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Exposure to air pollutant mixture and gestational diabetes mellitus in Southern California: Results from electronic health record data of a large pregnancy cohort

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Abstract

Background: Epidemiological findings are inconsistent regarding the associations between air pollution exposure during pregnancy and gestational diabetes mellitus (GDM). Several limitations

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exist in previous studies, including potential outcome and exposure misclassification, unassessed confounding, and lack of simultaneous consideration of air pollution mixtures and particulate matter (PM) constituents.

Objectives: To assess the association between GDM and maternal residential exposure to air pollution, and the joint effect of the mixture of air pollutants and PM constituents.

Methods: Detailed clinical data were obtained for 395,927 pregnancies in southern California (2008–2018) from Kaiser Permanente Southern California (KPSC) electronic health records. GDM diagnosis was based on KPSC laboratory tests. Monthly average concentrations of fine particulate matter < 2.5 μm ($PM_{2.5}$), <10 μm (PM_{10}), nitrogen dioxide (NO_2), and ozone (O_3) were estimated using kriging interpolation of Environmental Protection Agency's routine monitoring station data, while $PM_{2.5}$ constituents (i.e., sulfate, nitrate, ammonium, organic matter and black carbon) were estimated using a fine-resolution geoscience-derived model. A multilevel logistic regression was used to fit single-pollutant models; quantile g-computation approach was applied to estimate the joint effect of air pollution and PM component mixtures. Main analyses adjusted for maternal age, race/ethnicity, education, median family household income, pre-pregnancy BMI, smoking during pregnancy, insurance type, season of conception and year of delivery.

Results: The incidence of GDM was 10.9% in the study population. In single-pollutant models, we observed an increased odds for GDM associated with exposures to $PM_{2.5}$, PM_{10}, NO_2 and $PM_{2.5}$ constituents. The association was strongest for NO_2 [adjusted odds ratio (OR) per interquartile range: 1.176, 95% confidence interval (CI): 1.147–1.205]. In multi-pollutant models, increased ORs for GDM in association with one quartile increase in air pollution mixtures were found for both kriging-based regional air pollutants (NO_2, $PM_{2.5}$, and PM_{10}, OR = 1.095, 95% CI: 1.082–1.108) and $PM_{2.5}$ constituents (i.e., sulfate, nitrate, ammonium, organic matter and black carbon, OR = 1.258, 95% CI: 1.206–1.314); NO_2 (78%) and black carbon (48%) contributed the most to the overall mixture effects among all krigged air pollutants and all $PM_{2.5}$ constituents, respectively. The risk of GDM associated with air pollution exposure were significantly higher among Hispanic mothers, and overweight/obese mothers.

Conclusion: This study found that exposure to a mixture of ambient $PM_{2.5}$, PM_{10}, NO_2, and $PM_{2.5}$ chemical constituents was associated with an increased risk of GDM. NO_2 and black carbon $PM_{2.5}$ contributed most to GDM risk.

1. Introduction

Gestational diabetes mellitus (GDM), defined as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation (American Diabetes, 2021), is a major pregnancy complication affecting approximately 7.6% of pregnancies in the U.S. (Casagrande et al., 2018). The prevalence of GDM has continued to increase globally over the past decades (Ferrara, 2007; Zhu & Zhang, 2016). GDM is associated with higher risk of short- and long-term adverse health outcomes in both

mothers and their offspring. Specifically, mothers who have GDM are more likely to develop type 2 diabetes, metabolic syndrome, and cardiovascular disease later in life (Daly et al., 2018; Farahvar et al., 2019; Mirghani Dirar & Doupis, 2017; Tobias et al., 2017). For offspring, GDM increases the risk for several adverse outcomes, including preterm birth, fetal overgrowth, neonatal hypoglycemia, hyperbilirubinemia and hypocalcemia (Farrar et al., 2016; Martino et al., 2016; Yang et al., 2019), childhood autism, obesity, as well as diabetes and cardiometabolic disorders later in life (Clausen et al., 2008; Farahvar et al., 2019; Jo et al., 2019a; Metzger, 2007; Nijs & Benhalima, 2020; Tam et al., 2017; Xiang et al., 2015; Xu et al., 2014).

A number of maternal characteristics have been identified as risk factors for GDM, including ethnicity, age, parity, genetic susceptibility, family history of diabetes, a history of GDM in a prior pregnancy, as well as lifestyle behaviors, obesity and hypertension (Chiefari et al., 2017; Farahvar et al., 2019; Getahun et al., 2010; Hedderson & Ferrara, 2008). There is growing interest in understanding the potential role of environmental factors in triggering GDM and further providing preventive opportunities for vulnerable populations. Previous studies suggested that outdoor air pollution is related to the development of type 2 diabetes (Balti et al., 2014; Liu et al., 2019; Rao et al., 2015) through several pathways, including oxidative stress, systemic inflammation and endothelial dysfunction (Finch & Conklin, 2016; Rajagopalan & Brook, 2012), each of which may cause insulin resistance (Brook et al., 2013) and result in subsequent diabetes. Air pollution exposure during pregnancy may also affect the development of GDM by similar mechanisms (Ben-Haroush et al., 2004). The emerging evidence indicates that higher preconception exposure to air pollution might be associated with elevated blood glucose levels associated with increased insulin resistance and GDM development (Najafi et al., 2020). An increasing number of epidemiological studies have examined the relationship between air pollution exposure and the risk of GDM (Choe et al., 2019; Choe et al., 2018; Fleisch et al., 2014; Fleisch et al., 2016; Hu et al., 2015; Jo et al., 2019b; Malmqvist et al., 2013; Padula et al., 2019; Pan et al., 2017; Pedersen et al., 2017; Robledo et al., 2015; Shen et al., 2017; Yu et al., 2020; Zhang, et al., 2020a; Zheng et al., 2020), although conclusions are inconsistent regarding the effects of different air pollutants and exposure windows. A recent *meta*-analysis (Zhang, et al., 2020b) showed that maternal exposure to sulfur dioxide (SO_2) during the first trimester was associated with elevated risk of GDM [odds ratio (OR) = 1.39, 95% confidence interval (CI): 1.01–1.77], while pre-pregnancy ozone (O_3) exposure was inversely associated with GDM development. They did not observe any effect for fine particulate matter with diameter < 2.5 μm ($PM_{2.5}$), < 10 μm (PM_{10}) and nitrogen dioxide (NO_2). However, in another *meta*-analysis (Hu et al., 2020), only maternal first trimester exposure to nitrogen oxides (NO_x) and second trimester exposure to $PM_{2.5}$ and SO_2 increased the risk of GDM (OR = 1.03, 95% CI: 1.00–1.07, per 10 parts per billion increase in NO_x; OR = 1.04, 95% CI: 1.01–1.09, per 10 μg/m^3 increase in $PM_{2.5}$; and OR = 1.25, 95% CI: 1.02–1.53, for high versus low SO_2). High heterogeneity among studies were found in both *meta*-analyses. Reasons that may partially explain the variation in results include differences in study design, exposure assessment methods, exposure time windows, study region, population, covariates adjustment, and criteria for diagnosing GDM.

