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Modeling spatially varying compliance effects of PM2.5 exposure reductions on gestational diabetes mellitus in southern California: Results from electronic health record data of a large pregnancy cohort

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Abstract

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Gestational diabetes mellitus (GDM) is a major pregnancy complication affecting approximately 14.0% of pregnancies around the world. Air pollution exposure, particularly exposure to $PM_{2.5}$, has become a major environmental issue affecting health, especially for vulnerable pregnant women. Associations between $PM_{2.5}$ exposure and adverse birth outcomes are generally assumed to be the same throughout a large geographical area. However, the effects of air pollution on health can very spatially in subpopulations. Such spatially varying effects are likely due to a wide range of contextual neighborhood and individual factors that are spatially correlated, including SES, demographics, exposure to housing characteristics and due to different composition of particulate matter from different emission sources. This combination of elevated environmental hazards in conjunction with socioeconomic-based disparities forms what has been described as a "double jeopardy" for marginalized sub-populations. In this manuscript our analysis combines both an examination of spatially varying effects of a) unit-changes in exposure and examines effects of b) changes from current exposure levels down to a fixed compliance level, where compliance levels correspond to the Air Quality Standards (AQS) set by the U.S. Environmental Protection Agency (EPA) and World Health Organization (WHO) air quality guideline values. Results suggest that exposure reduction policies should target certain "hotspot" areas where size and effects of potential reductions will reap the greatest rewards in terms of health benefits, such as areas of southeast Los Angeles County which experiences high levels of $PM_{2.5}$ exposures and consist of individuals who may be particularly vulnerable to the effects of air pollution on the risk of GDM.

Keywords

Gestational diabetes mellitus; Spatially varying effects; Air pollution exposures; Bayesian modeling, multi-level models

1. Introduction

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation (American Diabetes Association Professional Practice Committee, 2021). GDM is a major pregnancy complication affecting approximately 14.0% of pregnancies around the world (Wang et al., 2022) and 7.6% of pregnancies in the U.S. (Casagrande et al., 2018) and is associated with higher risk of short- and long-term adverse health outcomes in both mothers and their offspring (Daly et al., 2018; Farahvar et al., 2019; Mirghani Dirar and Doupis, 2017; Tobias et al., 2017). Mothers who have GDM are more likely to develop preeclampsia during pregnancy, as well as type 2 diabetes, metabolic syndrome, and cardiovascular diseases after delivery (Daly et al., 2018; Farahvar et al., 2019; Lai et al., 2016; Mirghani Dirar and Doupis, 2017; Tobias et al., 2017). For offspring, a series of increased risk of adverse health outcomes in relation to GDM are reported, including preterm birth, macrosomia, 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., 2019; Metzger, 2007; Nijs and Benhalima, 2020; Tam et al., 2017; Xiang et al., 2015; Xu et al., 2014).

Air pollution has become a major environmental issue affecting health, especially for vulnerable pregnant women. Exposure to $PM_{2.5}$ has been shown to be associated with higher risk of adverse pregnancy and birth outcomes, such as GDM (Sun et al., 2021), hypertensive disorders of pregnancy (Bai et al., 2020), term low-birth weight ((Wilhelm et al., 2012)), and preterm birth (Lamichhane et al., 2015,(Ritz et al., 2007)). Generally, associations between $PM_{2.5}$ exposure and adverse birth outcomes are assumed to be the same throughout a large geographical area. However, the effects of air pollution on health can very spatially in subpopulations. For example, (Coker et al., 2015) found that the association of $PM_{2.5}$ exposure with term low-birth weight were greater within the urban core of Central and Southern Los Angeles County census tracts where large percentages of people of lower socioeconomic status (SES) resided. Such spatially varying effects are likely due to a wide range of contextual neighborhood and individual factors that are spatially correlated, including SES, demographics, exposure to violence ((Messer et al., 2006)), access to healthy food ((Walker et al., 2010)) or green space ((Hystad et al., 2014)), housing characteristics and due to different composition of particulate matter from different emission sources. To the best of our knowledge, no study has explored the spatial variation in $PM_{2.5}$ *effects* (not just concentration levels) on GDM in a large obstetric population. Simply estimating global pollutant effects may obscure disparities suggested by spatial patterns. In addition, identifying effect "hotspots", i.e., areas where policy interventions are likely to reap the biggest rewards in terms of reducing incidence of GDM, could help guide spatially targeted public health interventions and protect susceptible subpopulations.

While effects of unit-level reductions in exposure may vary spatially in a large geographical region, one must also consider the reality that base-line levels of air pollution exposures vary spatially as well. Such spatially varying levels of exposure mean that exposure reduction policies may result in larger reductions in some regions over others. One goal of exposure reduction policies is to reduce exposures from current levels down to *compliance* levels where compliance levels corresponds to National Ambient Air Quality Standards (NAAQS) set by the U.S. Environmental Protection Agency (EPA) (US EPA, 2020) and World Health Organization (WHO) air quality guideline values ((WHO)). These compliance levels are designed to guide policy makers in limiting the amount of $PM_{2.5}$ in the air, and thus protect public health by reducing exposure to harmful air pollutants. Here, ambient air quality standards are important in that they define the maximum amount of pollutant that can be present in outdoor air without harming human health. (CARB, 2023; Brook et al., 2010; Krewski, 2009; Laden et al., 2006).

Air pollution studies consistently show that communities of color and those containing large proportions of low-income residents are exposed to higher levels of air pollution as they are often located near major sources of exposures such as highways and industrial facilities (Hajat et al., 2015). In addition, these disadvantaged communities are more susceptible to the harmful effects of elevated exposures to social stressors such as poor diet, poor quality of housing stock, being lower on the social hierarchy, and other lifestyle factors such as smoking and the weathering effects of racism (Morello-Frosch et al., 2011; Geronimus et al., 2006). This combination of elevated environmental hazards in conjunction with socioeconomic-based disparities forms what has been described as a "double jeopardy"

for marginalized sub-populations, suggesting that individuals living in disadvantaged communities would suffer worse health effects compared to more advantaged people, even at the same levels of exposures (Li et al., 2022; Su et al., 2016; Molitor et al., 2011; Morello-Frosch and Bill, 2006). As such it is important to look at how air pollution reduction policies can affect individuals both in terms of addressing elevated exposure levels facing vulnerable subpopulations and deal with how such reductions differentially affect individuals because of their socio-economic status. Here, double jeopardy refers to inequalities in both exposure and susceptibility. In this manuscript our analysis combines both an examination of spatially varying effects of **a) *unit-changes in exposure*** and examines effects of ***b) changes from current exposure levels down to a fixed compliance levels***, Here, *different individuals may experience different levels of exposure reductions based on individual exposure reduction needs*. By looking at impacts of exposure reduction in regard to both *amount and effect* of reduction we appeal to certain aspects of the concept of equity in exposure effect modeling, which refers to "inequities in health systematically put groups of people who are already socially disadvantaged (for example, by virtue of being poor, female, and/or members of a disenfranchised racial, ethnic, or religious group) at further disadvantage with respect to their health." (Ramirez et al., 2008). This approach considers the possibility that ethnic minorities and people living in low and middle-income areas may be more vulnerable to air pollution due, in part, to the higher levels of air pollution to which they are exposed (Samet, 2004). As such, we examine spatially varying differential effects of exposure reduction on health in a manner that considers both subpopulation vulnerability and elevated exposure levels. Our reasons for examining such effects are two-fold: (1) We expect that different regions (census tracts in our case) will have different base-line levels of $PM_{2.5}$ and thus have different potentials for reduction, with regions containing very high levels of exposure having greater potential for large exposure reductions as a result of policy enforcement; (2) Unit-level effects of policy on exposure reductions and health improvements will likely be greater in areas of low SES compared to areas of high SES where individuals are somewhat insulated from effects of high exposure and will likely benefit less from measures used to reduce exposures. In this way, we focus on real-world issues related to effects of exposure reduction policy, with an eye towards the fact that policy implementation may result in greater health benefits in some regions than others. Note here that our results will be beneficial to policy makers as we establish links between $PM_{2.5}$ exposure and GDM and provide information regarding areas where policies related to air pollution reduction intervention will likely reap the biggest rewards in terms of health benefits related to GDM.

