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Associations of Gestational Diabetes Mellitus with Residential Air pollution Exposure in a Large Southern California Pregnancy Cohort

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Abstract

Background: Studies of effects of air pollution on gestational diabetes mellitus (GDM) have not been consistent, and there has been little investigation of effects of exposure preceding pregnancy. In previous studies, the temporal relationship between exposure and GDM onset has been difficult to establish.

Methods: Data were obtained for 239,574 pregnancies between 1999 and 2009 in a population-based health care system with comprehensive electronic medical records. Concentrations of

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Authors' contributions

AHX and RM served as co-senior authors on this study based on equal contributions and expertise in air pollution epidemiology (RM) and in the analytical approaches in this data set (AHX). HJ, AHX and RM designed the study and drafted the manuscript. HJ analyzed the data with contributions from SPE and AHX. All authors contributed to the interpretation of data, read and approved the final manuscript.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of University of Southern California and Kaiser Permanente Southern California. Consent to participate is not applicable since the study was based on de-identified electronic medical records data.

Availability of data and materials

The data that support the findings of this study are available from Kaiser Permanente Southern California but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of Kaiser Permanente Southern California.

Competing interests

The authors declare that they have no competing interests.

ambient nitrogen dioxide (NO_2), particulate matter (PM) ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$) and ≤10 μm (PM_{10}, and ozone (O_3) during preconception and the first trimester of pregnancy at the residential birth address were estimated from regulatory air monitoring stations. Odds ratios (ORs) of GDM diagnosed in the second and third trimesters in association with pollutant exposure were estimated using generalized estimating equation models adjusted for birth year, medical center service areas, maternal age, race/ethnicity, education, census-tract household income, and parity.

Results: In single-pollutant models, preconception NO_2 was associated with increased risk of GDM (OR = 1.10 per 10.4 ppb, 95% confidence interval [CI]: 1.07, 1.13). First trimester NO_2 was weakly associated with GDM, and this was not statistically significant (OR = 1.02 per 10.4 ppb, 95% CI: 0.99, 1.05). Preconception NO_2associations were robust in multi-pollutant models adjusted for first trimester NO_2 with another co-pollutant from both exposure windows. In single-pollutant models, preconception $PM_{2.5}$ and PM_{10} associations were associated with increased risk of GDM (OR = 1.04 per 6.5 μg/m^3, 95% CI: 1.01, 1.06; OR = 1.03 per 16.1 μg/m^3, 95% CI: 1.00, 1.06, respectively), but these effect estimates were not robust to adjustment for other pollutants. In single-pollutant models, preconception and first trimester O_3 were associated with reduced risk of GDM (OR = 0.94 per 15.7 ppb, 95% CI: 0.92, 0.95; OR = 0.95 per 15.7 ppb, 95% CI: 0.94, 0.97), associations that were robust to adjustment for co-pollutants.

Conclusions: Maternal exposure to NO_2 during the preconception trimester may increase risk of GDM.

Keywords

Air pollution; gestational diabetes mellitus; preconception; pregnancy

Introduction

Rates of diabetes, including gestational diabetes mellitus (GDM), among women of reproductive age increased during years 2000–2010 from 3.71 to 5.77 per 100 deliveries in the United States (Bardenheier et al. 2015). Pregnancy is a vulnerable period when women are naturally in an insulin-resistant state (American Diabetes Association 2004). Emerging evidence indicates the period before pregnancy may also be a critical time-window during which reducing harmful exposures may prevent subsequent GDM (Lassi et al. 2014). Preconception health care focused on improving lifestyle choices (e.g. diet, folic acid supplement, weight loss) and reducing adverse risk factors before pregnancy among women of reproductive age has been shown to prevent pregnancy and delivery complications, such as GDM, and adverse birth outcomes (Johnson et al. 2006). However, there has been limited study of effects of environmental exposures during the preconception period on risk of GDM.