Several limitations exist in previous studies, including potential outcome misclassification and unmeasured confounding in the administrative databases (e.g., birth certificate) (Devlin et al., 2009), and exposure misclassification due to the sparsely-distributed monitoring stations. For $PM_{2.5}$ exposure, most previous studies only examined $PM_{2.5}$ total mass neglecting the different chemical compositions which have large spatiotemporal variations and affect health differently (Bell et al., 2007). Heterogeneity of PM is related to differences in source types, climatic and topographic conditions, traffic intensity and land use (Austin et al., 2013; Merbitz et al., 2012). There has been limited study of maternal exposure to $PM_{2.5}$ constituents on the development of GDM (Robledo et al., 2015; Yu et al., 2020; Zheng et al., 2020). Nitrate (Robledo et al., 2015), organic matter, ammonium (Zheng et al., 2020) and black carbon (Yu et al., 2020) may be the main components that are associated with GDM, but results are still inconsistent. Moreover, existing studies regarding $PM_{2.5}$ constituents assigned exposure to either the mother's residence at delivery on birth records (Zheng et al., 2020) or to delivery hospital region (Robledo et al., 2015; Yu et al., 2020) without considering residential changes during pregnancy, which may induce differential exposure misclassifications. Further, most studies focused on exposure windows by trimester during pregnancy (e.g., the first and/or second trimester); only a few studies have examined effects of preconception exposures (Jo et al., 2019b; Rammah et al., 2020; Robledo et al., 2015; Shen et al., 2017). Finally, studies regarding the joint effects of multiple air pollutants are sparse. Recent methodological developments allow for the consideration of multiple, correlated exposures. Notably, quantile g-computation (Keil et al. 2020) is a novel approach to study the effects of complex exposure mixtures. To the best of our knowledge, no study has explored complex air pollution mixtures effects on pregnancy complications such as GDM. Therefore, it is crucial to address these limitations and provide evidence to better understand the underlying mechanisms between air pollutants and GDM and further to develop targeted interventions.

In this study, we aimed to 1) investigate the relationships between GDM and maternal residential exposures to various air pollutants, including $PM_{2.5}$, PM_{10}, NO_2, O_3, and $PM_{2.5}$ constituents in a large population-based pregnancy cohort based on the Kaiser Permanente Southern California (KPSC) electronic health records (EHR) data between 2008 and 2018, and 2) examine the joint effect of the mixture of air pollutants on the risk of GDM.

2. Method

2.1. Study population

This retrospective cohort study included women who gave birth to singleton children between January 1, 2008 and December 31, 2018 at KPSC facilities, including 15 hospitals and 234 medical offices across Southern California (Appendix A). Information on demographic characteristics, residential history, medical records, birth records and individual lifestyle was extracted from KPSC EHRs. Population selection process was outlined in Appendix B. In total, 395,927 pregnancies were included in the primary analysis after excluding women who were not KPSC members or with gestational age < 20 or > 47 weeks (n = 8,912), without address data (n = 680), or with multiple birth (n = 7,454). We also excluded pregnancies with preexisting diabetes (n = 5,518), or missing GDM status

due to missing lab test results (n = 30,355). All addresses of residence were geocoded with the Texas A&M, NAACCR, Automated Geospatial Geocoding Interface Environment (AGGIE) Geo-coder (Goldberg et al., 2008). Gestational age was calculated from date of last menstrual period (LMP) and corroborated by early pregnancy ultrasonography. If LMP was unknown or if disagreement was found between dates estimated from LMP and sonogram, the date generated from the latter was used (ACOG, 2017).

This study was approved by the Institutional Review Board of KPSC and the University of California, Irvine.

2.2. Outcome: GDM

Most pregnant women were routinely screened for GDM between 24 and 28 weeks of gestation, with the exception of women at higher risk for GDM who are screened earlier in gestation. Two criteria for GDM testing were used: the Carpenter-Coustan criteria [a 1-hr 50-g glucose challenge test (GCT) > 200 mg/dL or two abnormal values for 3-hour 100-g oral glucose tolerance test (OGTT), the cutoff values were fasting 95, 1hr 180, 2hr 155, 3hr 140 mg/dl (Carpenter & Coustan, 1982)]; or the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [one abnormal value for 2-hour 75-g OGTT, the cutoff values were fasting 92, 1hr 180, 2hr 153 mg/dl (Metzger, 2010)].

2.3. Air pollution exposures

As described in previous studies (Laurent et al., 2016; Wu et al., 2016), hourly ambient air pollution measurements for $PM_{2.5}$, PM_{10}, NO_2, and O_3 were obtained for years 2007–2018 from U.S. Environmental Protection Agency's monitoring stations. Daily averages (24 h for $PM_{2.5}$, PM_{10} and NO_2, and an 8-hour window of 10 AM-6 PM for O_3), and then monthly averages were calculated. Monthly averaged concentrations were spatially interpolated between stations using empirical Bayesian kriging (EBK). The EBK method was used in our previous research and showed cross-validation R^2 ranging 0.65 to 0.75 (Wu et al., 2016).