Our examination focuses on spatially varying reductions down to compliance, but in a manner which takes into account the spatially varying effects that each unit of reduction has on GDM. Thus, in this paper, we aim to examine the spatially varying effects of $PM_{2.5}$ on GDM in southern California with the broad hypothesis that such effects and policy-based reduction will vary spatially both in size and effect, and such variations will be affected by contextual-based factors such as living in a lower SES community and issues such as diminished access to care or occupational status.

2. Methods

2.1. Study population and GDM outcome

This retrospective cohort study used electronic health records (EHRs) from all Kaiser Permanente Southern California (KPSC) facilities, including women who gave birth to singleton children between January 1, 2008, and December 31, 2017. We excluded women who were not KPSC members or with gestational age 20 or 47 weeks (n = 8344), with multiple birth (n = 6694), with stillbirth (n = 1747), without address data (n = 653), with incomplete covariates data (n = 5337), or lived in rural areas (n = 13,262). We also excluded pregnancies with preexisting diabetes (n = 4598) or missing GDM lab test results (n = 30,201). In total, 341,909 women were included in this analysis. GDM diagnosis was based on KPSC laboratory tests using two criteria for GDM testing: the Carpenter-Coustan criteria (Carpenter and Coustan, 1982) or the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (Metzger, 2010). More details of this population and GDM diagnosis have been described in our previous work (Sun et al., 2022). This study was approved by the Institutional Review Board of KPSC and the University of California, Irvine.

2.2. $PM_{2.5}$ exposure

Historical ambient monthly $PM_{2.5}$ measurements from 2007 to 2018 were obtained from the fine-resolution geoscience-derived models (Meng et al., 2019; van Donkelaar et al., 2019), which provide validated and publicly available $PM_{2.5}$ outputs at a 1-km resolution over North America based on satellite remote sensing, GEOS-Chem chemical transport modeling and ground-based monitors with a geographically weighted regression. Simulated relative composition using relative-humidity-dependent and composition-dependent fixed size distribution was applied to the hybrid $PM_{2.5}$ mass to produce $PM_{2.5}$ constituents. All the 1-km grids that are within or intersecting a census tract were averaged to assess the census tract-level air pollution exposures. Air pollution estimates were spatiotemporally linked to each woman based on the geocoded maternal residential addresses. We calculated entire-pregnancy and trimester-specific and entire-pregnancy exposures by averaging the air pollution measurements in each specific time period: entire-pregnancy (from the date of conception to the date of delivery); the first trimester (1st - 3rd gestational months) and second trimester (4th - 6th gestational months). Our previous work showed that the patterns of the association between GDM and air pollution were similar for different exposure windows during pregnancy (Sun et al., 2021). In addition, most pregnant women were routinely screened for GDM between 24 and 28 weeks of gestation. Therefore, our main exposure for the GDM risk is total mass $PM_{2.5}$ in the first and second trimester. As a sensitivity, we also analyzed other $PM_{2.5}$ constituents: sulfate, nitrate, ammonium, organic matter, and black carbon. Correlations between various $PM_{2.5}$ constituents are displayed in the plot in Appendix F.

2.3. Covariates

Pregnancy-related covariates and potential confounders were selected *a priori* based on the existing literature (Eze et al., 2015; Thiering and Heinrich, 2015; Zhang et al., 2020) and

abstracted from the KPSC EHRs: 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 in the block group of residence at birth (CDC, 2023); pre-pregnancy body mass index [BMI, kg/m^2: underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9) and obese (30.0)]; maternal smoking status during pregnancy (never smoker, ever smoker, smoking during pregnancy, and passive smoker); insurance type; season of conception (warm: May–October; cool: November–April) and year of infant birth.

2.4. Statistical analysis

Here we employ hierarchical methods in the spirit of Spatially Varying Coefficient (SVC) models (Coker et al., 2015; Franco-Villoria et al., 2019a) in a Bayesian setting to estimate the varying effects of exposure in a unified multivariate manner. We model "intercepts", or baseline levels of log-odds of GDM, and "slopes", or spatially varying effects of increases in exposure, jointly via a level-2 multivariate normal distribution. Note that these spatially varying slopes reflects effect modification by spatially varying environmental conditions. (For a book-level discussion of hierarchical models and joint modeling of intercepts and slopes, see Gelman and Jennifer, 2006). Our analysis suggests that both intercepts and slopes are highly correlated, necessitating the multivariate approach. (For example, in analyzing PM$_{2.5}$ exposures the correlation coefficient between intercepts and slopes was $\rho = 0.426$.) Since the intercepts and slopes are modeled jointly, our model incorporates a kind of smoothing or "borrowing of strength" where parameter estimates corresponding to a region in question can inform estimates of other regions, and where estimates corresponding to regions with higher sample sizes exert more influence in the smoothing process compared to regions with smaller sample sizes.

Here, one could improve inference by incorporating spatial smoothing techniques, which utilize information regarding regions (in our case census tracts) in a manner that nearby regions influence region-specific parameter estimates more than those farther away, via models such as the Conditional Auto Regression (CAR) model (Besag et al., 1991) or the related Besag-York-Mollie (BYM) model (J. Besag, York, and Molli\'e 1991). It would seem to make sense to use these approaches to model both sets of parameters (intercepts and slopes) in a spatial manner as was done in (Franco-Villoria et al., 2019a). However, modeling both intercepts and slopes in this manner is potentially problematic due to issues of "spatial confounding" (Hodges et al., 2010), where, for example, spatially varying intercepts terms can compete with slopes (effects of exposure) and thus explain away or and "wash out" these important, real effects. This is less of an issue when utilizing the common disease mapping models employed by (Franco-Villoria et al., 2019a) where the focus in on predicting outcomes (relative risks) related to disease counts. Note that Franco-Villoria et al. did address this issue to some extent via the use of careful chosen informative prior specifcation via Penalized-Complexity (PC) priors. (Simpson et al., 2017). An alternative strategy to dealing with such confounding issues would be to adopt the approach of Coker et al. (2015) and only model exposure effects (slopes) spatially, thus sidestepping this spatial confounding issue to some extent. However, here we wish to model relatively highly

correlated spatially varying intercept terms along with effect (slope) parameters which would suggest that if spatial smoothing were desired one should model these intercepts and slopes jointly with multivariate spatial model such as the Multivariate-CAR model (Palmí-Perales et al., 2021). However, these models are difficult to fit, complicated in a Bayesian setting regarding prior specification, and may still suffer from spatial confounding issues. Here, for the most part, we forgo these complexities related to spatial smoothing and fit standard hierarchical models employed by Gelman and Jennifer (2006), which are sufficiently complex to capture the spatially varying effects for our analyses. We do, however, as a sensitivity analysis include an analysis utilizing spatial smoothing on slopes only as done by Coker et al. (2015) (See Fig. 4).

