



ENVIRONMENTAL HEALTH PERSPECTIVES

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<http://dx.doi.org/10.1289/ehp.1408456>

Received: 21 March 2014

Accepted: 17 March 2015

Advance Publication: 20 March 2015

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Association of Atmospheric Particulate Matter and Ozone with Gestational Diabetes Mellitus

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Running head: Air pollution and gestational diabetes

Acknowledgments: This work was supported by Grant Number K01ES019177 from the National Institute of Environmental Health Sciences (NIEHS). The data were provided by the Bureau of Vital Statistics, Florida Department of Health (DOH). All conclusions are the authors' own and do not necessarily reflect the opinion of the NIEHS or the Florida DOH.

Competing financial interests: The authors disclose that they have no actual or potential competing financial interests.

Abstract

Background: Ambient air pollution has been linked to the development of gestational diabetes mellitus (GDM). However, evidence of the association is very limited, and no study has estimated the effects of ozone.

Methods: We used Florida birth vital statistics records to investigate the association between the risk of GDM and two air pollutants ($PM_{2.5}$ and O_3) among 410,267 women who gave birth in Florida between 2004 and 2005. Individual air pollution exposure was assessed at women's home address at time of delivery using the Hierarchical Bayesian space-time statistical model. We further estimated associations between air pollution exposures during different trimesters and GDM.

Results: After controlling for nine covariates, increased odds of GDM with per $5 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ ($OR_{\text{Trimester1}}=1.16$; 95% CI: 1.11, 1.21; $OR_{\text{Trimester2}}=1.15$; 95% CI: 1.10, 1.20; $OR_{\text{Pregnancy}}=1.20$; 95% CI: 1.13, 1.26) and per 5 ppb increase in O_3 ($OR_{\text{Trimester1}}=1.09$; 95% CI: 1.07, 1.11; $OR_{\text{Trimester2}}=1.12$; 95% CI: 1.10, 1.14; $OR_{\text{Pregnancy}}=1.18$; 95% CI: 1.15, 1.21) were observed during both the first trimester and second trimester as well as the full pregnancy in single-pollutant models. Comparing to the single-pollutant model, the ORs for O_3 were almost identical in the co-pollutant model. However, the ORs for $PM_{2.5}$ during the first trimester and the full pregnancy attenuated, and no association was observed for $PM_{2.5}$ during the second trimester in the co-pollutant model ($OR=1.02$; 95% CI: 0.98, 1.07).

Conclusion: This population-based study suggests that exposure to air pollution during pregnancy is associated with increased risk of GDM in Florida, USA.

Introduction

Gestational diabetes mellitus (GDM) is a common complication during pregnancy. It is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (American Diabetes Association 2013). GDM complicates up to 14% of all pregnancies depending on the populations observed. More than 200,000 cases were reported annually in the United States (American Diabetes Association 2013). GDM has adverse effects on both the mother and the developing fetus. About one-third of women with GDM will eventually develop type 2 diabetes (Linné et al. 2002), and women with GDM also have higher long-term risks of cardiovascular diseases compared to those without GDM (Kitzmilller et al. 2007). In children, GDM has been associated with both perinatal and long-term adverse health outcomes such as macrosomia (Hughes et al. 1997), shoulder dystocia (Athukorala et al. 2007), birth injuries (Mitanchez 2010), sustained glucose tolerance impairment (Silverman et al. 1995), obesity (Pettitt et al. 1985), and impaired intellectual abilities (Rizzo et al. 1997). GDM has also been associated with metabolic disturbances in offspring of mothers with GDM (Boerschmann et al. 2010; Clausen et al. 2008; Lawlor et al. 2011), and the prevalence of type-2 diabetes or pre-diabetes at 18–27 years of age was almost eight times higher among offspring of women with GDM compared with other children in a case-control study (Clausen et al. 2008). Although previous studies have shown that treatment of GDM can reduce serious perinatal morbidity such as macrosomia at birth (Crowther et al. 2005), a recent study found no significant difference in BMI Z-scores or BMI \geq 85th percentile in children at 4–5 years of age whose mothers were treated for GDM (n = 94) compared with children whose mothers had GDM but received only routine care (n = 105) (Gillman et al. 2010). However, the sample size of this study was relatively small and may be underpowered.

