.01*
University teaching	39.6	46.9	

	Women without autoimmune disease (N=204384)	Type I Diabetes (N=507)	*p-value*[a]
Community teaching	52.6	48.3	
Community non-teaching	7.8	4.8	
Region			*<.01*
Northeast	19.0	13.2	
South	38.8	44.9	
Midwest	10.2	12.8	
West	31.9	28.9	

A p-values assessed using Fisher's Exact Test.

B asthma, depression, heart disease, hypertension, renal disease

Table 2.

Mean, range and interquartile range of criteria air pollutants by exposure window

Pollutant	Mean	Minimum	Maximum	IQR
3 months preconception				
$PM_{2.5}$ (μg/m^3)	11.63	4.60	22.03	5.36
PM_{10} (μg/m^3)	22.05	10.25	39.44	6.05
NO_x (ppb)	29.02	5.09	92.97	27.00
SO_2 (ppb)	4.06	0.80	21.00	3.46
CO (ppm)	553.61	171.68	1125.23	260.23
O_3 (ppb)	30.10	10.04	49.36	12.16
First trimester				
$PM_{2.5}$ (μg/m^3)	11.68	4.63	22.00	5.13
PM_{10} (μg/m^3)	21.96	10.29	38.95	6.22
NO_x (ppb)	30.26	5.51	89.62	29.06
SO_2 (ppb)	4.07	0.81	18.66	3.48
CO (ppm)	561.12	179.09	1102.43	269.82
O_3 (ppb)	29.42	10.23	48.73	12.16
Second trimester				
$PM_{2.5}$ (μg/m^3)	11.58	4.64	21.97	4.74
PM_{10} (μg/m^3)	21.73	10.14	41.89	6.19
NO_x (ppb)	30.13	5.76	90.65	28.98
SO_2 (ppb)	4.00	0.81	18.98	3.27
CO (ppm)	554.41	178.96	1103.11	269.55
O_3 (ppb)	29.64	10.33	49.52	11.86
Whole pregnancy				
$PM_{2.5}$ (μg/m^3)	11.63	5.73	19.64	4.58
PM_{10} (μg/m^3)	21.89	10.73	39.74	4.32
NO_x (ppb)	29.80	6.38	81.64	22.47
SO_2 (ppb)	4.01	0.96	15.83	3.04
CO (ppm)	551.17	224.90	1045.57	210.98
O_3 (ppb)	29.73	13.64	46.38	7.78

Table 3.

Rate per 1000[a] (and frequency) of obstetric and neonatal outcomes for singleton pregnancies from the Consortium of Safe Labor 2002-2008 (n=204951)

	Women without autoimmune disease (n=204,384)	Type I Diabetes (n=507)	*p-value*[b]
Cesarean Delivery	278.5 (56,926)	670.6 (340)	*<.05*
Prelabor cesarean	113.6 (23,218)	270.2 (137)	*<.05*
After spontaneous labor	93.0 (19,016)	195.3 (99)	*<.05*
After induced labor	71.9 (14,692)	205.1 (104)	*<.05*
Preterm Birth	111.0 (22,701)	426.0 (216)	*<.05*
Spontaneous	78.4 (16,038)	248.5 (126)	*<.05*
Indicated	17.8 (3,650)	145.9 (74)	*<.05*
Preeclampsia	46.4 (9,498)	159.7 (81)	*<.05*
NICU Admission	115.4 (23,593)	408.2 (207)	*<.05*
Neonatal Respiratory	31.1 (6,357)	130.1 (66)	*<.05*
Distress Syndrome			
Small for Gestational Age	109.3 (22,350)	65.0 (33)	*<.05*
Perinatal Mortality	5.9 (1,214)	13.8 (7)	*<.05*

*A*Rates per 1000 are specific for each autoimmune disease category (rate = (outcome n/autoimmune disease N)*1000)

*B*p-values obtained using generalized estimating equations to account for women who had more than one pregnancy in the study.

Table 4.