One aspect of standard hierarchal models (including SVC models) and of regression-based models in general is that effects are generally measured in terms of effects on health, Y_i for individual i, for one unit change in exposure X_i. For example, if X_i denotes $PM_{2.5}$ exposure then the "beta" coefficient (slope) in a regression model will indicate predicted change in health outcome Y_i (or perhaps log odds of Y_i equal to one) for a one-unit change (reduction) in exposure, say the change of $X(1) = X_i$ to $X(0) = X_{i-1}$. This is true weather or not the effect parameters vary by region. However, in this paper we examine spatially varying effects of single-unit reductions of $PM_{2.5}$ exposure but *in addition* we also examine effects of bringing exposures down from current levels to "compliance" levels, namely exposure levels consistent with Air Quality Standards (AQS) set by the U.S. Environmental Protection Agency (EPA) (US EPA, 2020), and World Health Organization (WHO) air quality guideline values (WHO).

In the case of total $PM_{2.5}$, individual-level compliance, denoted by δ, is set to a secondary annual standard of $\delta_{12} = 12.0$ $\mu g/m^3$, as defined by the U.S. EPA as an area that meets the standard "if the three-year average of its annual average $PM_{2.5}$ concentration is less than or equal to the level of the standard." (US EPA, 2020). We examine effects of changes from current levels of exposure down to compliance levels (with compliance defined above), or, more generally, the effect of going from exposure levels $X(1)$ to $X(0)$, where $X(1) = X_i$ (current exposure level) and $X(0) = \delta$. As a sensitivity analysis, we also define compliance as $\delta_5 = 5.0$ $\mu g/m^3$, which is the guideline values for fine particulate matter $PM_{2.5}$ as specified by the WHO (WHO).

We outline our model as follows. For individual i, we denote $Y_i = 1$ for presence of GDM and $Y_i = 0$ otherwise, p_i denotes probability of GDM for individual i, $PM_{2.5,i}$ denotes the neighborhood-level exposure. Our model is:

$$\text{logit}(p_i) = \beta_{0,r_i} + \boldsymbol{V}\boldsymbol{\eta}_i + \beta_{1,r_i}PM_{2.5,i} \tag{1}$$

where β_{0,r_i} and β_{1,r_i} represent baseline (intercepts) exposure levels and exposure effects (slopes) respectively for the region r to which individual i belongs (with census tract as region in this case), and $\boldsymbol{V}\boldsymbol{\eta}_i$ corresponds to baseline covariate adjustments corresponding to mother's age, race/ethnicity, insurance type, education, BMI, smoking status, household income at birth, season of conception, and year of infant birth. We model intercepts and

slope terms via standard random effects constructs with error terms which incorporates a multivariate structure. Our slopes and intercepts are as:

$$\beta_{0r} = \gamma^{inter} + \varepsilon_r^{inter} \tag{2}$$

$$\beta_{1r} = \gamma^{slope} + \varepsilon_r^{slope} \tag{3}$$

We jointly model intercepts and slopes as multivariate normal where $\beta_r = (\beta_{0r}, \beta_{1r})$ is modeled as multivariate normal as,

$$\beta_r \sim MVN\left[\begin{pmatrix} \gamma^{inter} \\ \gamma^{slope} \end{pmatrix}, \begin{pmatrix} \sigma_{inter}^2 & \rho\sigma_{inter}^2\sigma_{slope}^2 \\ \rho\sigma_{inter}^2\sigma_{slope}^2 & \sigma_{slope}^2 \end{pmatrix}\right] \tag{4}$$

Our analysis is conducted via the Bayesian software package R-INLA (Rue et al., 2009), a well-established software package which provides a fast Bayesian estimation of parameters for models utilized in complex spatially-orient problems. We were able to jointly model the error terms via use of the recently developed "copy" command in INLA (See Gómez-Rubio, 2020) Default flat priors were utilized, though all continuous covariates were standardized (subtracting mean and dividing by standard deviation), including exposures, which to some extent alleviated issues related to invertly providing highly informative prior specifications. (Compliance levels were subjected to the same standardization.)

Using the R-INLA package, we are able to compute relevant odds ratios (OR's) corresponding to unit reductions in exposure (Fig. 1a) and exceedance probabilities corresponding to the likelihood that the corresponding odds ratio (OR) is greater than one, namely $\Pr(\beta_{1,r} > 0) = \Pr(e^{\beta_{1,r}} > 1)$ for each census tract, $r = 1, ..., R$, in a manner consistent with (Coker et al., 2015) (See Fig. 1b.). In order to examine compliance effects, or effects on GDM for exposure reduction from current levels down to compliance level δ, we simply compute odds ratios corresponding to the average exposure for region r as compared to compliance, namely the odds ratio appropriate for an individual with exposure $\overline{PM}_r$ for region r compared to δ, corresponding to reductions $d_i = X_i - \delta$, where $\delta = \delta_{12}$ or $\delta = \delta_5$ (before standardization). We dub these ratios as Compliance Odds Ratios (COR's) as they incorporate different reductions for different individuals (d_i for individual i) throughout space *and* incorporate different unit-level effects β_{r_i} corresponding to the region r to which individual i belongs. We note that for some census tracts, the average $PM_{2.5}$ exposure levels are already below compliance. Since we are not interested in examining interventions which may correspond to exposure increases, we set $d_i = 0$ in these areas, thus denoting that no reduction in exposure is required to achieve compliance levels. For a small number of regions, the point estimates for β_r are negative, meaning that for these few areas the model is suggesting a protective effect of air pollution (though usually these protective effects are associated with high exceedance probabilities, i.e., high uncertainty.) Such effects may be due to exposure misclassification, residual confounding, or perhaps model misspecification. Note that we are modeling linear effects per region (but *not* a linear effect across the

whole geographical space is as often done) and this linearly could be distorting the exposure/ response relationship at low levels of PM$_{2.5}$ (See for example, (Weichenthal et al., 2022), for a discussion on supralineasr effects of very low levels of PM$_{2.5}$.). In these circumstances, where the β_r is negative, we fix $\beta_r = 0$ as we are trying to focus on areas where exposure reductions have the largest effect on reducing likelihood of GDM. With these restrictions in place we can then compute COR's for all census tracts which thus enable us to produce maps which display "hotspot" areas where reductions of individual-level exposures levels down to compliance present the greatest benefit in terms of reduction in probability of GDM.

3. Results

We first reiterate that all continuous variables used in the model, including exposures, have been standardized by subtracting off the relevant means and dividing by the standard deviations. Also, the correlation between intercepts and slopes is positive 0.426 (0.308, 0.538) (equation (4)), suggesting that higher effects of exposure reduction are aligned with higher baseline levels of GDM.

The distribution of selected demographic and pregnancy characteristics is presented in Table 1. Among 341,909 women included in our study population, 37,711 (11.0%) cases of GDM with clinical diagnosis were identified. The mean of maternal age in our study was 30.2 years. Compared to the entire cohort, GDM cases were found more frequently among older mothers, Asian or Hispanic mothers, mothers who lived in low-income neighborhoods, and overweight or obese mothers. Individual residential exposure levels of air pollution metrics during entire pregnancy were shown in Table 2. Overall, air pollution exposures were higher among mothers with GDM, younger mothers, African American or Hispanic mothers, mothers with low education, mothers who lived in low-income neighborhoods, and obese mothers for PM$_{2.5}$ and PM$_{2.5}$ chemical constituents. In addition, PM$_{2.5}$ total mass and PM$_{2.5}$ constituents, including nitrate, organic matter and black carbon, were higher among mothers who conceived in warm season, while PM$_{2.5}$ sulfate levels were higher for mothers who conceived in cool season.