Despite great improvements in air quality following the Clean Air Act (1963), air pollution remains a significant public health problem in the United States. According to the State of the Air 2013 report by the American Lung Association, 41% of the population in the United States still lives in counties that have unhealthy levels of air pollution (American Lung Association 2013). Evidence on the effects of air pollution on diabetes mellitus in the general population has been reported in several recent epidemiological studies. A study of the Danish Diet, Cancer and Health cohort reported that traffic-related air pollution, using NO₂ as a proxy, was associated with higher mortality from diabetes (Raaschou-Nielsen et al. 2013). Two studies in North America reported positive associations of NO₂ and PM_{2.5} with the prevalence of diabetes (Brook et al. 2008; Pearson et al. 2010). In addition, positive associations have been found between air pollution and insulin resistance, the pathological hallmark underlying diabetes (Andersen et al. 2012; Chuang et al. 2011; Coogan et al. 2012; Kelishadi et al. 2009; Kim and Hong 2012; Kramer et al. 2010; Puett et al. 2011; Sun et al. 2013).

Although the biological mechanisms leading to GDM are still unclear, it is plausible that air pollution during pregnancy may increase the risk of GDM by inducing oxidative stress, and consequently inflammation, insulin resistance, dyslipidemia, and systemic metabolic dysfunction (Andersen et al. 2012; Chuang et al. 2011; Coogan et al. 2012; Everett et al. 2010; Hotamisligil et al. 1993; Kelishadi et al. 2009; Kim and Hong 2012; Kramer et al. 2010; Lamb and Goldstein 2008; Puett et al. 2011; Sun et al. 2006; Sun et al. 2013). While evidence of adverse effects of air pollution on birth defects and pregnancy complications such as gestational hypertension has been widely reported in the last decade (Šrám et al. 2005; Xu et al. 2014), studies focusing on the association between ambient air pollution and GDM are still very limited. To our knowledge, only three previous studies have investigated air pollution and GDM. Malmqvist et al. reported a

positive association between NO_x exposure and GDM (Malmqvist et al. 2013), while an earlier study reported no association (van den Hooven et al. 2009). A recent study found that exposure to PM_{2.5} and other traffic-related pollutants during pregnancy has been associated with impaired glucose tolerance, but not GDM in women from Boston, USA (Fleisch et al. 2014). Given the inconclusive results and limited types of pollutants examined in previous studies, investigation of the association between GDM and other criteria air pollutants such as ozone (O₃) is warranted. In this study, we analyzed Florida birth vital statistics records comprising 410,267 women who gave birth during 2004-2005, to examine the association between the risk of GDM and two ambient air pollutants, PM_{2.5} and O₃, assessed using the Hierarchical Bayesian space-time statistical model (HBM) developed by the US EPA and CDC's National Environmental Public Health Tracking Network (U.S. EPA 2014). We also investigated whether associations between exposure to air pollution and GDM varied among different gestational periods (trimesters and full pregnancy).

Materials and Methods

Study population

We obtained birth record data from the Bureau of Vital Statistics & Office of Health Statistics and Assessment, Florida Department of Health (Jacksonville, Florida, <http://www.floridahealth.gov/certificates/certificates/>). The data included all registered live births in Florida, USA between January 1, 2004 and December 31, 2005 (n=445,028). Births with maternal residential addresses outside Florida (n=4,672) were excluded. We used ArcGIS V10.1 software (ESRI, Redlands, California, USA) to geocode the mother's residential address at birth, and 439,370 cases (99.8%) were successfully geocoded. Cases whose maternal residential address could not be geocoded were excluded (n=986). We further excluded 937 cases because

of missing values related to gestational age. In addition, we excluded women who had non-singleton deliveries (n=13,367), previous preterm births (n=5,591), or prepregnancy diabetes mellitus (n=2,821). Births with congenital abnormalities (n=5,450), with a birthweight <400 g (n=240), or with a gestational age <24 or >42 weeks (n=697) were also excluded. Following these exclusion criteria a total of 410,267 women remained in the study population. The research protocol for this study was approved by the Institutional Review Board at the University of Florida and the Florida Department of Health. The study was exempt from informed consent requirements since it involves no more than a minimal risk to the privacy of individuals and the research could not practicably be conducted without this exemption.