Recent epidemiological studies have found associations of air pollution with type 2 diabetes, insulin resistance and glucose homeostasis and diabetes-related mortality in adults (Chen et al. 2016; Eze et al. 2015; Thiering and Heinrich 2015). There has been limited study of effects of maternal exposure to air pollution on the development of GDM, and results have not been consistent (Baio 2014; Choe et al. 2018; Fleisch et al. 2014; Fleisch et al. 2016; Hu

et al. 2015; Malmqvist et al. 2013; Padula et al. 2018; Pedersen et al. 2017; Robledo et al. 2015; Shen et al. 2017; van den Hooven et al. 2009; Yorifuji et al. 2015). A few studies have found that increased risk of GDM was associated with nitrogen oxides (NO_x), including NO (Malmqvist et al. 2013; Pan et al. 2017; Robledo et al. 2015), particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$) (Choe et al. 2018; Fleisch et al. 2016; Hu et al. 2015; Padula et al. 2018; Shen et al. 2017), and PM <10 μm (PM_{10}) (Padula et al. 2018). Key uncertainties in previous studies include lack of accurate information on the date of GDM diagnosis; thus, it was not possible to determine if exposure preceded the development of GDM. Moreover, previous studies have generally not mutually adjusted exposure associations for other pollutants or for different windows of exposure (e.g. preconception and first trimester exposures). To date, only two studies have examined effects of preconception exposures (Robledo et al. 2015; Shen et al. 2017). These two studies assigned exposure to either the delivery hospital region or to city/township, rather than to the mother's residence.

To address gaps in our understanding of effects of air pollution on GDM, we investigated the association between maternal residential exposure to regional air pollution and the timing of development of GDM during pregnancy in a large population-based pregnancy cohort based on comprehensive electronic medical records (EMR) data. We aimed to establish clear temporal relationships by assessing pollutant exposures during preconception and during the first trimester and examining associations with subsequent development of GDM.

Methods

Study design and population

This population-based retrospective cohort study included women who gave birth to singleton children between January 1, 1999, and December 31, 2009 at Kaiser Permanente Southern California (KPSC) hospitals. KPSC covers Imperial, Kern, Los Angeles, Orange, Riverside, San Bernardino, San Diego, San Luis Obispo, Santa Barbara, and Ventura counties, with 14 medical center service areas (Additional file 1: Figure S1). Women with residential addresses at the time of child's birth outside Southern California (n = 636) or addresses that could not be accurately geocoded (n = 4,406) were excluded. Residential addresses at the time of birth were extracted from birth certificate records, which were linked by a unique KPSC membership identifier. The primary exposure windows included preconception, defined as 12 weeks before last menstrual period (LMP) date, and first trimester, defined as LMP to 12 weeks + 6 days (day 1–90). To assure that exposure occurred before the onset of disease, women with pre-existing diabetes (n = 4,093) or a GDM diagnosis before 13 weeks' gestation (n = 2,761) were excluded, leaving a total of 239,574 pregnancies from 188,782 women included in the primary analyses. Both outcome and covariate data were extracted from the KPSC EMR, as previously described (Xiang et al. 2015). This study was approved by the Institutional Review Boards of University of Southern California and KPSC.

Outcome data on GDM

KPSC follows the American College of Obstetricians and Gynecologists guidelines for GDM screening, which have remained consistent over the course of this study (Committee

on Practice Bulletins-Obstetrics 2018). Most pregnant women were routinely screened for GDM between 24 and 28 weeks of gestation, with exception of women at higher risk for GDM who get screened earlier in gestation. Diagnosis of GDM was based on laboratory values confirming a plasma glucose level of 200mg/dL or higher on the glucose challenge test or at least 2 plasma glucose values meeting or exceeding the following values on the 100-g or 75-g oral glucose tolerance test: fasting, 95 mg/dL; 1 hour, 180 mg/dL; 2 hours, 155 mg/dL; and 3 hours, 140 mg/dL, as previously described (American Diabetes Association 2004; Xiang et al. 2015). Gestational age at GDM diagnosis was calculated using the date of the first glucose test result that met the GDM diagnosis criteria, date of delivery, and gestational age at delivery based on prenatal clinical care ultrasound scans available in the electronic medical record.