Table 3 provides results from the regression analysis corresponding to "fixed" effects, though our focus here is on examination of spatially varying slopes which indicate spatially varying effects of exposure, which consist of linear combinations of the fixed and random effects in equation (3), which can be computed via the "lincomb" function in R-INLA. These slopes form the basis for computation of the kind of spatially varying Odds Ratios (OR's) which address our interest in spatially varying effects of exposure reductions. Fig. 1a below provides estimates these OR's corresponding to unit reductions in exposure, which could be used to inform decisions as to where policy interventions would be most beneficial. However, Fig. 1b reveals that many of the areas in Fig. 1 with high OR's have relatively low exceedance probabilities, Pr($\beta_r > 0$), suggesting high levels of uncertainty regarding some of these OR estimates. Fig. 1a and b thus suggest that policy-interventions be focused in areas such as southeast Los Angeles County and parts of Kern, San Bernadino, Riverside and San Diego Counties. However, as Fig. 2 reveals, some of these areas, such as parts of Riverside

and San Diego Counties, have relatively low levels of exposure, making these areas less relevant from a "hotspot" exposure reduction point of view. Further, certain southwest parts of Kern County with the highest exposures (representing potentially prime areas for exposure reductions) are associated with some of the lowest exceedance probabilities. If we focus on the COR maps corresponding to δ_{12} (Fig. 3a) we see that areas in southeast Los Angeles County have high OR, high exceedance probabilities, and display high levels of exposures. This is a somewhat disadvantaged area of Los Angeles County that has a high population of Hispanics. The COR map thus provides perhaps the most useful display of areas where individual-level exposure reductions are likely to reap the greatest rewards in terms reduction in prevalence of GDM. We further note that the COR map related to δ_5 (Fig. 3b) represents much more extreme exposure reductions, and this map suggest interventions in additional areas of potential intervention if such large exposure reductions are to be proposed in the hotspot areas of intervention. When we examine $PM_{2.5}$ constituents (see relevant Appendices), we see high exceedance probabilities effects of $PM_{2.5}$ ammonium, black carbon, and nitrate in the same area of southeast Los Angeles in a manner similar to what was observed for $PM_{2.5}$ total mass, though for $PM_{2.5}$ sulfate and organic matter the exceedance probabilities are low throughout the whole study region, suggesting that these components are less influential regarding the overall effect of exposure on likelihood of GDM.

Though issues of the aforementioned spatial confounding are a continual concern in these kind of analyzes, we did, as a sensitivity analysis, analyze the $PM_{2.5}$ exposures using a model with random intercepts and slopes ("effects") as before, but this time without the joint multivariate normal specification and modeled the slopes using a spatially smoothed intrinsic Conditional Autoregressive (iCAR) model (Besag et al., 1991). We used "vague" uniform priors on the variance component for the random intercepts and on the variance component of the spatial model used for the slopes. The results were nearly identical with alternative priors such as the half normal. (Both priors are specified and coded in (Gómez-Rubio, 2020) Results were quite similar to those obtained without the spatial smoothing, though there is an obvious effect of smoothing on results. For a comparison, see smoothed graphs of compliance effect for Compliance OR's for $PM_{2.5}$ values of 12 ug/m^3 and 5 ug/m^3 (Fig. 4) and to jointly modeled (with no spatial smoothing) plots of similar OR's in Fig. 3. We did experiment with addition of spatial smoothing terms for the intercepts; however, results were somewhat sensitive to prior specification and presence/absence of smoothing constructs. In models with spatially smoothed effects (or "slopes") the spatially distributed error terms are weighted by the exposure and are thus not expected to be orthogonal to it. As such, spatial confounding is less of an issue in this situation. Nevertheless, while we recognize the value of incorporation of spatially smoothed terms into the modeling process, one must be extra cautious regarding issues related to model and prior specification when these spatially smoothed error terms are included in these kinds of models.

4. Discussion

Our analysis provides insights as to where policy interventions, in terms of reducing prevalence of GDM, will be most effective among a cohort of women living throughout

Southern California. A Bayesian statistical model was fit providing spatially varying effects of unit level reduction in exposure, in conjunction with OR's which take into account effects of exposure reductions down to compliance levels. This combination of size and effect of air pollution reductions helps focus on areas which are likely to benefit most from exposure policy interventions.

To the best of our knowledge, no study has explored the spatial variation in $PM_{2.5}$ effects on GDM in a large obstetric population. Spatial modeling approaches have been used in previous studies to investigate spatial structure in relationship between air pollution and health outcomes. The major advantage gained in using this approach is to not only examine spatial varying effects of air pollution on health but also develop public health interventions to optimize the potential benefits and promote environmental health equity. First, our findings imply that uniform air quality regulation and intervention may not be sufficiently protective to susceptible population subgroups, and that such policies may need to be spatially tailored for these subregions. Second, our approach could identify 'hotspots' to help guide spatially targeted interventions to protect susceptible subpopulations from outdoor air pollution (e.g., use of air filter and purifier to reduce indoor air pollution at home and workplace). Further, potential public health interventions (e.g., earlier GDM screening, and healthier lifestyles) could be also conducted to reduce the risk of air pollution on GDM among subpopulations who live in the hotspot regions. In summary, interventions targeting the hotspot areas may translate into a more pronounced reduction of GDM in southern California and maximize the benefits of reducing air pollution exposure during pregnancy.

Our results also underscore the need to prioritize such hotspot regions for addressing environmental health disparities. For example, these hotspots of southeast Los Angeles County have a high population of Hispanics, who may be particularly vulnerable to air pollution on the risk of GDM (Sun et al., 2021). Moreover, some hotspot regions in Kern County, and southern Los Angeles County and downwind areas are disadvantaged communities with higher $PM_{2.5}$ level, but which also lack an air quality monitoring network (Sun et al., 2022). Therefore, such hotspot regions are in the greatest need of public health interventions and air pollution regulations to close the gap of environmental health inequity.

One could examine interactions between SES-based susceptibility factors and exposure effects throughout space, which could improve interpretability of results. However, such an analysis is quite complex, may require additional data, and is thus beyond the scope of the paper. We note that in our previous work we have utilized Bayesian Profile Regression (BRP) (Molitor et al., 2010) to construct SES-based clusters and to examine effects of exposure for each cluster in question. Such work can be quite involved as effects of exposure can vary according to SES cluster and other, unobserved factors as well (Coker et al., 2016) and careful selection of SES variables must be considered.

Our study has its limitations as the data are observational, and as such one cannot be sure that all necessary confounders have been accounted for or that the confounders used where adjusted using the proper mathematical form. From a modeling perspective, we assumed logit-linear models at the CT-level, though modeling such linearity at the small-region level does not mean that we assume such a linear relationship between exposures and

log-outcome throughout the entire study region. Also, potential non-linear time trends in exposures and log-odds of GDM where not explicitly modeled and spatially smoothing techniques where forgone to sidestep issues of spatial confounding. As such, there could be some loss of information compared to what would be obtained using richer, though perhaps harder to interpret models. Further, many areas contain high amounts of parameter estimation error (and thus low exceedance probabilities), corresponding relevant quantities such as OR's COR's, etc. This may be due to low effects sizes in these areas, or it may simple be a data issue related to low regional sample sizes or a lack of exposure-level variability, making effect estimation difficult for these areas in question. Of further note is the fact that we only considered $PM_{2.5}$ and its constituents, and no other gaseous pollutants such as O_3 and NO_2. However, if limited resources are available for intervention purposes, our results can still point policy makers towards areas where exposure reduction is likely to have a high impact on health improvement, as opposed to areas where the success of such interventions is highly uncertain.