Outcome assessment

All pregnant women are requested to screen for GDM through an oral glucose challenge test (OGCT) between the 24th and 28th weeks of the pregnancy in Florida. This test requires each pregnant woman to drink about 5 ounce of a syrupy glucose solution that contains 50 grams of sugar and then have her blood drawn an hour after drinking the solution. If a blood glucose level reaches above 140 mg/dL 1 hour after the OGCT, it indicates the possibility of GDM. Then, the pregnant woman is further referred to another 3-hour fasting 100-g oral glucose tolerance test (OGTT). The test measures fasting blood glucose level and blood glucose levels at one, two and three hours after drinking the solution. The following values are considered to be abnormal during the OGTT: Fast blood glucose level ≥ 95 mg/dl, 1 hour blood glucose ≥ 180 mg/dl, 2 hour blood glucose ≥ 155 mg/dl and 3 hour blood glucose ≥ 140 mg/dl. Pregnant women are classified as having GDM if two abnormal values are recorded during the OGTT (American Diabetes Association 2003).

Air pollution exposure assessment

Air pollution exposure data was obtained from the EPA and CDC's National Environmental Public Health Tracking Network (2003-2005) (U.S. EPA 2014). The US EPA provided the hierarchical Bayesian space-time statistical modeling (HBM) data from 2001-2008 for two air pollutants, PM_{2.5} and O₃ with spatial resolutions of 12km×12km and 36km×36km across the continental areas in US. Daily air pollution concentration for each grid was also included. Compared to the widely-used air monitoring data from EPA's Air Quality System (AQS, <http://www.epa.gov/airquality/airdata>), the HBM data could provide pollutant values at unobserved locations across the entire spatial field of interest. The EPA has used two important advanced methods, the Community Multiscale Air Quality (CMAQ) model, and the Hierarchical Bayesian space-time statistical model (HBM) (McMillan et al. 2010), to produce the interpolated concentrations of air pollutants in space and time. The HBM approach combines the AQS monitoring data with CMAQ modeled data, which includes emission, meteorology, and chemical modeling components, to predict air quality data for a specific time and spatial scale (McMillan et al. 2010). Given the limited and sparsely located air monitors in Florida, we decided to use the 12km grid output from the HBM data which can account for the poor spatial coverage of air monitoring data.

Each mother's geocoded residential address at the time of their child's birth was spatially linked to the corresponding grid of the HBM data. Exposures were calculated as daily concentrations averaged over each of the first two trimesters (trimester 1: 1-13 weeks and trimester 2: 14-26 weeks) and the full gestational period determined by gestational age and delivery date of each woman. Gestational age was mainly determined by ultrasound. When ultrasound data was not available, clinical examination or last menstrual period was used to estimate gestational age.

Covariates

Information on maternal characteristics such as age, race/ethnicity, marital status, pregnancy smoking status, season and year of conception, and prenatal care status were obtained directly from the births records. Maternal age at delivery was categorized into six groups, with 5-year increments for women aged 20-40 years old as well as two additional groups for <20 and \geq 40 years old. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Mexican American, Puerto Rican, Cuban American, Haitian American, and others. In addition, a dichotomous variable was used to indicate marital status. Maternal education was divided into three categories: <high school, high school or equivalent, and >high school. Pregnancy smoking status was categorized into three levels based on self-reported number of cigarettes smoked per day during pregnancy: non-smokers, smokers with <10 cigarettes/day, and smokers with \geq 10 cigarettes/day. Season [warm (June-November) or cool (December-May)] and year (2003, 2004, or 2005) of conception were also treated as categorical variables. Prenatal care status was categorized into five groups: no care, began in first trimester, second trimester, or third trimester, as well as an additional group for subjects with missing values. Furthermore, we extracted census block group level median household income from the 2000 Census, and linked it to each woman. Household income was categorized into quartiles (<US\$29,663, US\$29,663-US\$38,056, US\$ 38,056-US\$49,375, and \geq US\$49,375). We also obtained cartographic boundary file for urban areas from the 2000 Census to determine the urbanization status (urban or rural) where each woman lived. No information was available on other risk factors for GDM such as maternal pre-pregnancy BMI, family history of type 2 diabetes, and low physical activity.