Adjusted relative risks and their 95% confidence intervals (95% CI) for the association between 1 IQR increase in ozone, particulate matter$_{2.5}$, and sulfur dioxide exposure and adverse obstetric and neonatal outcomes among women with type 1 diabetes and their infants in the Consortium of Safe Labor Singleton Pregnancies, 2002-2008

Ozone	**Preconception**		**First Trimester**		**Second Trimester**		**Whole Pregnancy**	
	Type I Diabetes RR (95% CI) (n=507)	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**
Cesarean	**1.01 (1.00, 1.01)**	**0.99 (0.99, 0.99)**	**1.00 (1.00, 1.01)**	**0.99 (0.99, 0.99)**	**1.00 (1.00, 1.01)**	**0.99 (0.99, 0.99)**	**1.00 (1.00, 1.01)**	**0.99 (0.99, 0.99)**
Prelabor	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.99, 0.99)	0.99 (0.99, 0.99)	**0.99 (0.99, 0.99)**	**0.99 (0.99, 0.99)**
After Induction	0.99 (0.97, 1.01)	0.98 (0.98, 0.98)	0.98 (0.96, 1.00)	0.98 (0.98, 0.98)	0.97 (0.95, 0.99)	0.98 (0.98, 0.98)	0.95 (0.93, 0.98)	0.96 (0.95, 0.96)
After Spontaneous	**1.01 (1.00, 1.03)**	**0.99 (0.99, 0.99)**	**1.01 (1.00, 1.03)**	**0.99 (0.99, 1.00)**	**1.02 (1.00, 1.03)**	**0.99 (0.99, 1.00)**	1.01 (1.00 (1.03)	0.99 (0.99, 0.99)
Preterm	1.00 (0.99, 1.02)	1.00 (1.00, 1.00)	**1.01 (1.00, 1.03)**	**0.99 (0.99, 1.00)**	1.00 (0.98, 1.01)	1.00 (1.00, 1.00)	1.01 (0.99, 1.03)	1.01 (1.00, 1.01)
Indicated	**1.01 (0.98, 1.04)**	**0.99 (0.98, 0.99)**	**1.04 (1.01, 1.07)**	**0.99 (0.99, 0.99)**	**1.03 (0.99, 1.06)**	**0.99 (0.98, 0.99)**	**1.00 (0.97, 1.03)**	**0.98 (0.97, 0.99)**
Spontaneous	1.00 (0.98, 1.02)	1.00 (1.00, 1.01)	1.00 (0.98, 1.02)	1.00 (1.00, 1.01)	0.99 (0.97, 1.01)	1.01 (1.00, 1.01)	1.02 (1.00, 1.04)	1.02 (1.01, 1.02)
Preeclampsia	1.00 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)
Small for Gestational Age	0.99 (0.94, 1.03)	0.99 (0.99, 0.99)	1.01 (0.97, 1.05)	0.99 (0.99, 1.00)	1.01 (0.97, 1.05)	0.99 (0.99, 0.99)	1.01 (0.96, 1.07)	0.99 (0.98, 0.99)