While our study contains weaknesses, it contains many strengths as well. In particular, our study contains a relatively large number of individuals, and represents a large and diverse set of regions throughout southern California. In addition, the high-quality and comprehensive information on diagnosis, demographic characteristics, and individual lifestyle from the KPSC EHRs can minimize the screening biases and enable deeper understanding of air pollution and GDM by adjusting for a wide range of confounders. Moreover, well-validated air pollution models can provide a wide range of chemical compositions of $PM_{2.5}$ and enhance the accuracy for the air pollution exposure assessments. Further, both WHO and national compliance levels of $PM_{2.5}$ were considered in this analysis.

There is a long tradition in environmental epidemiology research where effects of exposures are summarized based on the concept of "statistical significance" and often accompanied with a p-value and an associated confidence interval. However, from an intervention perspective, interest often lies in the size of the relevant effect and how that effect varies spatially regarding SES and other geographically varying modifiers. Such spatially varying effects and associated modeling frameworks are well established. However, due to potential complexities in implementation, such methods are often underutilized. In this paper we provide an example of how to model spatially varying effects using a relatively simple model, but also combine such analysis with consideration for spatially varying amounts of exposure reductions based on the idea that more highly exposed areas provide greater opportunity for exposure reduction compared to regions which already experience low levels of exposure and are thus unlikely to be greatly affected by exposure-reduction oriented policies. This approach, examining both size and effect of exposure reductions, provided a meaningful and useful set of maps and results that can be utilized to provide targeted intervention policies designed to optimize effects of exposure reductions on health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

Data availability

The data that has been used is confidential.

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a.

b.
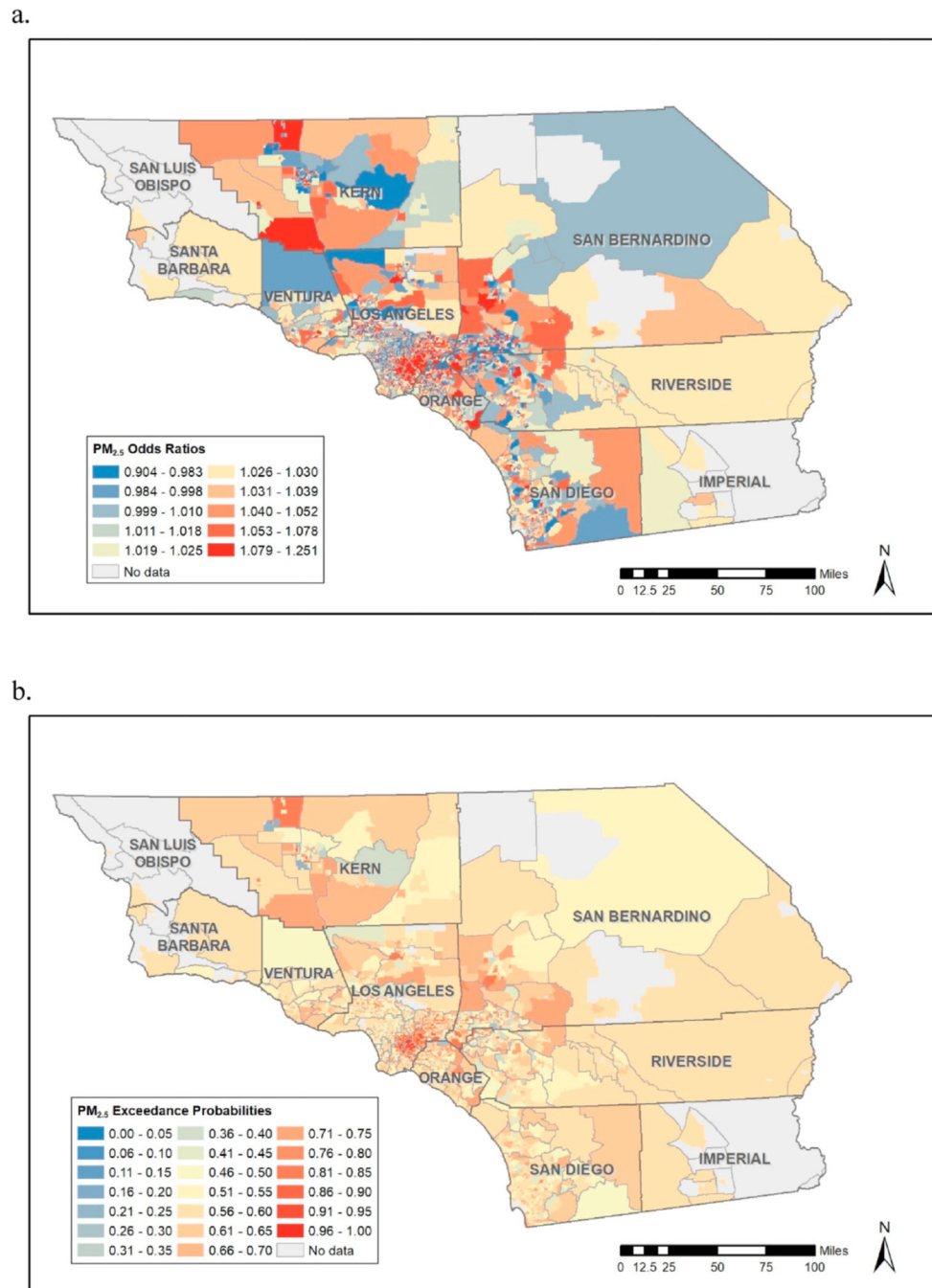
Fig. 1.
PM$_{2.5}$ total mass (a) odds ratios corresponding to unit changes on exposure and (b) exceedance probabilities corresponding unit reductions in exposure $Pr(\beta_r^{slope} > 0)$.
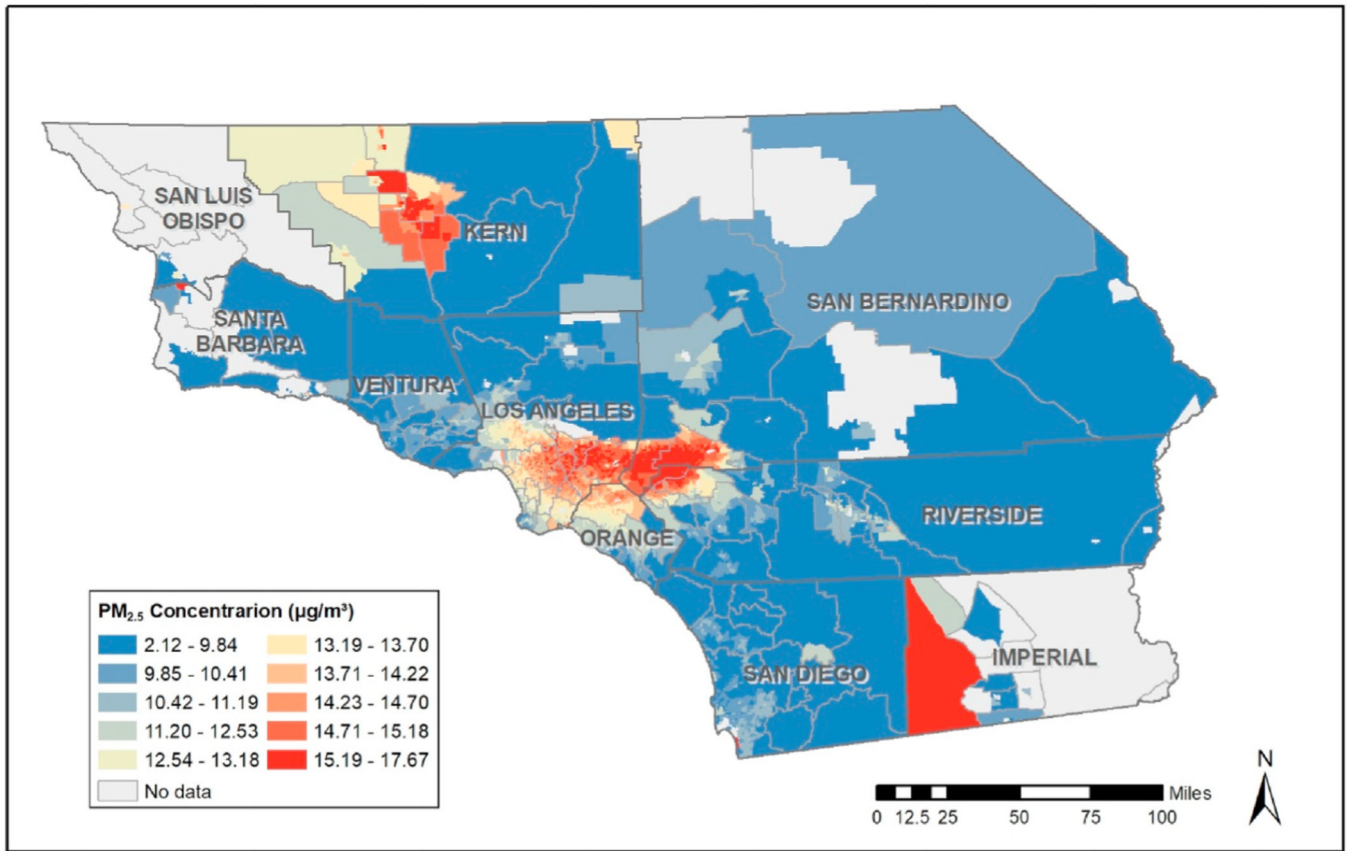
Fig. 2.
Average census tract exposure levels for PM₂.₅ total mass.