Statistical analysis

Distribution of categorical covariates and continuous exposures between women with GDM and those without GDM were examined. Logistic regression models were used to investigate the association between exposure to air pollution during different trimesters of pregnancy and risks of GDM. Subjects with missing values of maternal age (n=45), race/ethnicity (n=6), education (n=3,821), marital status (n=83) were excluded, leaving 13,943 women with GDM out of a total of 406,334 women with complete covariate data. PM_{2.5} and O₃ were analyzed as continuous variables. Both an unadjusted model and an adjusted model controlling for maternal age, race/ethnicity, education, marital status, prenatal care, season and year of conception, urbanization, and median household income at census block group level were used. ORs and 95% CI (per 5 µg/m³ increase in PM_{2.5} or per 5 ppb increase in O₃) were reported for each pollutant during specific pregnancy periods. Co-pollutant logistic models were also implemented to evaluate potential confounding by co-pollutants.

Sensitivity analyses: We conducted several sensitivity analyses to test the robustness of our results. Firstly, to account for the potential bias created by using an indicator for missing data of prenatal care, multiple imputation was conducted for all missing data using chained equations (White et al. 2011). All covariates as well as exposure and outcome variables were included in the imputation process, and 50 imputed datasets were generated. Secondly, to account for the potential underdiagnoses of GDM, an underreported rate of 0.5% and 1.0% was assumed among women without GDM, and simulated datasets were generated by randomly assigning 0.5% and 1.0% of subjects without GDM as GDM cases with 500 repeats using the Monte Carlo method. Then, we made the comparisons between the results from the simulated data and our original results to check whether the underdiagnosed cases have influenced the observed effects. Thirdly,

to account for the potential misclassification of exposure, we performed two sets of sensitivity analyses. In the first set of capture-area analyses, only women living within 5 miles from any AQS monitors were included, and two separated analyses were conducted for all eligible women and only for eligible women with non-missing data for at least 75% of days. In the second set of analyses, we used interpolated 1km×1km data for the exposure assessment. To create the 1km×1km exposure field, we applied a bicubic spline to the 12km×12km gridded HBM product and output on a 1km×1km grid that included the original 12km vertices. This approach provides finer resolution, but cannot reproduce sub-12km concentration peaks or troughs. Fourthly, we performed the analyses without adjusting for season of conception to account for the possibility that conception season may adjust away all seasonal influences on the variation in the pollutants such that only spatial differences were left, which might be much more easily confounded by SES related factors. We also performed the analyses after additionally adjusting for smoking during pregnancy. Finally, to account for the potential over adjusting of urbanization due to its correlation with air pollutants, we performed a stratified analyses by urban-rural areas. All statistical analyses were conducted using SAS V9.3 (Cary, North Carolina, USA).

Results

Of the 410,267 women included in this study, 14,032 (3.4%) had GDM, including 406,334 with complete data for all covariates (n = 13,943 with GDM). Table 1 shows the distribution of exposures to PM_{2.5} and O₃ for each pregnancy period analyzed in this study. Women with GDM had slightly higher levels of PM_{2.5} and O₃ exposure compared to those without GDM during all pregnancy periods (all p<0.001). Weak correlations were observed between PM_{2.5} and O₃ in all gestational periods (Pearson's correlation coefficient range from 0.21 to 0.39).

Table 2 shows the demographic characteristics of women by GDM status. Women with GDM were older and less likely to belong to non-Hispanic Black racial/ethnic categories. Higher proportions of women with GDM were married and had higher education and income levels. GDM cases were more likely to be observed among women who started prenatal care early and whose conception began in the warm season or recent years.

Table 3 provides the unadjusted and adjusted ORs of single-pollutant logistic regression models predicting GDM from exposure to PM_{2.5} and O₃ during different pregnancy periods. After controlling for all nine covariates, increased odds of GDM for per 5 µg/m³ increase in PM_{2.5} were observed during both the first and second trimesters (OR_{Trimester1}=1.16; 95% CI: 1.11, 1.21; OR_{Trimester2}=1.15; 95% CI: 1.10, 1.20) and the full pregnancy (OR=1.20; 95% CI: 1.13, 1.26). Associations were also found between GDM and O₃. The odds of GDM were higher for per 5 ppb increase in exposure to O₃ during the first and second trimesters (OR_{Trimester1}=1.09; 95% CI: 1.07, 1.11; OR_{Trimester2}=1.12; 95% CI: 1.10, 1.14), and over the course of the entire pregnancy (OR=1.18; 95% CI: 1.15, 1.21).