Exposure assessment

Ambient exposures to regional air pollutant exposures were estimated at residential addresses recorded on birth certificates. These birth addresses were geocoded using MapMarker USA Version 28.0.0.11.

Pollutant exposures estimated at each geocoded address included $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2), and ozone (O_3). Monthly averages for each pollutant between 1998 and 2009 were obtained from data compiled from the EPA regional air quality monitoring network across Southern California. To estimate the exposure at the residential location, we used the inverse distance-weighted monthly average from four closest monitoring stations within 50 km, except for geocoded locations within 0.25 km of a monitor, for which only data from the nearest monitoring station were used. Although the distance-weighted approach has limited accuracy in areas with sparse monitoring networks, performance is acceptable in Southern California due to the dense geographical network of historical measurements covering the region. (See Additional file 1: Figure S1). In a previous Southern California study evaluating this method using leave-one-out validation for monthly monitoring station data, the coefficients of determination (R^2) were 0.76, 0.73, 0.53, and 0.46 for O_3, NO_2, $PM_{2.5}$and PM_{10}, respectively, with lower R^2 values for PM attributed to the local (primary emission) dust component that is not regional (Eckel et al. 2016). Bias was less than 1 ppb or 1 $\mu g/m^3$.

Each address was assigned the monthly average of the 24-hour concentrations of $PM_{2.5}$, PM_{10}, and NO_2. For O_3, the monthly average of daily maximum 8-hour concentrations was estimated. Averages of the monthly concentrations during preconception and first trimester of pregnancy were then aggregated from these monthly estimates, with each specific time window determined based on the LMP date. For months overlapping different exposure windows (e.g. preconception and first trimester), the exposure was assigned proportional to the number of days in each window.

Covariates

Potential confounding variables chosen a priori, based on previous associations with GDM (Eze et al. 2015; Thiering and Heinrich 2015), included birth year, maternal age at delivery (continuous), and self-reported race/ethnicity. To control for spatial confounding, KPSC medical center service areas were adjusted as proxies for unmeasured geographical

characteristics associated with GDM. Other covariates available in the EMR included parity, education [high school or lower, some college, college graduate or higher] and median family household income in the census tract of residence. Additional pregnancy-related covariates that may be in the causal pathways included maternal pre-pregnancy body mass index (BMI) that was categorized as underweight, normal, overweight and obese. This covariate was routinely recorded in the EMR starting in late 2006 and was available for 72,044 of the 239,574 total pregnancies. An indicator variable was created for each missing value for each covariate (parity [n = 3,956], education [n = 2,131], household income [n = 1,819], except BMI.

Statistical analyses

Maternal characteristics were compared between women with GDM diagnosed after the first trimester exposure (≥ 13 weeks gestation; n = 18,244) and women who did not develop GDM during the pregnancy (n = 221,330). Partial Pearson correlation coefficients were calculated between regional pollutant exposures during preconception and the first trimester, adjusting for birth year and KPSC medical center service areas. Restricted cubic splines identified no evidence of non-linear associations of GDM with pollutants. Therefore, each pollutant was treated as a continuous variable and modeled linearly. Generalized Estimating Equations models with the logit function and binomial distribution were used to estimate the odds ratios (ORs) for GDM associated with each pollutant exposure, adjusting for potential confounders. To account for within-cluster correlation for women with more than one singleton pregnancy during the study period, we used an exchangeable covariance structure.

Potential confounding due to temporal changes in rates of GDM and of pollution levels was addressed by adding calendar birth year as a continuous covariate. We controlled for broad geographic characteristics associated with GDM by adjusting for 14 KPSC medical center service areas. Because the analysis of estimated GDM effects of each pollutant was adjusted for year and for service areas, we scaled each OR to be representative of exposure contrasts both within-service area and within-year. For each pollutant, this effect estimate was scaled to the difference between the 95^{th} and the 5^{th} percentile of the distribution of deviations of each mother's pregnancy exposure from the average for pregnant women in the same service area in the same year. Deviations were calculated as each residential pollutant exposure value minus the within-service area, within-year mean exposure. For example, for each of the 14 service areas and 11 years (154 in total) the average $PM_{2.5}$ residential exposure and the deviations of individual $PM_{2.5}$ from this average were calculated. The 95^{th} percentile (3.0 $\mu g/m^3$) minus the 5^{th} percentile (−3.5 $\mu g/m^3$) of $PM_{2.5}$ deviation distributions resulted in the within-service area and within-year scale of 6.5 $\mu g/m^3$for $PM_{2.5}$. The same procedure was used to calculate the within-service area, within-year scales for other pollutants: 16.1 $\mu g/m^3$for PM_{10}, 10.4 ppb for NO_2, and 15.7 ppb for O_3.