a.
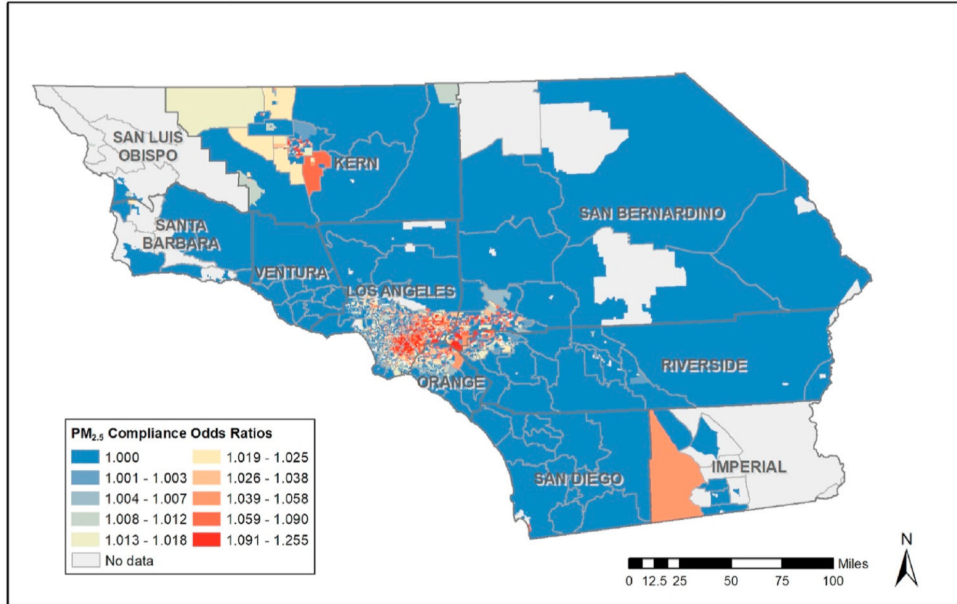
b.
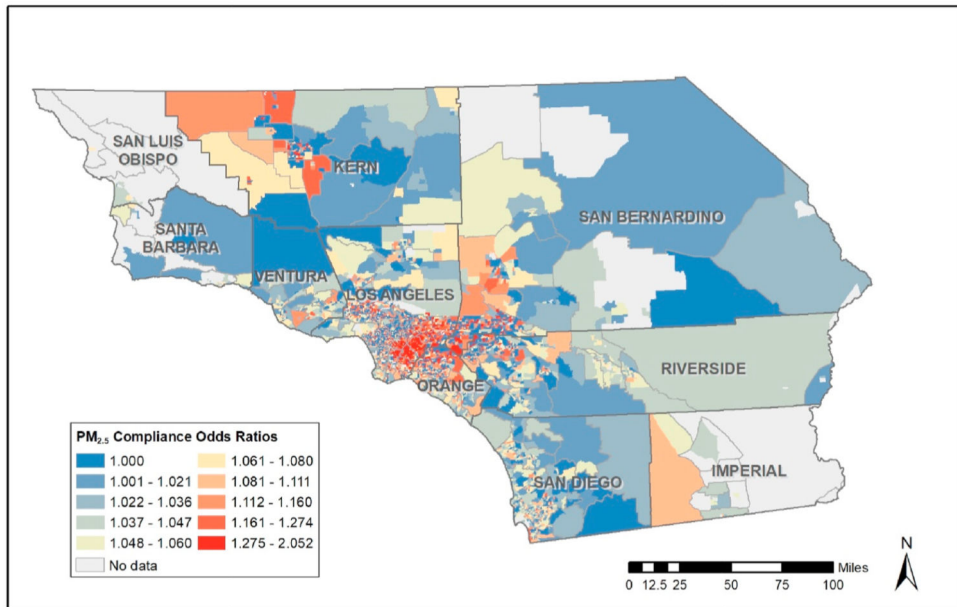
Fig. 3.
Compliance Odds Ratios for PM$_{2.5}$ total mass corresponding to the standard of (a) the U.S. EPA: 12 $\mu g/m^3$ and (b) the WHO: 5 $\mu g/m^3$.

a.

b.

Fig. 4.
Spatial Smoothing: Compliance Odds Ratios for $PM_{2.5}$ total mass corresponding to the standard of (a) the U.S. EPA: 12 $\mu g/m^3$ and (b) the WHO: 5 $\mu g/m^3$.

Table 1

Descriptive statistics for selected population characteristics by Gestational diabetes (GDM) groups, 2008–2017.