Historical ambient monthly $PM_{2.5}$ total mass and constituents (i.e., sulfate, nitrate, ammonium, organic matter and black carbon) from 2007 to 2017 were obtained from the fine-resolution geoscience-derived models developed by Dalhousie University, Canada (Meng et al., 2019b; van Donkelaar et al., 2019). This model provides validated and publicly-available $PM_{2.5}$ outputs at a 1-km resolution over North America by combining chemical transport modeling (GEOS-Chem), satellite remote sensing of aerosol optical depth, and ground-based observations with a geographically weighted regression. The $PM_{2.5}$ mass estimates were generally consistent with ground $PM_{2.5}$ measurements since 1999 (R^2: 0.6–0.85) (Meng et al., 2019a). For $PM_{2.5}$ species, long-term cross-validated agreement of the model were high ($R^2 = 0.57$–0.96) (van Donkelaar et al., 2019). In our study region of the southwestern US, agreement was highest for nitrate ($R^2 = 0.78$) and ammonium ($R^2 = 0.75$), followed by sulfate ($R^2 = 0.59$), organic matter ($R^2 = 0.52$), and black carbon ($R^2 = 0.42$).

Air pollution estimates were spatiotemporally linked to each woman based on the geocoded residential addresses during pregnancy. Residential histories with information on residential changes (address, start date and end date) were abstracted from KPSC EHRs. In our analysis, approximately 44% of the population moved during pregnancy, and 13% of them moved more than once. We temporally interpolated the monthly air pollution metrics to generate daily exposures from three months before pregnancy to delivery date using the TIMESERIES Procedure of the SAS 9.4 software (SAS Institute, Cary, NC). We then calculated month/trimester-specific and entire-pregnancy exposures by averaging the air pollution measurements in each specific time period: preconception (three months before conception), the first trimester (1st – 3rd gestational months) and second trimester (4th – 6th gestational months). Entire exposure was defined for the period from the date of conception to the date of delivery.

2.4. Covariates

Covariate data were abstracted from KPSC EHRs. Pregnancy-related covariates and potential confounders were selected *a priori* based on the existing literature (Eze et al., 2015; Thiering & Heinrich, 2015; Zhang, et al., 2020b), including maternal age, race/ethnicity (African American, Asian, Hispanic, non-Hispanic white, and others including Pacific Islanders, Native American/Alaskan and mothers with multiple race/ethnicities specified) and educational level (8th grade, 9th grade to high school, college < 4 years, and college 4 years); median household income at block group level in 2013 (Nielsen) (CDC, 2020); pre-pregnancy body mass index (BMI, kg/m^2); exposure to active or passive (i.e., secondhand smoke) smoking during pregnancy; season of conception (warm: May-October; cool: November–April) and year of infant birth. Pre-pregnancy BMI was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9) and obese (30.0). Pre-pregnancy weight and delivery weight were used to estimate gestational weight gain that was categorized as inadequate, appropriate or excessive based on the Institute of Medicine and National Research Council guidelines (Rasmussen et al., 2009).

2.5. Statistical analysis

Distribution of selected population characteristics and exposures to $PM_{2.5}$, PM_{10}, NO_2, O_3 and $PM_{2.5}$ constituents were assessed, comparing women with and without GDM. Pearson's correlation was used to examine the correlation between air pollution metrics; *t*-test was applied to determine the difference between GDM and non-GDM groups. To examine the associations between GDM and air pollution, we first used logistic regression to fit single-pollutant models on exposure to $PM_{2.5}$, PM_{10}, NO_2, O_3 and each of the five selected $PM_{2.5}$ constituents during the entire pregnancy, in the preconception period and in the first and second trimesters. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated per interquartile range (IQR) increment for each air pollutant. Main analyses adjusted for maternal age, race/ethnicity, education, median household income, pre-pregnancy BMI, active or passive smoking during pregnancy, insurance type, season of conception and year of birth. Given the large spatial scale of the data, Moran's I was used to test the spatial clustering for GDM. The Moran's I was 0.07 (z = 20.01, p < 0.001). The spatial correlation is weak despite its statistical significance. County was fitted as a random effect to account for potential spatial clustering for GDM. Further, zip codes were fitted as a random effect

in the sensitivity analyses to account for smaller spatial scale clustering for the $PM_{2.5}$ chemical constituent model. Zip code was not included in the EBK model since the coarse exposure estimates based on kriging interpolation of monitoring stations can only reflect regional-level exposures and cannot accurately capture within-zip code exposure variability.

Further, we analyzed the joint effects of air pollution mixtures using the "qgcomp" package in R. G-computation is a causal inference method that can be seen as a generalization of standardization and computes estimates of the expected outcome distribution under specific exposure patterns. Quantile g-computation yields estimates of the effect of increasing all exposures by one quantile simultaneously, which is useful to estimate a causal dose–response parameter of the entire exposure mixture in air pollution study. Quantile g-computation can be described as a flexible extension of weighted quantile sum regression, a historical approach to model mixtures which uses a quantized exposure index with empirical weights for each exposure obtained from quantiles of the exposures (Keil et al., 2020). Yet, quantile g-computation can handle exposures that are not associated with the outcome of interest on the same direction, both negative and positive weights, and allows for non-linear and non-additive effects of individual exposures and the mixture. In multi-pollutant models, we included the following air pollutants that had positive associations with GDM in the single-pollutant models, simultaneously: 1) three krigged air pollutants (i.e., $PM_{2.5}$, PM_{10}, NO_2); 2) five $PM_{2.5}$ constituents (i.e., sulfate, nitrate, ammonium, organic matter and black carbon) with additional adjustment for $PM_{2.5}$ total mass.