The results from the sensitivity analyses were presented in the Supplemental Materials. Specifically, multiple imputation was conducted in the first set of sensitivity analyses to assess the potential effects of missing data on the results, and we observed ORs almost identical to the original results (see Supplemental Materials, Table S1). Secondly, Monte Carlo method was used to generate two sets of simulated datasets assuming the underreported rate of GDM was 0.5% and 1.0%. Compared to the original results, the ORs from the simulated datasets slightly attenuated, but the conclusions remain consistent (see Supplemental Material, Table S2). Thirdly, we examined the effects of potential misclassifications of exposure on the results separately using capture-area analyses and the interpolated 1km×1km HBM data. Compared to the original

results, we observed comparable ORs for O₃ during the second trimester and PM_{2.5} during the second trimester and full pregnancy period in the capture-area analyses. However, attenuated ORs were observed for O₃ during the first trimester and the full pregnancy period, and no significant association was found for PM_{2.5} in the first trimester. On the other hand, the results from the interpolated HBM in the 1km×1km resolution showed consistent ORs with the original results (see Supplemental Material, Table S3). Fourthly, we assessed whether adjusting for smoking during pregnancy may bias the findings, and we observed consistent ORs with the original results. We also analyzed the data without adjusting for season of conception, and consistent results were observed except for the slightly attenuated OR for O₃ in the first trimester (see Supplemental Material, Table S4). Lastly, a stratified analyses by urbanization was performed to examine the potential over adjustment of it, and no statistically difference was observed between the non-stratified results and the stratified results (see Supplemental Material, Table S5).

The results of the co-pollutant models are provided in Supplemental Material, Table S6. Figure 1 compares the results obtained from single- and co-pollutant continuous models. The ORs for O₃ after adjusting for PM_{2.5} were almost identical to the ORs from the single pollutant model. However, the ORs for PM_{2.5} during the first trimester and the full pregnancy attenuated after adjusting for O₃, and no association was observed for PM_{2.5} during the second trimester in the co-pollutant model (OR=1.02; 95% CI: 0.98, 1.07 compared with OR=1.15; 95% CI: 1.10, 1.20 from the single pollutant model).

Discussion

We examined the association of GDM with PM_{2.5} and O₃ during different pregnancy periods using Florida birth vital statistics records and the EPA and CDC's HBM air pollution data which

has both good spatial and temporal coverage. When assessed in single-pollutant models, GDM was significantly associated with per 5-unit increases in both PM_{2.5} and O₃ during the first and second trimesters and the full pregnancy. The associations were also found in co-pollutant models for PM_{2.5} exposure during first trimester and O₃ exposure during all pregnancy periods we examined. The associations persisted with adjustment for confounding by maternal characteristics such as age, race/ethnicity, education, marital status, prenatal care, season and year of conception, urbanization, and median household income at census block group level. The results of this study add to the emerging evidence linking air pollution exposure during pregnancy to pregnancy complications such as GDM.

The causal mechanisms underlying the associations between air pollution and GDM are still unclear; however, the results observed in this study are consistent with several potential pathways suggested by previous studies. Ambient air pollutants such as PM and O₃ have been reported to be associated with increased insulin resistance, dyslipidemia, and systemic metabolic dysfunction (Andersen et al. 2012; Chuang et al. 2011; Coogan et al. 2012; Kelishadi et al. 2009; Kim and Hong 2012; Kramer et al. 2010; Puett et al. 2011; Sun et al. 2013), which are all precursors associated with GDM. PM contains many toxic chemicals that are regarded as reactive oxygen species (ROS) (Lemaire and Livingstone 1997; Sun et al. 2006), which can cause oxidative damage on target tissues (Ames et al. 1993). The imbalance between the production of ROS and antioxidant defenses is acknowledged as one of the main causes of insulin signaling pathways alternations (Lamb and Goldstein 2008), and a number of studies have linked ROS to insulin resistance (Goldstein et al. 2005; Schulz et al. 2007). In addition, a recent animal study also showed O₃'s ability to induce glucose intolerance and systemic metabolic effects (Bass et al. 2013). In their study on young and aged brown Norway rats, Bass

et al. observed increased α_2 -macroglobulin, adiponectin and osteopontin as well as decreased phosphorylated insulin receptor substrate-1 in liver and adipose tissues following acute O_3 exposure. Endoplasmic reticular stress was suggested to be the consequence of O_3 induced acute metabolic impairment. Furthermore, another potential pathway induced by air pollution is inflammation, which may also lead to the development of insulin resistance (Everett et al. 2010; Hotamisligil et al. 1993).