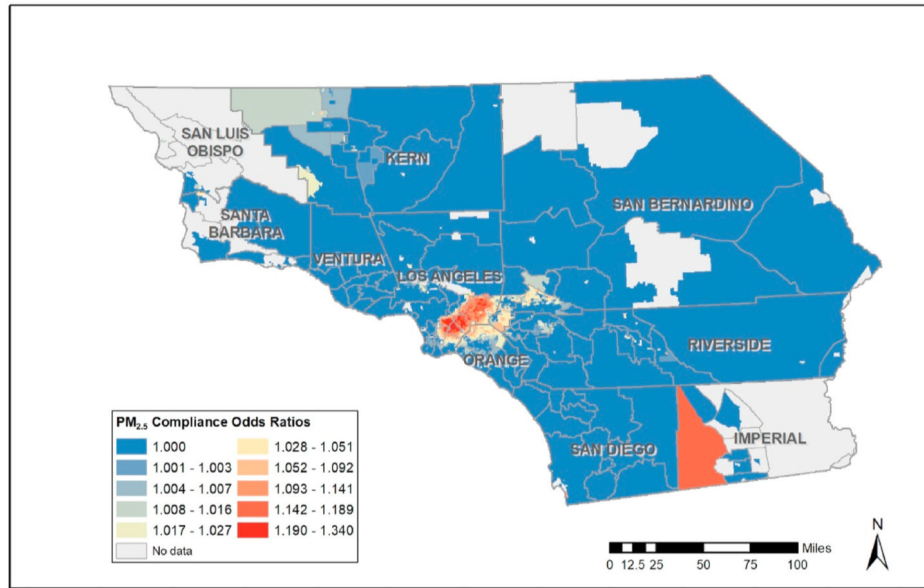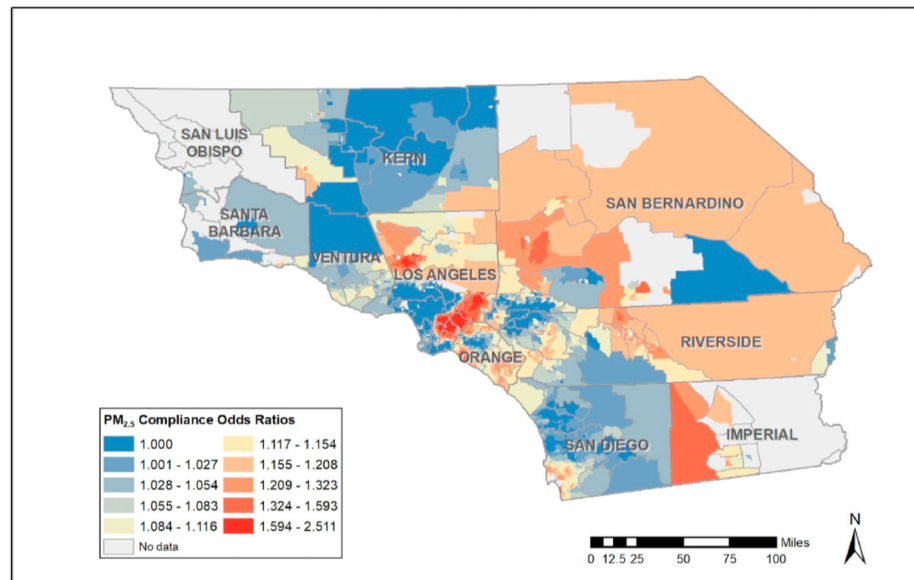| Characteristics	Total births		GDM		Non-GDM	
	N	mean/percent	N	mean/percent	N	mean/percent
Maternal age, years	341,909	30.21	37,711	32.56	304,198	29.91
Median household income, $	341,909	60,137.68	37,711	58,474.69	304,198	60,343.84
Maternal race/ethnicity						
African American	25,263	0.07	1962	0.05	23,301	0.08
Non-Hispanic Asian	44,210	0.13	7680	0.20	36,530	0.12
Hispanic	172,342	0.50	20,712	0.55	151,630	0.50
Non-Hispanic white	91,432	0.27	6568	0.17	84,864	0.28
Multiple/other	8662	0.03	789	0.02	7873	0.03
Maternal education						
8th grade	3521	0.01	738	0.02	2783	0.01
9th grade – high school	103,794	0.30	11,070	0.29	92,724	0.30
College (<4 years)	77,773	0.23	8581	0.23	69,192	0.23
College (4 years)	110,240	0.32	12,477	0.33	97,763	0.32
College	46581	0.14	4845	0.13	41736	0.14
Smoking						
Never Smoker	284,956	0.83	31,509	0.84	253,447	0.83
Ever Smoker	39,273	0.11	4410	0.12	34,863	0.11
Smoking during pregnancy	17,680	0.05	1792	0.05	15,888	0.05
Pre-pregnancy BMI in categories						
Underweight (<18.5)	8525	0.02	473	0.01	8052	0.03
Normal (18.5–24.9)	150,602	0.44	10,421	0.28	140,181	0.46
Overweight (25.0–29.9)	96,246	0.28	11,233	0.30	85,013	0.28
Obese (30.0)	86,536	0.25	15,584	0.41	70,952	0.23
Season of conception						
Cool season	173,652	0.51	19,707	0.52	153,945	0.51
Warm season	168,257	0.49	18,004	0.48	150,253	0.49
Year of infant birth						

Characteristics	Total births		GDM		Non-GDM	
	N	mean/percent	N	mean/percent	N	mean/percent
2008	31,368	0.09	3483	0.09	27,885	0.09
2009	30,680	0.09	3265	0.09	27,415	0.09
2010	30,687	0.09	3397	0.09	27,290	0.09
2011	32,313	0.09	4557	0.12	27,756	0.09
2012	33,833	0.10	4435	0.12	29,398	0.10
2013	33,580	0.10	3446	0.09	30,134	0.10
2014	35,166	0.10	3668	0.10	31,498	0.10
2015	36,542	0.11	3828	0.10	32,714	0.11
2016	38,455	0.11	3658	0.10	34,797	0.11
2017	39,285	0.11	3974	0.11	35,311	0.12

Table 2

Individual air pollution levels during pregnancy by selected population characteristics.

Characteristics	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
Total births	12.93 (2.53)	1.28 (0.26)	2.42 (0.62)	0.95 (0.31)	5.43 (1.27)	1.50 (0.61)
Gestational diabetes						
Yes	13.20 (2.44)	1.29 (0.26)	2.49 (0.60)	0.98 (0.30)	5.51 (1.22)	1.59 (0.62)
No	12.91 (2.54)	1.28 (0.26)	2.42 (0.63)	0.95 (0.31)	5.41 (1.28)	1.49 (0.61)
Maternal age						
<25	13.22 (2.55)	1.30 (0.27)	2.47 (0.64)	0.98 (0.31)	5.57 (1.29)	1.54 (0.60)
25–35	12.89 (2.54)	1.28 (0.26)	2.42 (0.62)	0.95 (0.31)	5.40 (1.27)	1.49 (0.61)
>35	12.82 (2.48)	1.27 (0.26)	2.40 (0.59)	0.93 (0.30)	5.36 (1.24)	1.50 (0.62)
Maternal race/ethnicity						
African American	13.20 (2.23)	1.28 (0.25)	2.45 (0.53)	0.97 (0.27)	5.55 (1.17)	1.59 (0.57)
Asian	12.95 (2.37)	1.28 (0.26)	2.43 (0.57)	0.95 (0.29)	5.40 (1.20)	1.54 (0.60)
Hispanic	13.34 (2.48)	1.30 (0.26)	2.51 (0.61)	0.98 (0.30)	5.60 (1.26)	1.57 (0.62)
Non-Hispanic white	12.14 (2.59)	1.24 (0.26)	2.26 (0.65)	0.89 (0.32)	5.09 (1.29)	1.33 (0.57)
Multiple/other	12.38 (2.51)	1.26 (0.26)	2.30 (0.61)	0.89 (0.31)	5.20 (1.25)	1.36 (0.58)
Maternal education						
8th grade	13.74 (2.39)	1.34 (0.28)	2.57 (0.58)	1.06 (0.29)	5.92 (1.29)	1.63 (0.52)
9th grade – high school	13.07 (2.54)	1.30 (0.26)	2.45 (0.64)	0.97 (0.31)	5.50 (1.29)	1.49 (0.59)
College (<4 years)	13.18 (2.53)	1.29 (0.26)	2.47 (0.62)	0.97 (0.30)	5.53 (1.28)	1.56 (0.62)
College (4 years)	12.74 (2.51)	1.27 (0.26)	2.38 (0.62)	0.93 (0.31)	5.34 (1.25)	1.47 (0.61)
> College	12.68 (2.48)	1.25 (0.25)	2.37 (0.59)	0.92 (0.30)	5.28 (1.23)	1.48 (0.62)
Block group household income						
$43,839	13.39 (2.37)	1.29 (0.25)	2.50 (0.60)	0.97 (0.29)	5.66 (1.21)	1.60 (0.61)
$43,839–$56,170	13.22 (2.46)	1.29 (0.26)	2.48 (0.59)	0.97 (0.29)	5.57 (1.25)	1.55 (0.61)
$56,170–$71,582	12.81 (2.54)	1.27 (0.26)	2.40 (0.62)	0.94 (0.30)	5.38 (1.27)	1.48 (0.61)
$71,582	12.33 (2.60)	1.26 (0.27)	2.33 (0.65)	0.93 (0.33)	5.09 (1.27)	1.38 (0.57)
Smoking						
Never Smoker	12.97 (2.53)	1.28 (0.26)	2.43 (0.62)	0.95 (0.31)	5.43 (1.27)	1.51 (0.61)
Ever Smoker	12.75 (2.53)	1.27 (0.25)	2.37 (0.62)	0.93 (0.31)	5.35 (1.26)	1.47 (0.60)