In sensitivity analyses, we further examined the influence of adjusting for gestational weight gain, which may be affected by the endocrine disruptors from air pollution and in the causal pathway of the development of GDM (Elobeid & Allison, 2008). However, gestational weight gain was not included in the main analysis as it may run the risk of conditioning on potential intermediate or collider. We also conducted sensitivity analysis restricting to non-movers, movers, frequent movers (i.e., mothers moved more than once during pregnancy), and solely using residential address at delivery without considering address history to explore the impact of residential changes. We further included daily mean temperature derived from a spatiotemporal, 4-km gridded, surface meteorological dataset (Abatzoglou, 2013) as a sensitivity analysis. Furthermore, we included a sensitivity analysis using a weighted quantile sum (WQS) regression approach as an alternative method of quantile g-computation. To examine potential critical windows at the monthly level, we further implemented distributed lag models that consider current exposure at a given time t, past exposure before time t (using an inverse weighting approach to consider non-linear lagged effects), and potential interactions between past and current exposures as a sensitivity analysis. Given that socioeconomic status and race/ethnicity have been shown to act as important modifiers of air pollution effects on health (Hajat et al., 2021), we performed analyses stratified by maternal race/ethnicity and neighborhood household income. Due to potential differential susceptibility across population subgroups with different outcome-related characteristic and co-morbidity, we also conducted stratified analyses by pre-pregnancy BMI categories, and maternal co-morbidity based on the availability of data in KPSC EHRs, including asthma, acute upper respiratory infections, chronic hypertension and gestational hypertension, to explore the differences between population subgroups.

Cochran Q tests were used to measure the heterogeneity among subgroups. All analyses were conducted with SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R 4.0.4.

3. Results

The distribution of selected demographic and pregnancy characteristics and air pollution levels is presented in Table 1. In total, among 395,927 women included in the primary analysis, 42,970 (10.9%) cases of GDM with clinical diagnosis were identified. The mean (standard deviation) of maternal age in our study was 30.3 (5.7) years. Compared to the entire cohort, GDM cases were found more frequently among older mothers, Asian or Hispanic mothers, mothers who live in low-income neighborhoods, overweight or obese mothers, and mothers with chronic hypertension. Residential exposure levels of air pollution metrics during entire pregnancy were higher among GDM cases for $PM_{2.5}$, NO_2 and $PM_{2.5}$ chemical constituents, including nitrate, ammonium, organic matter and black carbon (P < 0.001), but not for PM_{10} (P = 0.24). Table 2 describes summary statistics and Pearson correlation coefficients between air pollutant metrics during entire pregnancy. $PM_{2.5}$ mass concentrations from the EBK model were highly correlated with those from the chemical constituent model (r = 0.83), and moderately correlated with krigged PM_{10} (r = 0.66) and NO_2 (r = 0.61). For $PM_{2.5}$ and its chemical constituents from the chemical constituent model, we observed moderate to high correlations between $PM_{2.5}$ total mass, nitrate, ammonium, organic matters and black carbon (r: 0.53–0.91). The correlations between sulfate and other $PM_{2.5}$ constituents were weak, with correlation coefficients of 0.49 or smaller. Overall, O_3 is negatively correlated with most air pollution metrics, except PM_{10}, sulfate and ammonium.

Fig. 1 illustrates the associations between exposure to air pollution during entire pregnancy and the risk of GDM in the single-pollutant models. For krigged air pollutants, positive associations were observed between GDM and $PM_{2.5}$, PM_{10} and NO_2. The adjusted OR per IQR increase was strongest for NO_2 (1.18, 95% CI: 1.15–1.21), followed by $PM_{2.5}$ (OR = 1.12, 95% CI: 1.09–1.14) and PM_{10} (OR = 1.09, 95% CI: 1.007–1.11). O_3 was inversely associated with GDM (OR = 0.77, 95% CI: 0.75–0.78). Exposure to $PM_{2.5}$ total mass and its constituents during entire pregnancy were also associated with increased GDM risks. We found similar patterns of the increased GDM risks for other exposure windows: preconception, first trimester, second trimester and the first two trimesters. Details on the effect sizes of specific exposure periods are provided in Appendix C. In the monthly time window analyses (Appendix D), relatively stronger associations were observed during 4th – 6th gestational months (second trimester) for most air pollutants of interest, except $PM_{2.5}$ black carbon, with higher odds in early pregnancy. In sensitivity analyses (Appendix E), associations between air pollution and GDM were slightly decreased in magnitude after further adjusting for gestational weight gain, temperature, or including zip code as a random effect in the $PM_{2.5}$ component mixture analysis, respectively. Associations between solely using the address at delivery or considering residential mobility were close.

In multi-pollutant models (Table 3), β coefficients > 0 indicate positive weights of individual exposure components; β coefficients < 0 indicate negative weights of individual exposure components. The g-computation estimator ψ is the sum of all regression β coefficients of

the exposures of interest, corresponding to the change in GDM risk expected for one quartile change in all exposures simultaneously. For example, a change in exposure to the mixture of krigged air pollutants of interest by one quartile would be associated with a 10% increase in odds of GDM (OR = 1.10, 95% CI: 1.08–1.11), and overall mixture effects were driven by NO_2 (78%), followed by $PM_{2.5}$ (22%). It is noteworthy that the weight of an individual pollutant is a scaled effect size based on which pollutants are included in the current analysis. For instance, if another hazardous pollutant were to be included, the contribution of NO_2 might be<78%. For the $PM_{2.5}$ chemical constituent model, there was a 26% increase in risk of GDM associated with exposure to a mixture of $PM_{2.5}$ chemical constituents during entire pregnancy (OR = 1.26, 95% CI: 1.21–1.31), and black carbon gave the greatest contribution of overall mixture effects (48%) among all individual constituents, followed by nitrate (29%) and ammonia (23%). In sensitivity analyses of multi-pollutant models, associations between air pollution mixtures and GDM using WQS regression (Appendix F) were similar to the results from quantile g-computation. NO_2 (85%) and black carbon (45%) gave the greatest contribution among all krigged air pollutants and all $PM_{2.5}$ constituents, respectively.