Neonatal Respiratory Distress Syndrome	1.00 (0.98, 1.03)	1.00 (1.00, 1.00)	1.00 (0.97, 1.03)	1.01 (1.01, 1.01)	0.99 (0.96, 1.02)	1.01 (1.01, 1.02)	1.00 (0.95, 1.04)	1.03 (1.03, 1.04)
NICU Admission	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)
Perinatal Mortality	**0.92 (0.84, 1.01)**	**0.99 (0.99, 1.00)**	**0.93 (0.85, 1.02)**	**1.01 (1.00, 1.02)**	**0.94 (0.86, 1.02)**	**1.01 (1.00, 1.02)**	**1.10 (1.02, 1.17)**	**1.02 (1.00, 1.04)**
Particulate Matter 2.5	**Preconception**		**First Trimester**		**Second Trimester**		**Whole Pregnancy**	
	Type I Diabetes RR (95% CI) (n=507)	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**
Cesarean	1.00 (0.98, 1.02)	1.00 (0.99, 1.00)	1.00 (0.98, 1.02)	0.99 (0.99, 1.00)	1.00 (0.98, 1.02)	0.99 (0.99, 1.00)	1.00 (0.98, 1.02)	0.99 (0.99, 1.00)
Prelabor	**1.01 (1.00, 1.02)**	**1.00 (1.00, 1.00)**	**1.01 (1.01, 1.02)**	**1.00 (1.00, 1.00)**	**1.01 (1.01, 1.02)**	**1.00 (1.00, 1.00)**	**1.01 (1.01, 1.02)**	**1.00 (1.00, 1.00)**
After Induction	**0.96 (0.90, 1.02)**	**1.02 (1.01, 1.02)**	0.96 (0.90 (1.03)	1.01 (1.01, 1.02)	0.96 (0.90 (1.03)	1.01 (1.01, 1.02)	0.97 (0.91, 1.04)	1.02 (1.02, 1.03)
After Spontaneous	**1.02 (0.99, 1.05)**	**0.99 (0.99, 0.99)**	**1.02 (0.99, 1.05)**	**0.99 (0.99, 0.99)**	**1.02 (0.99, 1.05)**	**0.99 (0.99, 0.99)**	1.01 (0.99, 1.05)	0.98 (0.98, 0.99)
Preterm	0.98 (0.94, 1.01)	0.97, 0.96, 0.97)	**1.01 (0.98, 1.04)**	**0.97 (0.96, 0.97)**	0.99 (0.95, 1.01)	0.97 (0.97, 0.97)	**1.00 (0.96, 1.05)**	**0.95 (0.95, 0.96)**
Indicated	**0.88 (0.81, 0.96)**	**0.98 (0.97, 0.99)**	0.98 (0.91, 1.06)	0.99 (0.98, 1.00)	**0.88 (0.81, 0.97)**	**0.99 (0.98, 1.01)**	**0.88 (0.81, 0.97)**	**0.99 (0.98, 1.01)**
Spontaneous	**1.01 (0.96, 1.07)**	**0.96 (0.96, 0.97)**	**1.05 (1.00, 1.10)**	**0.96 (0.96, 0.97)**	**1.07 (1.02, 1.13)**	**0.96 (0.96, 0.97)**	**1.06 (1.00, 1.11)**	**0.94 (0.93, 0.95)**