Additionally adjusting for season did not change the effect estimates appreciatively, and thus were not included as confounders in the final models. Maternal pre-pregnancy BMI (that may also be on the causal pathway) was also not included in the final models because this covariate was only recorded for the subset of pregnancies after 2006. In a sensitivity analysis restricted to the subset of pregnancies since 2006 with data for pre-pregnancy BMI,

adjustment for BMI did not appreciably change the estimates of effect. Additionally, a sensitivity analysis was conducted by restricting to women with complete covariate information (n = 231,701), and the patterns of pollutant associations were almost identical as in models using a missing value indicator.

Furthermore, to assess possible exposure misclassification due to denser network of monitoring stations in urban areas and less so in rural areas, we conducted a sensitivity analysis restricting to KPSC service areas covering the most urban areas with denser network of monitoring stations (medical center service areas 1, 2, 3, 6, 7, 9, 13, Figure S1). Finally, to assess potential confounding by exposure during preconception and first trimester, we conducted data analysis using multi-pollutant models mutually adjusting for both preconception and first trimester exposures of each pollutant, and in addition for each of the co-pollutants in both exposure windows.

Two-sided statistical tests were conducted at the alpha level of 0.05, and precision was measured using 95% confidence intervals (CIs). Data analyses were conducted using SAS 9.4 (SAS Institute, Inc, Cary, NC).

Results

In this study, 18,244 (7.7%) women had a GDM diagnosis ≥13 weeks' gestation, and 221,330 women did not have GDM. The crude prevalence of GDM increased over the course of the study from 7.14% in 1999 to 7.95% in 2009. Women with GDM were more likely to be multiparous; to be Asian/Pacific Islander; and to be overweight or obese before pregnancy compared to women without GDM (Table 1). Women with GDM were older at delivery (32.4 years; standard deviation (SD) 5.4) than women without GDM (29.4 years; SD 5.8). Proportions of maternal education and census-tract household income levels were similar among women with and without GDM.

Overall mean levels of $PM_{2.5}$, PM_{10}, NO_2, and O_3 during preconception were 18.2 $\mu g/m^3$ (SD 5.5; range 1.7–39.8 $\mu g/m^3$), 38.4 $\mu g/m^3$ (SD 10.9; range 3.3–113.1 $\mu g/m^3$), 25.8 ppb (SD 8.2; range 3.2–58.6 ppb), and 41.3 ppb (SD 14.2; range 7.6–109.4 ppb) respectively. Mean levels of pollutants during the first trimester were similar to exposure levels during preconception. Mean levels of both $PM_{2.5}$and NO_2 during preconception and during the first trimester decreased across birth years from 1999 to 2009 (Additional file 1: Figure S2). PM_{10} exposure estimates fluctuated across time while mean O_3 levels remained relatively stable across years. Mean concentrations of pollutants also varied between KPSC medical center service areas, with highest mean $PM_{2.5}$ and PM_{10}levels across years in Ontario (21.9 $\mu g/m^3$, 50.4 $\mu g/m^3$), and lowest $PM_{2.5}$ and PM_{10} levels in San Diego (13.4 $\mu g/m^3$, 31.0 $\mu g/m^3$); results not shown. Highest mean levels of NO_2 were in LA (32.3 ppb), and lowest in Irvine (17.2 ppb). Highest mean O_3 levels were in Moreno Valley (51.8 ppb), and lowest mean levels were in Downey (31.4 ppb).