Furthermore, our results of subgroup analyses (Appendix G) showed that the risk of GDM associated with air pollution exposure (i.e., $PM_{2.5}$, NO_2, and $PM_{2.5}$ chemical constituents) was significantly higher among Hispanic mothers, and overweight/obese mothers. Specifically, an IQR increase of NO_2, $PM_{2.5}$ total mass, nitrate, ammonium and black carbon were associated with greater increase in odds of GDM among Hispanic mothers, followed by black mothers, than Asian mothers in this population. For maternal co-morbidity, despite Cochran's Q tests not revealing any significant heterogeneity, ORs for GDM in association with most air pollutants were found to be slightly higher for mothers with chronic hypertension.

4. Discussion

In this large retrospective cohort study of 395,927 pregnant women residing in southern California from 2008 to 2018, we found that exposures to $PM_{2.5}$, PM_{10}, NO_2, and $PM_{2.5}$ chemical constituents were associated with an increased risk of GDM. Analyses focusing on air pollution mixtures showed that NO_2, $PM_{2.5}$ total mass and its constituents, particularly black carbon, nitrate and ammonium were associated with elevated odds of GDM. Further, Hispanic mothers, and overweight/obese mothers may be more likely to be affected by air pollution on the risk of GDM.

An increasing number of epidemiological studies have examined the relationship between air pollution exposure and the risk of GDM. Consistent with our findings, results from a recent *meta*-analysis (Zhang, et al., 2020b) that included 13 epidemiological studies showed that pre-pregnancy O_3 exposure was inversely associated with GDM (OR = 0.98, 95% CI: 0.98–0.99) when not considering a multi-pollutant model. In another *meta*-analysis that included 11 epidemiological studies (Hu et al., 2020), the authors found second trimester $PM_{2.5}$ exposure was associated with increased GDM risk (OR = 1.04, 95% CI: 1.01–1.09, per 10 μg/m^3 increase in $PM_{2.5}$). Although several studies found potential positive associations between air pollution and GDM, no significant pooled estimates were

observed for other exposure windows or other pollutants (i.e., PM_{10} and NO_2). However, our results showed that GDM was positively associated with exposure to NO_2 and PM_{10} for all exposure windows during pregnancy. Further, the single pollutant models of our study showed that preconception O_3 was associated with reduced risk of GDM, while preconception $PM_{2.5}$, PM_{10} and NO_2 may increase risk of GDM, which agreed with a previous study that was also conducted in southern California using KPSC EHRs between 1999 and 2009. However, the positive associations between first trimester $PM_{2.5}$, PM_{10}, NO_2 and GDM in this study were not observed in the previous KPSC pregnancy cohort (Jo et al., 2019b). Overall, our results add further evidence to the growing body of research that air pollution exposure may increase the risk of GDM. It is also noteworthy that we cannot conclude that O_3 is protective on the risk of GDM. The inverse associations between O_3 and GDM could be caused by the inverse association of O_3 with the other traffic-related pollutants (correlation of -0.36 with NO_2) that act as ozone precursors (Crutzen, 1979). Future studies are warranted considering different air pollutants, susceptible windows as well as study regions.

$PM_{2.5}$ constituents have large spatiotemporal variations (Bell et al., 2007), but few studies examined the association between different $PM_{2.5}$ constituents and the risk of GDM. The first epidemiological study concerning $PM_{2.5}$ constituents and GDM was conducted by Robledo et al. in the U.S. in 2015 using hospital referral regions to estimate exposures, which observed that first trimester high levels of nitrate was associated with an increased GDM risk while preconception and first trimester sulfate was associated with a decreased GDM risk (Robledo et al., 2015). Recently, a study in Florida (Zheng et al., 2020) found that exposures to $PM_{2.5}$ constituents, including sulfate, nitrate, ammonium, organic matter and black carbon, during the second trimester are positively associated with GDM. Another study in Texas (Rammah et al., 2020) observed increased odds of GDM for ammonium and sulfate exposure during the first trimester. A study conducted in China (Yu et al., 2020) reported that organic matter, black carbon and nitrate may be the main culprits for the association between $PM_{2.5}$ and GDM. In our single pollutant models, we found that $PM_{2.5}$ constituents, including sulfate, nitrate, ammonium, organic matter and black carbon were associated with increased GDM risk during the entire pregnancy. To date, although our results are partially consistent with previous findings, associations between $PM_{2.5}$ constituents and GDM are still unclear due to limited relevant studies and large variations in the exposure levels, windows and assessment methods among studies. For example, there was a large difference in the concentrations and primary components of $PM_{2.5}$ across studies. The primary $PM_{2.5}$ constituents were organic matter and sulfate in previous studies conducted in the U.S. (Rammah et al., 2020; Robledo et al., 2015; Zheng et al., 2020); while organic matter, nitrate, and black carbon may be more prevalent in Southern California, which may lead to the heterogeneity in findings.

Another potential reason that may partially explain the equivocal results in the existing literature is the inconsistency in adjustment for multiple air pollutants. Most previous studies estimated the risk of adverse health outcomes associated with the exposure to a single air pollutant (Hu et al., 2020). However, humans are simultaneously exposed to a complex mixture of air pollutants from various sources. Therefore, it is important to measure the joint health effects of air pollution exposure using a multi-pollutant approach. Only few

studies reported effects from multi-pollutant models, and most of them only adjusted for other pollutants (Choe et al., 2019; Hu et al., 2015; Jo et al., 2019b; Shen et al., 2017) or simultaneously included all $PM_{2.5}$ constituents (Rammah et al., 2020; Zheng et al., 2020) in the model. In our study, we applied a new approach to estimate the joint effects of air pollution mixtures and the weight of each exposure. Unlike other inferential approaches that examine the effects of individual exposures while holding other exposures constant, this "quantile g-computation" approach combines the inferential simplicity of weighted quantile sum regression with the flexibility of g-computation to help address the effects of exposure mixtures and design potential public health interventions that act on specific exposure sources (Keil et al., 2020). In the multi-pollutant model with kriging-based NO_2, $PM_{2.5}$, and PM_{10}, the main effect of increased GDM risk was driven by NO_2 (78%) among the three air pollutants. In the multi-pollutant model with $PM_{2.5}$ constituents (i.e., sulfate, nitrate, ammonium, organic matter and black carbon), black carbon (48%) contributed most to the risk of GDM. Thus, interventions targeting the sources of such air pollutants, mainly fuel emissions, may translate into a more pronounced reduction of GDM in southern California and optimize the potential benefits of reducing air pollution exposure during pregnancy.