Characteristics	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
Smoking during pregnancy	12.90 (2.54)	1.29 (0.26)	2.40 (0.64)	0.96 (0.31)	5.45 (1.28)	1.49 (0.58)
Pre-pregnancy BMI						
Underweight (<18.5)	12.85 (2.53)	1.27 (0.27)	2.40 (0.61)	0.96 (0.30)	5.40 (1.28)	1.50 (0.60)
Normal (18.5–24.9)	12.80 (2.55)	1.27 (0.26)	2.39 (0.62)	0.94 (0.31)	5.37 (1.28)	1.49 (0.61)
Overweight (25.0–29.9)	13.00 (2.51)	1.28 (0.26)	2.44 (0.62)	0.96 (0.31)	5.45 (1.27)	1.51 (0.61)
Obese (30.0)	13.09 (2.49)	1.29 (0.26)	2.46 (0.62)	0.96 (0.30)	5.49 (1.25)	1.51 (0.61)
Season of conception						
Cool season	12.89 (2.40)	1.41 (0.23)	2.38 (0.57)	0.95 (0.30)	5.29 (1.21)	1.45 (0.61)
Warm season	12.99 (2.66)	1.15 (0.23)	2.47 (0.66)	0.95 (0.31)	5.57 (1.32)	1.55 (0.61)

Mean (standard deviation). The units are μg/m^3 for PM$_{2.5}$ total mass and PM$_{2.5}$ constituents.

Table 3

Mean (95% Credible Interval). Continuous variables, including air pollution exposures in the first and second trimester, have been standardized.

Characteristics	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
Intercept	−3.23 (−3.38, −3.09)	−3.26 (−3.40, −3.11)	−3.24 (−3.39, −3.09)	−3.24 (−3.36, −3.08)	−3.24 (−3.39, −3.09)	−3.23 (−3.38, −3.08)
Exposure	0.03 (0.01, 0.04)	−0.03 (−0.04, −0.02)	0.04 (0.02, 0.05)	0.03 (0.01, 0.04)	0.04 (0.02, 0.05)	0.07 (0.05, 0.08)
Maternal age	0.49 (0.48, 0.51)	0.49 (0.48, 0.51)	0.49 (0.48, 0.51)	0.49 (0.48, 0.51)	0.49 (0.48, 0.51)	0.49 (0.48, 0.51)
Block group household income	−0.08 (−0.10, −0.06)	−0.08 (−0.10, −0.07)	−0.08 (−0.10, −0.06)	−0.08 (−0.10, −0.07)	−0.08 (−0.10, −0.06)	−0.08 (−0.09, −0.06)
Year of infant birth	−0.09 (−0.10, −0.08)	−0.11 (−0.12, −0.10)	−0.10 (−0.11, −0.09)	−0.09 (−0.10, −0.08)	−0.10 (−0.11, −0.09)	−0.09 (−0.10, −0.07)
Maternal race/ethnicity						
African American	–	–	–	–	–	–
Asian	1.29 (1.23, 1.35)	1.29 (1.23, 1.35)	1.29 (1.23, 1.35)	1.29 (1.23, 1.35)	1.29 (1.23, 1.35)	1.29 (1.23, 1.35)
Hispanic	0.52 (0.47, 0.57)	0.52 (0.47, 0.58)	0.52 (0.47, 0.57)	0.52 (0.47, 0.57)	0.52 (0.47, 0.57)	0.52 (0.47, 0.57)
Non-Hispanic white	0.19 (0.13, 0.24)	0.18 (0.12, 0.24)	0.19 (0.13, 0.24)	0.19 (0.13, 0.24)	0.19 (0.13, 0.24)	0.20 (0.14, 0.26)
Multiple/other	0.39 (0.29, 0.48)	0.38 (0.29, 0.48)	0.39 (0.29, 0.48)	0.39 (0.29, 0.48)	0.39 (0.29, 0.48)	0.40 (0.30, 0.49)
Maternal education						
8th grade	–	–	–	–	–	–
9th grade – high school	−0.21 (−0.30, −0.11)	−0.21 (−0.30, −0.11)	−0.21 (−0.30, −0.11)	−0.21 (−0.30, −0.12)	−0.21 (−0.30, −0.11)	−0.21 (−0.30, −0.12)
College (<4 years)	−0.23 (−0.32, −0.14)	−0.23 (−0.32, −0.13)	−0.23 (−0.32, −0.13)	−0.23 (−0.33, −0.14)	−0.23 (−0.32, −0.13)	−0.24 (−0.33, −0.15)
College (4 years)	−0.33 (−0.42, −0.24)	−0.33 (−0.42, −0.23)	−0.33 (−0.42, −0.24)	−0.33 (−0.42, −0.24)	−0.33 (−0.42, −0.23)	−0.34 (−0.43, −0.25)
>College	−0.48 (−0.57, −0.38)	−0.48 (−0.57, −0.38)	−0.48 (−0.57, −0.38)	−0.48 (−0.57, −0.38)	−0.48 (−0.57, −0.38)	−0.49 (−0.59, −0.39)
Smoking						
Smoking during pregnancy	–	–	–	–	–	–
Never Smoker	−0.01 (−0.04, 0.03)	−0.01 (−0.04, 0.03)	−0.01 (−0.04, 0.03)	−0.01 (−0.04, 0.03)	−0.01 (−0.04, 0.03)	−0.01 (−0.04, 0.03)
Ever Smoker	0.05 (−0.00, 0.11)	0.05 (−0.00, 0.10)	0.05 (−0.00, 0.11)	0.05 (−0.00, 0.11)	0.05 (−0.00, 0.10)	0.05 (−0.01, 0.10)
Pre-pregnancy BMI in categories						
Underweight (<18.5)	–	–	–	–	–	–
Normal (18.5–24.9)	0.22 (0.11, 0.32)	0.22 (0.11, 0.32)	0.22 (0.11, 0.32)	0.22 (0.11, 0.32)	0.22 (0.11, 0.32)	0.22 (0.11, 0.32)
Overweight (25.0–29.9)	0.83 (0.72, 0.93)	0.83 (0.72, 0.93)	0.83 (0.72, 0.93)	0.83 (0.72, 0.93)	0.83 (0.72, 0.93)	0.83 (0.72, 0.93)
Obese (30.0)	1.40 (1.30, 1.50)	1.40 (1.30, 1.51)	1.40 (1.39, 1.50)	1.40 (1.30, 1.51)	1.40 (1.30, 1.50)	1.40 (1.30, 1.51)
Season of conception						
Cool season	–	–	–	–	–	–

Characteristics	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
Warm season	−0.06 (−0.08, −0.04)	−0.03 (−0.06, −0.01)	−0.05 (−0.08, −0.03)	−0.06 (−0.09, −0.04)	−0.06 (−0.08, −0.03)	−0.07 (−0.09, −0.04)