Cigarette smoking has been widely reported to be associated with type 2 diabetes (Willi et al. 2007; Zhu et al. 2014), and we initially considered it as a potential confounder in our analyses. However, given the fact that smoking is not generally considered a risk factor for GDM as well as the consistent results we observed with or without adjusting for it in the sensitivity analyses, we finally present results without adjusting for smoking. In addition, although the underlying mechanisms remain unknown, our findings that air pollution may have an impact on risk of GDM does not conflict with the null association between smoking and GDM since their toxic components are largely different.

Our study has several strengths. First, compared to the air monitoring data that have been widely used in other studies, the daily temporal resolution and the 12km \times 12km spatial resolution of HBM air pollution data used in this study allowed us to estimate mean air pollution concentrations during different pregnancy periods without excluding subjects not covered by air monitors, thus reducing the potential for selection bias. Second, previous studies focused only on small areas and examined limited types of air pollutants. With the HBM air pollution data, we are able to include all pregnant women in the study period throughout the entire state of Florida and investigate the association between GDM and two common air pollutants, $PM_{2.5}$ and O_3 , which have not been reported in the extant literature. Furthermore, we used both single- and co-

pollutant models to examine the association between air pollution and GDM. The robust results of O₃ observed from different models suggest that it may have effects on GDM independent of PM_{2.5}. This finding is consistent with recent experimental studies (Bass et al. 2013). It is also consistent with the positive association found between NO_x and GDM (Malmqvist et al. 2013) since NO_x is one main precursor of O₃ (Sillman 1999). Finally, the robust results from the sensitivity analyses suggested that the study was not likely to be largely biased by the missing data, exposure and outcome misclassifications, and under-adjustment of smoking during pregnancy or over-adjustments of season of conception and urbanization.

This study had several limitations. First, it is possible that GDM may be underdiagnosed in the source vital statistics records. Second, as reported by American Diabetes Association, more women of childbearing age have type 2 diabetes due to an epidemic of obesity and diabetes in recent years (American Diabetes Association 2013). This trend may result in an increase in the number of women with undiagnosed type 2 diabetes, leading to potential misclassification of GDM in this study. However, since our study period covered the years 2003-2005, our results are less likely to be biased by the effects of undiagnosed diabetes in recent years. Third, information on daily mobility and behavior patterns were not available for this study. The absence of these factors may introduce misclassifications of exposure. A high correlation between personal monitored air pollution measurement and monthly-aggregated modeled air pollution measurement has been reported in a cohort of 85 pregnant women in Manchester and Blackpool, UK (Hannam et al. 2013), although we cannot assess its comparability to our study due to the lack of daily mobility data. Fourth, residential mobility during pregnancy was also not available in this study. It may be possible that some subjects in this study lived elsewhere in the early stage of their pregnancy and thus were exposed to different levels of air pollution. Fifth, although the

use of HBM air pollution data can avoid selection bias, the 12km×12km resolution is very crude. While the spatial variability of O₃ is low, the variability of PM_{2.5} may be a concern, which includes a large-scale regional component and a local source component. Isakov et al (2012) suggested that the regional component provides most of the mass, going as far as to use PM_{2.5} as an example of spatially homogenous pollutants. Therefore, exposure to PM_{2.5} is not likely to have extremely fine-scale variability in most places in Florida. In addition, highly variable exposure fields would also be inappropriate for use with residential address only. However, future studies with higher spatial resolution modelling data and detailed time-activity patterns are warranted. Sixth, although several important confounders have been included in this study, no information on other risk factors for GDM such as pre-pregnancy BMI, family history of type-2 diabetes, and physical activity was available. These unadjusted factors may influence the results. For example, if obese women are more likely to live in areas with higher air pollution, the observed effects of air pollution on GDM in this study may be overestimated without controlling for this factor. In addition, low population densities, poor street connectivity and lack of sidewalks in rural areas have been linked to increased physical inactivity and obesity (Eberhardt and Pamuk 2004), which are also characterized by having higher O₃ concentrations. Although we adjusted for urbanization in this study, residual confounding may still exist. Thus, future studies with more detailed information on these factors were warranted to confirm our findings. Another potential limitation of the study is the unavailability of traffic noise data. Traffic noise induces a stress response and disturbs sleep, which has been associated with higher levels of stress hormone and decreased insulin levels and sensitivity (Sørensen et al. 2013). Both maternal stress and/or disturbances of sleep during pregnancy increase the risk of GDM. Since road traffic is the main source for both air pollution with PM_{2.5} and noise in urban areas, the mutual