Maternal characteristics and lifestyle behaviors such as maternal race/ethnicity, socioeconomic status, smoking, BMI, gestational weight gain, and co-morbidity during pregnancy have been associated with GDM (Alves et al., 2019; Anna et al., 2008; Goldstein et al., 2017; Hedderson & Ferrara, 2008; Schwartz et al., 2015; Zhang et al., 2014). The relationship between air pollution and GDM might be confounded and modified by these potential driving forces. However, most previous studies used administrative data (e.g. birth registry system) without individual-level information on lifestyle and co-morbidity (Zhang, et al., 2020b). In our stratified analysis, various potential modifiers were collected for individual pregnant women from KPSC EHRs. Higher risks of GDM were observed among Hispanic mothers, overweight/obese mothers, and mothers with pre-existing hypertension, alone and in combination, suggesting that these population subgroups may be more vulnerable to air pollution on GDM risk and that prevention strategies and earlier screening could be recommended for these subpopulations. Potential biological mechanisms regarding higher susceptibility of the obese group to air pollution exposure could be 1) air pollution-induced inflammation: study based on high fat diet-induced obese mice demonstrated that $PM_{2.5}$ exposure was associated with signs of marked insulin resistance, systemic inflammation, and an increase in visceral adiposity (Sun et al., 2009), which make them particularly vulnerable to air pollution-induced inflammation; and 2) toxin accumulation in adipose tissue: existing evidence suggest that environmental toxicants can be accumulated in adipose tissue. Sequestration of environmental toxicants in adipocytes may minimize their harmful effect; however, it may also pose cumulative effects of low-level chronic stimulation leading to low-grade inflammation (Jackson et al., 2017). We also found that the proportion of overweight/obese mothers was high (approximately 64%) among Hispanic populations. The results from the sensitivity analysis showed that air pollution concentrations and neighborhood socioeconomic conditions solely using the address at delivery or considering residential mobility were close. One potential reason is that the air pollution exposure based on kriging may have captured only regional-level exposure variation rather than localized exposure. Although $PM_{2.5}$ constituents estimates had an improved spatial resolution at 1 km

resolution, they may still have limited capability in capturing the true variation of specific chemical constituents at a local scale. Additionally, the median distance between the old address and new one was approximately 6 km in this population. Thus, most of women who moved during pregnancy may likely have moved within the same sub-region, which would not significantly change their estimated exposure levels.

This study has several strengths. First, the diagnosis of GDM for all KPSC members followed standard guidelines and was obtained using laboratory glucose tolerance tests rather than through recall information or diagnostic codes, thus minimizing the selection and screening biases. In addition, the KPSC EHRs contain comprehensive maternal lifestyle and co-morbidity information, which may not be available from administrative databases. This can enable deeper understanding of air pollution and GDM by adjusting for a wide range of confounders and investigating potential modifiers. Further, the mobility of women during pregnancy was documented from the KPSC database. In this population, approximately 44% women moved during pregnancy. Air pollution exposure estimation without considering residential changes may lead to misclassifications bias. More accurate residential addresses in combination with well-validated air pollution models can enhance the accuracy for the air pollution exposure assessments in this study. Moreover, an innovative statistical method was used to estimate the joint effects of exposure mixtures, which may provide insights about air pollution mixtures-GDM relationship and help develop targeted interventions. In addition, a wide range of air pollutants (i.e., $PM_{2.5}$, PM_{10}, NO_2, O_3 and five main components of $PM_{2.5}$) and exposure windows (i. e., preconception, first trimester, second trimester and entire pregnancy) were considered in this analysis.

However, several limitations in our study should be noted. First, we focused on air pollution exposure windows by trimester since only monthly air quality data were obtained. Thus, narrower exposure windows cannot be examined in this study. Second, although the date of GDM diagnosis is available in the KPSC database, the time-varying exposure based on the exact date of diagnosis was not accounted for. Some high-risk women may be screened and diagnosed with GDM early in their pregnancy (12% during the first trimester). However, the trimester-specific analyses (i.e., preconception, first, and second trimester) can reflect the exposure levels for most pregnant women since about 78% GDM cases were diagnosed after late second trimester. Further, missing lab tests for GDM diagnosis and self-reported covariates used for adjustment may lead to potential bias. In addition, potential exposure misclassifications may exist since indoor and personal exposure levels could not be estimated without data on activity patterns or personal monitors. More advanced exposure models with finer resolution would also help alleviate exposure misclassification. Moreover, previous studies have reported protective associations between built environment (e.g., green space and walkability) and GDM or diabetes (DenBraver et al., 2018; Liao et al., 2019); specifically, we found near-road pollutants (e.g., NO_2 and $PM_{2.5}$ black carbon) contributed most to the increased GDM risk. Although KPSC EHRs allowed us to control for a number of covariates in our analysis, other potential confounders, including family history of diabetes, diet, physical activity, and other maternal co-morbidities, such as hyperlipidemia, were not taken into account. Further research is also needed exploring the joint effects of air pollution and other related exposures, such as green space, noise and additional meteorological factors. Finally, air pollution exposure levels could vary in different regions

and might cause different health impacts. Therefore, more studies conducted in other regions, especially in developing countries with severe air pollution, are warranted.