Adjusting for year and KPSC service areas, the partial correlations between pollutants were positive, except for O_3, which was negatively correlated with both NO_2 and $PM_{2.5}$(Table 2). The partial correlations were moderately positive across preconception and first trimester for

$PM_{2.5}$(R = 0.54), PM_{10} (R = 0.55), NO_2 (R = 0.58); with O_3 having the smallest positive correlation (R = 0.17) between exposure windows.

In single-pollutant models, maternal preconception exposure to NO_2 was associated with increased risk of GDM diagnosed >13 weeks (OR = 1.10 per 10.4 ppb, 95% CI: 1.07, 1.13). (See Table 3). The effect estimate for first trimester exposure was substantially weaker (OR = 1.02 per 10.4 ppb, 95% CI: 0.99, 1.05) and not statistically significant (p=0.09). We fitted multi-pollutant models that mutually adjusted for preconception and first trimester NO_2 exposure and for a co-pollutant in both exposure windows ("mutually adjusted" in Table 3). The preconception NO_2 effect estimate was robust to adjustment for $PM_{2.5}$ or for PM_{10}. For example, the OR was 1.09 per 10.4 ppb, 95% CI: 1.05, 1.13), after adjustment for NO_2 in the first trimester and for $PM_{2.5}$ preconception and first trimester exposure. Mutually adjusting for O_3 attenuated this effect estimate (OR = 1.04 per 10.4 ppb, 95% CI: 1.00, 1.08). First trimester NO_2 association remained null in multi-pollutant models mutually adjusted for preconception NO_2 and a co-pollutant in both exposure windows. Preconception $PM_{2.5}$ exposure was associated with GDM (OR = 1.04 per 6.5 μg/m^3, 95% CI: 1.01, 1.06) but the effect was markedly reduced by adjustment for first trimester $PM_{2.5}$ and either NO_2 or O_3 in both exposure windows. First trimester $PM_{2.5}$ exposure was associated with a reduction in risk for GDM (OR = 0.98 per 6.5 μg/m^3, 95% CI: 0.95, 1.00; p=0.07), and this association was statistically significant in multi-pollutant models including preconception $PM_{2.5}$ exposure and either NO_2 or PM_{10}, but not O_3, in both exposure periods. The preconception $PM_{2.5}$exposure association (OR = 1.03 per 16.1 μg/m^3, 95% CI: 1.00, 1.06; p=0.04) was also attenuated by co-adjustment for first trimester exposure and any other pollutant. Preconception O_3 exposure was associated with decreased risk of GDM (OR = 0.94 per 15.7 ppb, 95% CI: 0.92, 0.95).

Sensitivity analysis restricting to KPSC service areas covering the most urban areas with denser network of monitoring stations reduced the sample size by 47% (from n = 239,574 to n = 126,520). The point estimates and direction of associations of all the pollutants with GDM remained similar to the results using the full cohort (Additional file 1: Table S1).

Discussion

In this large retrospective cohort study, increased risk of GDM was associated with exposure to NO_2 during the 12 weeks before conception, an association that was robust to adjustment for multiple covariates, including co-exposure to NO_2 during the first trimester and models including another pollutant exposure during both preconception and first trimester. The study was novel in examining effects of preconception exposures and in adjusting for first trimester and other pollutant exposures. A key strength of the study, compared to several previous studies, was to refine the temporal relationship between pollutant exposures both before and after conception with subsequent development of GDM. This was possible because laboratory measurements and dates from the KPSC EMR were used to specify the date of diagnosis.