confounding is a concern. Finally, the results observed in birth registry data may also be influenced by the fixed cohort bias (Strand et al. 2011). Fixed cohort bias is a type of selection bias which could happen in retrospective cohorts with a fixed start and end date when short pregnancies are missed at the start of the study, and longer pregnancies are missed at the end. As GDM is linked to preterm birth, fixed cohort bias may exist if GDM cases are more likely to be excluded at the beginning and to be included at the end of the study. However, given the facts that fixed cohort bias tend to decrease when the study has longer study period and/or when it has day and month of the start date (i.e. January 1st, 2004) just before day and month of the end date (i.e. December 31st, 2005), the potential for this bias was reduced in this study.

Conclusion

Using Florida birth vital statistics records, we observed a positive association between increased prevalence of GDM and exposure to PM_{2.5} and O₃ during each trimester of pregnancy and the full pregnancy among women giving birth in 2004 and 2005. This study suggests the need for greater attention on stronger air pollution controls to improve the health of pregnant women and their offspring.

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Table 1. Exposure information concerning PM_{2.5} and O₃ by gestational diabetes mellitus (GDM) status among women who gave birth from 2004 to 2005 in Florida, USA (n=14,032 with GDM, n=396,235 without GDM, and total n=410,267).

Exposure	Statistics	Trimester 1			Trimester 2			Full Pregnancy		
		GDM	No GDM	Total	GDM	No GDM	Total	GDM	No GDM	Total
PM _{2.5} (µg/m ³)										
	Mean±SD	9.84±2.16	9.72±2.07	9.73±2.07	9.94±2.09	9.88±2.06	9.88±2.06	10.03±1.71	9.93±1.67	9.93±1.67
	Median	9.75	9.64	9.65	9.87	9.76	9.76	9.97	9.90	9.91
	IQR	2.68	2.61	2.61	2.63	2.61	2.61	2.06	2.02	2.02
O ₃ (ppb)										
	Mean±SD	37.71±6.14	37.20±6.04	37.22±6.04	38.17±6.10	37.52±6.10	37.54±6.10	37.85±4.01	37.38±4.10	37.40±4.10
	Median	36.73	36.48	36.48	37.65	36.92	36.95	38.40	37.82	37.84
	IQR	8.24	7.82	7.83	8.46	7.99	8.00	6.94	7.10	7.09
Correlation between PM _{2.5} and O ₃		0.39	0.39	0.39	0.35	0.34	0.34	0.21	0.22	0.22

Table 2. Maternal characteristics by gestational diabetes mellitus (GDM) status among women who gave birth from 2004 to 2005 in Florida, USA.