5. Conclusions

In conclusion, this large study found that maternal exposures to ambient residential $PM_{2.5}$, PM_{10}, NO_2, and $PM_{2.5}$ chemical constituents were associated with an increased risk of GDM. The main effect of increased GDM risk was driven by NO_2 and $PM_{2.5}$ black carbon. Targeted interventions focusing on air quality regulation and intervention (e.g., use of air filter and purifier), earlier screening, and promoting healthier lifestyles could be conducted to reduce the risk of air pollution on GDM, especially among Hispanic mothers and overweight/obese mothers in Southern California.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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Pollutants	OR	95% CI
Krigged air pollution		
Krigged $PM_{2.5}$	1.116	(1.094, 1.138)
Krigged PM_{10}	1.094	(1.074, 1.114)
Krigged NO_2	1.176	(1.147, 1.205)
Krigged O_3	0.765	(0.748, 0.782)
$PM_{2.5}$ constituents		
$PM_{2.5}$ total mass	1.134	(1.109, 1.161)
$PM_{2.5}$ sulfate	1.077	(1.054, 1.110)
$PM_{2.5}$ nitrate	1.211	(1.186, 1.237)
$PM_{2.5}$ ammonium	1.156	(1.132, 1.179)
$PM_{2.5}$ organic matter	1.038	(1.017, 1.060)
$PM_{2.5}$ black carbon	1.178	(1.143, 1.214)
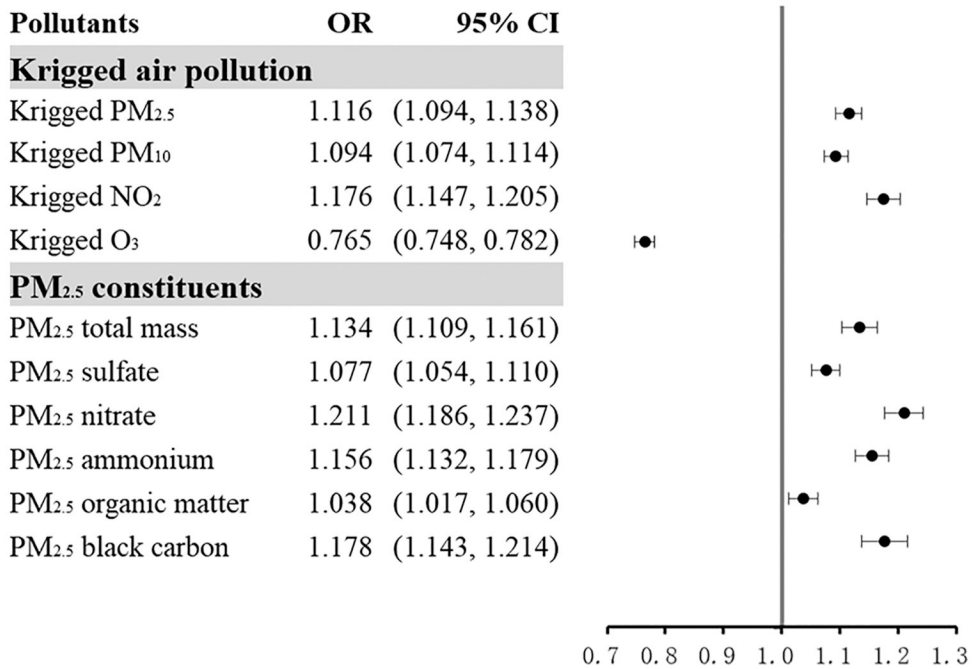
Fig. 1.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of GDM associated with air pollution during pregnancy in single-pollutant models. GDM, gestational diabetes mellitus; ORs and 95% CIs were calculated for per interquartile range (IQR) increment for each air pollutant; Model adjusted for maternal age, race/ethnicity, education, block group household income, pre-pregnancy BMI, smoking during pregnancy, insurance type, season of conception and year of birth; county was fitted as a random effect.

Table 1

Selected population characteristics and air pollution concentrations during the entire pregnancy by Gestational diabetes (GDM) groups, 2008–2018.

Characteristics	GDM n = 42,970	Non-GDM n = 352,957	Total births n = 395,927
Maternal age, years, mean (SD)	32.6 (5.3)	30.0 (5.7)	30.3 (5.7)
Maternal race/ethnicity, n (%)			
African American	2273 (5.3)	27,776 (7.9)	30,049 (7.6)
Asian	8833 (20.6)	42,775 (12.1)	51,608 (13.1)
Hispanic	22,549 (52.6)	166,627 (47.3)	189,176 (47.8)
Non-Hispanic white	7445 (17.4)	97,702 (27.7)	105,147 (26.6)
Multiple/other	1804 (4.2)	17,597 (5.0)	19,401 (4.9)
Maternal education, n (%)			
8th grade	778 (1.8)	2974 (0.9)	3752 (1.0)
9th grade – high school	12,319 (29.2)	104,595 (30.2)	116,914 (30.1)
College (<4 years)	9594 (22.7)	78,448 (22.7)	88,042 (22.7)
College (4 years)	14,026 (33.2)	111,956 (32.4)	125,982 (32.4)
> College	5485 (13.0)	48,078 (13.9)	53,563 (13.8)
Median household income at block group level in 2013, n (%)			
$43,973	11,401 (26.6)	87,270 (24.8)	98,671 (25.0)
$43,973–$56,396	11,292 (26.4)	87,382 (24.8)	98,674 (25.0)
$56,396–$72,032	10,806 (25.2)	87,903 (25.0)	98,709 (25.0)
$72,032	9360 (21.8)	89,261 (25.4)	98,621 (25.0)
Smoking, n (%)			
Never Smoker	35,967 (83.7)	294,903 (83.6)	330,870 (83.6)
Ever Smoker	4992 (11.6)	40,189 (11.4)	45,181 (11.4)
Smoking during pregnancy	2011 (5.1)	17,852 (4.7)	19,863 (5.0)
Passive smoker, n (%)			
Yes	693 (1.6)	7686 (2.2)	8379 (2.1)
No	42,267 (98.4)	345,013 (97.8)	387,280 (97.9)
Insurance type, n (%)			
Medicaid	3241 (7.6)	32,967 (9.5)	36,208 (9.3)
Other insurance type	39,240 (92.4)	315,331 (90.5)	354,571 (90.7)
Season of conception, n (%)			
Warm season	20,492 (47.7)	174,705 (49.5)	195,197 (48.5)
Cool season	22,478 (52.3)	178252(50.5)	200,730 (51.5)
Pre-pregnancy BMI in categories, n (%)			
Underweight (<18.5)	521 (1.2)	9135 (2.6)	9656 (2.5)
Normal (18.5–24.9)	11,610 (27.2)	159,565 (45.5)	171,175 (43.5)
Overweight (25.0–29.9)	12,635 (29.6)	98,469 (28.1)	111,104 (28.2)
Obese (30.0)	17,904 (42.3)	83,467 (23.8)	101,374 (25.8)
Gestational weight gain in IOM categories, n (%)			
Inadequate	17,091 (40.1)	85,828 (24.5)	102,919 (26.2)