Preconception substance abuse and exposures to radiation and chemicals such as organic solvents have been associated with adverse birth outcomes (Lassi et al. 2014). Less is known

about environmental effects during preconception on pregnancy complications, including GDM. Although positive associations between air pollution, mainly $PM_{2.5}$, NO_2 or NO_X, and type 2 diabetes have been consistently reported, GDM associations have been inconsistent across only a small number of studies, and there has been little study to date of GDM associations with preconception pollutant exposures (Eze et al. 2015; Thiering and Heinrich 2015). We did not examine effects of maternal early life or lifetime air pollution exposures that may also have been relevant to GDM. Exposure to another combustion product, maternal smoking during pregnancy, for example, has been associated in the female offspring with increased risk of subsequent GDM during her pregnancy (Bao et al. 2016). Reasons for a pattern of NO_2 preconception effect that was more robust than the first trimester association are not clear. We speculate that preconception NO_2 may interact with other behavioral characteristics that promote insulin resistance, such as lack of exercise or a high fat, high carbohydrate diet, resulting in a synergistic effect on GDM with the onset of pregnancy. If mothers modified these behaviors in response to being informed that they were pregnant, reduced effects of NO_2 during the first trimester might be observed as a result of reduced co-exposure to lifestyle factors. Further study, including animal toxicological investigation, is warranted to assess whether the preconception NO_2 associations could be causal.

GDM likely shares pathways for development in common with type 2 diabetes, since both are characterized by insulin resistance, and women with GDM are at increased risk of developing type 2 diabetes after pregnancy (Xiang et al. 2011). $PM_{2.5}$ causes diabetes in animal models (Rao et al. 2015), but the effects of NO_2 exposure are less studied. NO_2 causes oxidative stress and increased levels of proinflammatory cytokines (Lodovici and Bigagli 2011) that also characterize GDM (Bowers and Zhang 2011). NO_2 can also be a surrogate for the mixture of near-roadway air pollution that results in increased local concentrations of NO_2, or for other regional pollutant mixtures correlated with NO_2 that may explain the observed associations of NO_2 with GDM (Hoek et al. 2008). Although we have not examined the effects of near-roadway air pollution, our findings indicate that the NO_2 associations were not explained by $PM_{2.5}$ exposure.

Only two studies have assessed associations of pollutant exposures before conception with subsequent GDM (Robledo et al. 2015; Shen et al. 2017). Our findings are consistent with those of a hospital-based cohort study in the US that reported positive associations between GDM diagnosis and preconception NO_x(Robledo et al. 2015). However, unlike our study, that study also identified an association with first trimester NO_x. A case-control study from Taiwan reported no associations of GDM with preconception NO_2 exposure (Shen et al. 2017). Other studies have reported null trimester-specific NO_2 exposure associations with GDM (Pedersen et al. 2017; Shen et al. 2017). Early gestational exposures have also been associated with protective GDM associations with NO_2 (Padula et al. 2018); positive associations with NO_x (Malmqvist et al. 2013); and positive associations with NO (Pan et al. 2017). Reasons for these different results between studies merit further investigation.

Why we observed consistently negative O_3 associations with GDM is not clear, as protective effects are not biologically plausible. However, if exposures to O_3 were causing fetal loss in early pregnancy before a GDM diagnosis could have occurred, then we might see protective

effects of O_3 on GDM (Padula et al. 2018). One recent epidemiologic study reported that exposures to O_3 and $PM_{2.5}$ during pregnancy were associated with increased risk of fetal loss (Ha et al. 2018). Residual confounding by protective factors such as healthy diet and physical activity could have explained protective associations, if these protective factors were correlated with O_3 exposure. However, preconception and first trimester O_3 exposures had very small positive correlations (R = 0.05 and 0.03, respectively) with maternal pre-pregnancy BMI, a proxy for diet and physical activity that was available in the EMR, and adjusting for BMI did not change our effect estimates. Negative O_3 associations with GDM observed in this study merit further investigation.

There were several strengths to this study. KPSC follows the standard guidelines for screening of GDM during pregnancy for all members and GDM status was obtained using laboratory glucose values rather than through recall or diagnostic codes. This approach largely eliminated screening and ascertainment biases, although some women with GDM may have had pre-gestational diabetes that was not identified until glucose screening during pregnancy and they would have been incorrectly classified as GDM. All women followed during pregnancy in the KPSC system administrative database were included in this study; therefore, selection bias was unlikely to have influenced these results. The large, well-characterized population with residential exposure for multiple criteria air pollutants was another strength. Exposure assessment based on the child's birth residential address rather than delivery hospital referral region (Robledo et al. 2015) or city/township (Pan et al. 2017; Shen et al. 2017), used in some previous studies, likely reduced exposure misclassification in our study. Our analysis controlled for individual-level confounders available through the KPSC EMR, such as maternal education and medically relevant covariates, which are generally not available outside a single healthcare system. The KPSC membership comprised approximately 16% of the census reference population, with eligibility largely based on employment, so the findings are generalizable to the working population of Southern California and probably to other similar populations across the country (Koebnick et al. 2012).