Maternal Characteristics		GDM (n=14,032) n (%)	No GDM (n=396,235) n (%)	Total (n=410,267) n (%)
Maternal age (years)				
	<20	451(3.2)	44,064(11.1)	44,515(10.9)
	20-24	2,125(15.1)	103,600(26.2)	105,725(25.8)
	25-29	3,466(24.7)	103,679(26.2)	107,145(26.1)
	30-34	4,265(30.4)	87,758(22.2)	92,023(22.4)
	35-39	2,844(20.3)	44,608(11.3)	47,452(11.6)
	≥40	880(6.3)	12,482(3.2)	13,362(3.3)
	Missing	1(0.0)	44(0.0)	45(0.0)
Race/ethnicity				
	Non-Hispanic White	6,674(47.6)	188,029(47.5)	194,703(47.5)
	Non-Hispanic Black	2,041(14.6)	70,355(17.8)	72,396(17.7)
	Mexican American	1,253(8.9)	28,370(7.2)	29,623(7.2)
	Puerto Rican	634(4.5)	18,831(4.8)	19,465(4.7)
	Cuban American	590(4.2)	20,123(5.1)	20,713(5.1)
	Haitian American	541(3.9)	12,573(3.2)	13,114(3.2)
	Others	2,299(16.4)	57,948(14.6)	60,247(14.7)
	Missing	0(0.0)	6(0.0)	6(0.0)
Maternal education				
	<High school	2,524(18.0)	83,066(21.0)	85,590(20.9)
	High school or equivalent	4,207(30.0)	126,013(31.8)	130,220(31.7)
	>High school	7,213(51.4)	183,423(46.3)	190,636(46.5)
	Missing	88(0.6)	3,733(0.9)	3,821(0.9)
Marital status				
	Married	9,697(69.1)	232,727(58.7)	242,424(59.1)
	Not married	4,335(30.9)	163,425(41.2)	167,760(40.9)
	Missing	0(0.0)	83(0.0)	83(0.0)
Smoking during pregnancy				
	No	12,769(91.0)	360,016(90.9)	37,2785(90.9)
	Yes, and <10 cigarettes/day	483(3.4)	14,163(3.6)	14,646(3.6)
	Yes, and ≥10 cigarettes/day	581(4.1)	16,852(4.3)	17,433(4.3)
	Missing	199(1.4)	5,204(1.3)	5403(1.3)
Season of conception				
	Warm	6,942(49.5)	192,430(48.6)	199,372(48.6)
	Cool	7,090(50.5)	203,805(51.4)	210,895(51.4)
Year of conception				
	2003	4,131(29.4)	142,945(36.1)	147,076(35.9)
	2004	7,479(53.3)	199,682(50.4)	207,161(50.5)
	2005	2,422(17.3)	53,608(13.5)	56,030(13.7)
Prenatal care began				
	No care	59(0.4)	4,987(1.3)	5,046(1.2)
	First trimester	7,698(54.9)	188,869(47.7)	196,567(47.9)
	Second trimester	2,022(14.4)	57,504(14.5)	59,526(14.5)
	Third trimester	570(4.1)	14,115(3.6)	14,685(3.6)
	Missing	3,683(26.3)	130,760(33.0)	134,443(32.8)
Urbanization of Residential Area				
	Urban	12,017(85.6)	342,936(86.6)	354,953(86.5)
	Rural	2,015(14.4)	53,299(13.5)	55,314(13.5)
Median household income (US \$)				
	<29,663	3,326(23.7)	99,224(25.0)	102,550(25.0)
	29,663-38,056	3,494(24.9)	99,047(25.0)	102,541(25.0)
	38,056-49,375	3,648(26.0)	98,825(24.9)	102,473(25.0)
	≥49,375	3,564(25.4)	99,139(25.0)	102,703(25.0)

Table 3. ORs for risk of gestational diabetes mellitus (GDM) by air pollutants (PM_{2.5} and O₃) and pregnancy period of exposure among women who gave birth from 2004 to 2005 in Florida, USA.

Exposure	n (GDM/Total)	Unadjusted OR (95% CI)	n (GDM/Total)^a	Adjusted OR^b (95% CI)
PM _{2.5} (per 5 µg/m ³)				
Trimester 1	14,032/410,267	1.15(1.10, 1.19)	13,943/406,334	1.16(1.11, 1.21)
Trimester 2	14,032/410,267	1.08(1.04, 1.12)	13,943/406,334	1.15(1.10, 1.20)
Full pregnancy	14,032/410,267	1.19(1.13, 1.25)	13,943/406,334	1.20(1.13, 1.26)
O ₃ (per 5 ppb)				
Trimester 1	14,032/410,267	1.07(1.06, 1.09)	13,943/406,334	1.09(1.07, 1.11)
Trimester 2	14,032/410,267	1.09(1.08, 1.10)	13,943/406,334	1.12(1.10, 1.14)
Full pregnancy	14,032/410,267	1.16(1.13, 1.18)	13,943/406,334	1.18(1.15, 1.21)

^aWomen with complete data for all covariates. ^bAdjusted for maternal age, race, education, marital status, season of conception, year of conception, prenatal care began, urbanization, and median household income.

Figure legend

Figure 1. Adjusted log(OR) for risk of gestational diabetes mellitus with per 5 units increase in gestational exposure to pollutant for single- and co-pollutant models among women who gave birth from 2004 to 2005 in Florida, USA. The diamond reflects the central estimate; the horizontal line represents the 95% CI.

Figure 1.