Characteristics	GDM n = 42,970	Non-GDM n = 352,957	Total births n = 395,927
Appropriate	12,653 (29.7)	112,546 (32.1)	125,199 (31.8)
Excess	12,919 (30.3)	152,189 (43.4)	165,108 (42.0)
Chronic hypertension, n (%)			
Yes	2682 (6.2)	9198 (2.6)	11,880 (3.0)
No	40,288 (93.8)	343,759 (97.4)	384,047 (97.0)
Air pollutants from kriging model, 2008–2018, mean (SD)			
Krigged $PM_{2.5}$	11.8 (2.2)	11.6 (2.3)	11.6 (2.3)
Krigged PM_{10}	28.6 (5.3)	28.5 (5.4)	28.6 (5.4)
Krigged NO_2	16.1 (4.0)	15.6 (4.1)	15.6 (4.1)
Krigged O_3	43.1 (6.5)	44.2 (6.3)	44.1 (6.4)
$PM_{2.5}$ constituents, 2008–2017, mean (SD)			
$PM_{2.5}$ total mass	13.2 (2.5)	12.8 (2.6)	12.9 (2.6)
$PM_{2.5}$ sulfate	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)
$PM_{2.5}$ nitrate	2.5 (0.6)	2.4 (0.6)	2.4 (0.6)
$PM_{2.5}$ ammonium	1.0 (0.3)	0.9 (0.3)	0.9 (0.3)
$PM_{2.5}$ organic matter	5.5 (1.2)	5.4 (1.3)	5.4 (1.3)
$PM_{2.5}$ black carbon	1.6 (0.6)	1.5 (0.6)	1.5 (0.6)

SD, standard deviation; BMI, body mass index; IOM, Institute of medicine. The units are $\mu g/m^3$ for PM_{10}, $PM_{2.5}$ mass and $PM_{2.5}$ constituents, and parts per billion for NO_2 and O_3.

Table 2

Summary statistics and Pearson correlation coefficients between air pollutant exposure metrics during pregnancy.

	IQR	Krigged air pollutants[a]				PM$_{2.5}$ constituents[b]					
		Krigged PM$_{2.5}$	Krigged PM$_{10}$	Krigged NO$_2$	Krigged O$_3$	PM$_{2.5}$total mass	PM$_{2.5}$ sulfate	PM$_{2.5}$ nitrate	PM$_{2.5}$ ammonium	PM$_{2.5}$ organic matter	PM$_{2.5}$ black carbon
Krigged PM$_{2.5}$	3.08	1.00									
Krigged PM$_{10}$	6.16	0.66	1.00								
Krigged NO$_2$	5.73	0.61	0.31	1.00							
Krigged O$_3$	9.13	−0.10	0.23	−0.36	1.00						
PM$_{2.5}$ total mass	3.85	0.83	0.50	0.68	−0.05	1.00					
PM$_{2.5}$ sulfate	0.35	0.48	0.46	0.21	0.28	0.49	1.00				
PM$_{2.5}$ nitrate	0.94	0.75	0.51	0.58	−0.06	0.86	0.36	1.00			
PM$_{2.5}$ ammonium	0.40	0.69	0.48	0.57	0.003	0.75	0.46	0.80	1.00		
PM$_{2.5}$ organic matter	1.78	0.75	0.46	0.65	−0.09	0.91	0.35	0.66	0.55	1.00	
PM$_{2.5}$ black carbon	1.05	0.60	0.18	0.62	−0.28	0.79	0.25	0.54	0.53	0.72	1.00

IQR, interquartile range.

[a] air pollutants from kriging interpolation of Environmental Protection Agency's routine monitoring station data

[b] PM$_{2.5}$ constituents from a fine-resolution geoscience-derived model. The units are μg/m^3 for PM$_{10}$, PM$_{2.5}$ and PM$_{2.5}$ constituents, and parts per billion for NO$_2$ and O$_3$.

Table 3

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of GDM associated with air pollution during pregnancy in multi-pollutant models.

Pollutants	Coefficient β	Effect of mixtures ψ (log OR)	95% CI	OR	95% CI
Model 1: Krigged air pollutants					
Krigged $PM_{2.5}$	0.031				
Krigged PM_{10}	−0.051	0.091	(0.079, 0.103)	1.095	(1.082, 1.108)
Krigged NO_2	0.111				
Model 2: $PM_{2.5}$ constituents					
$PM_{2.5}$ sulfate	−0.004				
$PM_{2.5}$ nitrate	0.082				
$PM_{2.5}$ ammonium	0.065	0.229	(0.187, 0.273)	1.258	(1.206, 1.314)
$PM_{2.5}$ organic matter	−0.050				
$PM_{2.5}$ black carbon	0.135				

GDM, gestational diabetes mellitus;

Model adjusted for maternal age, race/ethnicity, education, block group household income, pre-pregnancy BMI, smoking during pregnancy, insurance type, season of conception, year of birth and county.