There were also some limitations to the study, including the use of exposure at the child's birth address as a proxy for personal exposure. Measurement error could have occurred from not taking into account residential mobility during pregnancy, and time spent away from home. Exposure measurement error may also be greater for rural areas with sparse coverage compared to urban areas with a denser network of monitoring stations; however, estimates from a sensitivity analysis restricting to KPSC service areas covering the most urban areas with denser network of monitoring stations were similar to estimates from the entire cohort. If the effect of this bias were non-differential with respect to the outcome, then the true effect of exposure may have been larger than we observed (Rothman et al. 2008).

Conclusions

NO_2 exposure in the 12 weeks prior to conception was associated with an increased risk of development of GDM. Large cohort studies using high quality electronic medical records and standardized diagnostic algorithms have the potential to further understanding of effects of preconception air pollution exposure and of causes of GDM. Given the recent increase in

GDM among women of reproductive age, the findings have potentially large public health implications, because GDM increases the risk of subsequent development of maternal type 2 diabetes, and of childhood obesity, neurodevelopmental disorders and their consequences; and NO_2 exposure can be reduced with regulatory intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The date of GDM diagnosis was used to refine temporality with pollutant exposures.
- Independent associations of each pollutant and exposure window were assessed.
- Maternal exposure to NO_2 during preconception was robustly associated with GDM.

Table 1.

Demographic characteristics by GDM for singleton deliveries in 1999–2009

	GDM (n=18,244)	No GDM (n=221,330)
	n (column %)[a,b]	n (column %)[a,b]
Age (years), mean (SD)	32.4 (5.4)	29.4 (5.8)
Parity		
0	6486 (35.6)	88309 (39.9)
1	5326 (29.2)	70964 (32.1)
≥2	6107 (33.5)	58426 (26.5)
Missing	325 (1.8)	3631 (1.6)
Race/ethnicity		
Non-Hispanic white	3461 (19.0)	58077 (26.2)
Non-Hispanic black	1289 (7.1)	22028 (10.0)
Hispanic	9753 (53.5)	112620 (50.9)
Asian/Pacific Islander	3451 (18.9)	25136 (11.4)
Other	290 (1.6)	3469 (1.6)
Education		
High school or lower	7706 (42.4)	91397 (41.3)
Some College	5009 (27.5)	61716 (27.9)
College graduate or higher	5377 (29.5)	66238 (29.9)
Missing	152 (0.8)	1979 (0.9)
Household annual income[c]		
< $30,000	1376 (7.5)	18044 (8.2)
$30,000–$49,999	6318 (34.6)	73942 (33.4)
$50,000–$69,999	5872 (32.3)	70911 (32.0)
$70,000–$89,999	2871 (15.7)	35876 (16.2)
≥ $90,000	1807 (9.9)	22557 (10.2)
Prepregnancy body mass index[d]		
Underweight (< 18.5 kg/m^2)	61 (0.3)	1832 (0.8)
Normal (≥18.5–< 25 kg/m^2)	1761 (9.7)	30465 (13.8)
Overweight (≥ 25–< 30 kg/m^2)	1828 (10.0)	18780 (8.5)
Obese (≥ 30 kg/m^2)	2308 (12.7)	15009 (6.8)
Missing	12286 (67.3)	155244 (70.1)

[a] Defined as GDM diagnosed at ≥ 13 weeks' gestation

[b] All characteristics were significantly different based on the χ^2–squared test for proportions and analysis of variance for means (p<0.001), except for maternal education (p=0.09)

[c] Based on census tract median

[d] nformation available starting in late 2006

Table 2.