Ozone	Preconception		First Trimester		Second Trimester		Whole Pregnancy	
	Type I Diabetes RR (95% CI) (n=507)	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**
Preeclampsia	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)	**0.99 (0.98, 1.00)**	**1.00 (1.00, 1.00)**	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)
Small for Gestational Age	1.10 (0.98, 1.24)	1.00 (1.00, 1.01)	1.06 (0.95, 1.17)	1.00 (1.00, 1.01)	**1.12 (0.99, 1.26)**	**1.00 (1.00, 1.00)**	**1.15 (0.99, 1.33)**	**1.01 (1.00, 1.01)**
Neonatal Respiratory Distress Syndrome	0.99 (0.92, 1.06)	0.95 (0.94, 0.96)	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)	0.99 (0.92, 1.07)	0.96 (0.95, 0.96)	0.98 (0.89, 1.08)	0.93 (0.92, 0.94)
NICU Admission	1.00 (0.99, 1.01)	0.99 (0.99, 0.99)	1.00 (0.99, 1.01)	0.99 (0.99, 0.99)	1.00 (0.99, 1.01)	0.99 (0.99, 0.99)	1.00 (099, 1.01)	0.99 (0.99, 0.99)
Perinatal Mortality	0.85 (0.72, 1.02)	0.96 (0.95, 0.98)	0.84 (0.71, 0.99)	0.96 (0.94, 0.98)	0.85 (0.72, 1.00)	0.98 (0.96, 1.00)	1.07 (0.76, 1.49)	0.95 (0.93, 0.98)
Sulfur Dioxide	**Preconception**		**First Trimester**		**Second Trimester**		**Whole Pregnancy**	
	Type I Diabetes RR (95% CI) (n=507)	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**	**Type I Diabetes RR (95% CI) (n=507)**	**No Autoimmune RR (95% CI) (n= 204,384)**
Cesarean	0.97 (0.94, 1.00)	0.96 (0.96, 0.96)	0.96 (0.93, 0.99)	0.96 (0.95, 0.96)	0.96 (0.93, 0.99)	0.96 (0.95, 0.96)	0.95 (0.92, 0.98)	0.94 (0.93, 0.94)
Prelabor	**1.00 (0.99, 1.02)**	**0.99 (0.99, 0.99)**	**1.00 (0.99, 1.02)**	**0.99 (0.99, 0.99)**	1.00 (0.99, 1.02)	0.99 (0.99, 0.99)	**1.00 (0.99, 1.01)**	**0.99 (0.99, 0.99)**
After Induction	0.92 (0.82, 1.02)	0.96 (0.95, 0.97)	0.91 (0.82, 1.02)	0.96 (0.95, 0.97)	0.91 (0.82, 1.01)	0.96 (0.95, 0.97)	0.90 (0.80, 1.00)	0.94 (0.93, 0.95)
After Spontaneous	1.00 (0.95, 1.05)	0.96 (0.96, 0.97)	0.99 (0.94, 1.04)	0.96 (0.95, 0.96)	0.98 (0.93, 1.03)	0.96 (0.95, 0.96)	**0.97 (0.92, 1.02)**	**0.94 (0.93, 0.94)**
Preterm	0.97 (0.92, 1.03)	0.95 (0.94, 0.95)	0.97 (0.92, 1.03)	0.95 (0.94, 0.95)	0.96 (0.90, 1.01)	0.95 (0.94, 0.96)	0.96 (0.90, 1.02)	0.94 (0.93, 0.94)
Indicated	**1.00 (0.99, 1.02)**	**0.99 (0.99, 0.99)**	**0.99 (0.98, 1.01)**	**0.99 (0.99, 0.99)**	**0.99 (0.98, 1.01)**	**0.99 (0.99, 0.99)**	**1.00 (0.99, 1.02)**	**0.99 (0.99, 0.99)**
Spontaneous	**1.02 (0.94, 1.11)**	**0.94 (0.93, 0.95)**	**1.04 (0.96, 1.12)**	**0.94 (0.93, 0.95)**	**1.01 (0.95, 1.08)**	**0.94 (0.93, 0.95)**	**0.99 (0.92, 1.08)**	**0.92 (0.91, 0.94)**
Preeclampsia	0.99 (0.97, 1.00)	1.00 (1.00, 1.00)	**0.99 (0.97, 1.00)**	**1.00 (1.00, 1.00)**	**0.99 (0.97, 1.00)**	**1.00 (1.00, 1.00)**	**0.99 (0.97, 1.00)**	**1.00 (1.00, 1.00)**
Small for Gestational Age	1.14 (1.00, 1.31)	1.03 (1.02, 1.03)	**1.13 (1.01, 1.26)**	**1.03 (1.02, 1.03)**	**1.10 (1.00,1.22)**	**1.03 (1.03, 1.04)**	**1.15 (1.01, 1.31)**	**1.05 (1.05, 1.06)**
Neonatal Respiratory Distress Syndrome	0.92 (0.80, 1.05)	0.92 (0.90, 0.94)	0.91 (0.80, 1.04)	0.92 (0.90, 0.93)	0.92 (0.81, 1.04)	0.91 (0.89, 0.93)	0.91 (0.79, 1.04)	0.89 (0.87, 0.91)
NICU Admission	**1.01 (0.99, 1.02)**	**0.99 (0.99, 0.99)**	**1.02 (1.00, 1.03)**	**0.99 (0.99, 0.99)**	1.00 (0.99, 1.02)	0.99 (0.99, 0.99)	**1.01 (0.99, 1.02)**	**0.99 (0.99, 0.99)**
Perinatal Mortality	1.16 (0.82, 1.65)	0.97 (0.94, 1.00)	1.14 (0.81, 1.62)	0.96 (0.93, 0.99)	1.15 (0.81, 1.62)	0.97 (0.93, 1.00)	1.14 (0.80, 1.62)	0.95 (0.91, 1.00)

Models adjusted for maternal age, maternal race/ethnicity, preconception body mass index, health insurance, marital status, smoking in pregnancy, alcohol use in pregnancy, other chronic diseases, and census region. **Bold** indicates statistically significant interaction (p<.10) between air pollution and type 1 diabetes status.