Pearson partial correlations[a] of pollutants during preconception and first trimester

		Preconception				First trimester			
		$PM_{2.5}$	**PM_{10}**	**NO_2**	**O_3**	**$PM_{2.5}$**	**PM_{10}**	**NO_2**	**O_3**
Preconception	**$PM_{2.5}$**	1.00	0.65	0.60	−0.13	0.54	0.33	0.44	−0.30
	PM_{10}		1.00	0.48	0.16	0.49	0.55	0.46	−0.33
	NO_2			1.00	−0.42	0.28	0.18	0.58	−0.37
	O_3				1.00	0.24	0.26	0.06	0.17
First trimester	**$PM_{2.5}$**					1.00	0.66	0.63	−0.14
	PM_{10}						1.00	0.49	0.15
	NO_2							1.00	−0.42
	O_3								1.00

[a]All correlations were adjusted for birth year and KPSC medical center service areas and were statistically significant ($p < 0.0001$). Gray cells indicate correlations between pollutants across exposure windows during preconception and first trimester.

Table 3.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for association between GDM ≥ 13 weeks' gestation and each pollutant preconception or first trimester exposure alone (single-pollutant) and mutually adjusted for preconception and first trimester exposures of each pollutant and a co-pollutant from both exposure windows (multi-pollutant)

Model	Pollutant	Preconception	First trimester
		OR[a,b] (95%CI)	**OR[a,b] (95% Cl)**
Single-pollutant	NO_2	**1.10 (1.07–1.13)**	1.02 (0.99–1.05)
Multi-pollutant[c]	Adjusted for $PM_{2.5}$	**1.09 (1.05–1.13)**	1.02 (0.98–1.05)
	Adjusted for PM_{10}	**1.10 (1.06–1.13)**	1.00 (0.96–1.03)
	Adjusted for O_3	**1.04 (1.00–1.08)**	1.01 (0.97–1.04)
Single-pollutant	PM2.5	**1.04 (1.01–1.06)**	0.98 (0.95–1.00)
Multi-pollutant[c]	Adjusted for PM_{10}	**1.04 (1.01–1.08)**	**0.96 (0.93–0.99)**
	Adjusted for NO_2	1.01 (0.97–1.04)	**0.97 (0.93–1.00)**
	Adjusted for O_3	1.01 (0.98–1.04)	0.99 (0.96–1.02)
Single-pollutant	PM_{10}	**1.03 (1.00–1.06)**	0.98 (0.95–1.01)
Multi-pollutant[c]	Adjusted for $PM_{2.5}$	1.02 (0.98–1.06)	0.99 (0.96–1.03)
	Adjusted for NO_2	1.00(0.97–1.04)	0.99(0.95–1.02)
	Adjusted for O_3	1.02(0.99–1.06)	1.02(0.98–1.05)
Single-pollutant	O_3	**0.94 (0.92–0.95)**	**0.95 (0.94–0.97)**
Multi-pollutant[c]	Adjusted for $PM_{2.5}$	**0.94 (0.92–0.96)**	**0.96 (0.94–0.97)**
	Adjusted for PM_{10}	**0.93 (0.91–0.95)**	**0.96 (0.94–0.98)**
	Adjusted for NO_2	**0.95 (0.93–0.97)**	**0.97 (0.95–0.99)**

[a]Adjusted for family correlation, birth year, KPSC medical center service areas, maternal age, race/ethnicity, education, household income, parity

[b]NO_2 per 10.4 ppb, $PM_{2.5}$ per 6.5 μg/m^3, PM per 16.1 μg/m^3,O_3 per 15.7 ppb (scaled as described in the statistical analyses section)

[c]Odds ratios mutually adjusted for preconception and first trimester exposures of the pollutant plus a co-pollutant from both preconception and first trimester exposure windows. For example, the estimate for preconception NO_2 exposure mutually adjusted for $PM_{2.5}$ included first trimester NO_2 + preconception $PM_{2.5}$ + first trimester $PM_{2.5}$ exposures.

Bold=statistically significant at $p<0.05$