# **Supplemental Online Content**

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This supplemental material has been provided by the authors to give readers additional information about their work.

### **eMethods**

#### **Study Population**

KPSC is a large integrated healthcare provider with 15 medical centers and 235 medical offices, serving approximately 21% of the Southern California population in 2020<sup>1</sup>. The membership of KPSC has been reported to reflect the demographic and socioeconomic diversity of those living in this region <sup>2-4</sup>. There were 448,846 pregnancies from 341,341 individuals initially included in this cohort from 2008-2018. Pregnancies from individuals who were not KPSC members, with a gestational age of fewer than 20 weeks or larger than 47 weeks, without residential data, and resulting in multiple births or stillbirths were excluded from the cohort (eFigure 1). More details of this population have been described elsewhere 5,6.

#### **Outcome Ascertainment**

The gestational age was recorded in KPSC's electronic health records, ranging from 20 to 47 weeks (eFigure 1)<sup>7</sup>. For those who had early pregnancy ultrasound examinations, it was estimated mainly based on the first-trimester sonographic estimates <sup>7,8</sup>. For about 5% of pregnancies without sonographic estimates, it was estimated based on self-reported last menstrual period. Pregnancies less than 20 weeks of gestation were defined as miscarriages and excluded. Estimates based on self-reported last menstrual period may be inaccurate and result in extreme outliers. Hence, extremely post-term pregnancies with a gestational age of more than 47 weeks were further excluded from the cohort. A sensitivity analysis was conducted by restricting the study population to pregnancies with a gestational age between 20 and 43 weeks to avoid the potential impact of extreme outliers of gestational age.

#### **Air Pollution Exposure Assessment**

The ensemble model used to estimate daily total  $PM_{2.5}$  concentrations incorporated multiple machine-learning algorithms (i.e., gradient boosting machine, random forest, and deep learning) with a large set of explanatory variables (e.g., satellite-derived aerosol properties, meteorological conditions, land-use variables, and thermal inversions)<sup>9</sup>. It showed a good performance with a prediction  $\mathbb{R}^2$  of 0.83 for all monitoring sites of the Environmental Protection Agency's Air Quality System in California.

In terms of the validated geoscience-derived model, it provided public data on  $PM_{2.5}$  total mass and constituents based on ground-based measurements, satellite data, and chemical transport modeling 10,11. The cross-validated annual performance was high for nitrate ( $R^2 = 0.78$ ) and ammonium ( $R^2 = 0.75$ ), followed by sulfate ( $R^2 = 0.59$ ), organic matter ( $\mathbb{R}^2 = 0.52$ ), and black carbon ( $\mathbb{R}^2 = 0.42$ ) in the Southwestern United States <sup>10,11</sup>.

For sensitivity analysis, we further obtained monthly data on nitrogen dioxide (NO2), ozone (O3-8h, the daily maximum from 10 AM to 6 PM), and  $PM_{2.5}$  concentrations in California by implementing empirical Bayesian kriging (EBK) modeling relying on the ground-based measurements. The cross-validation  $R^2$  of the EBK model was 0.74 for NO<sub>2</sub>, 0.72 for O<sub>3</sub>, and 0.65 for PM<sub>2.5</sub>. Our previous publications have provided a detailed description of the EBK model 12,13.

Given the residential mobility, we excluded pregnancies if their residential information did not cover at least 75% of the entire pregnancy period ( $n = 20,802, 4.8\%$ ), similar to our previous studies <sup>7</sup>. Our previous publication has indicated that, compared to included pregnancies, there were higher percentages of excluded pregnancies from individuals of a younger age, more self-identified as Asian or Hispanic, with lower educational attainment or lower household income, or supported by Medicaid<sup>7</sup>. The electronic health records of KPSC documented the residential mobility during pregnancy for individuals who were members of KPSC. Individuals with a relatively lower socioeconomic status (e.g., a lower income level or with publicly funded insurance such as Medicaid) tend to be highly mobile and may find it hard to maintain a long-term KPSC membership, making it difficult to collect their full residential histories during pregnancy. For pregnancies whose missing residential data does not exceed 25% of the pregnancy period, we filled in the missing data using the address information from the later period for which data is available ( $n = 13,465, 3.1\%$ ). To check the robustness of our results, we estimated exposures and conducted the sensitivity analysis based on the original residential information of all pregnancies in the KPSC cohort ( $n =$ 429,839).

#### **Green Space Exposure Assessment**

For the street-view green space exposure assessment, we obtained street images from four main cardinal directions (i.e.,  $0^\circ$ ,  $90^\circ$ ,  $180^\circ$ , and  $270^\circ$ ) at each sampling point positioned at a 200-meter interval along the roadway. The validated deep learning model incorporated semantic segmentation to distinguish three types of vegetation: tree

(e.g., canopy), low-lying vegetation (e.g., shrub, bush), and grass. The accuracy was high with a mean intersection over union (IoU) of 92.5%, indicating its effectiveness in actual image segmentation <sup>14,15</sup>.

In sensitivity analysis, we applied additional buffers (i.e., 200 m and 500 m) and further examined green space exposure based on the Normalized Difference Vegetation Index (NDVI) and tree canopy coverage. The NDVI measurements were based on the Terra (MOD13Q1) satellite instrument of Moderate Resolution Imaging Spectroradiometer products from NASA with a spatial resolution of  $250 \text{ m} \times 250 \text{ m}$  and a temporal resolution of every 16 days <sup>15</sup>. Then, we obtained the percentage of tree canopy cover data at a 30 m resolution from the National Land Cover Database. We estimated the green space exposure for our study population mainly based on the NDVI and tree canopy data of the year 2013 (the mid-year of the study period), given that the annual green space coverage did not change substantially in our study region <sup>16</sup>. Detailed information on the green space exposure assessment has been provided in our previous publication <sup>15</sup>.

#### **Sensitivity analysis**

Based on the main analyses for total  $PM_2$ , exposure during the entire pregnancy, we conducted the following sensitivity analyses to check the robustness of our findings: a) We performed models by further adjusting for different sets of confounders, including the average exposure to ambient temperature during pregnancy, insurance type, parity, smoking status, and some pre-gestational medical conditions (i.e., diabetes and chronic hypertension); b) We included only the first delivery of each individual in our cohort during the study period to avoid the potential impacts of any multiple pregnancies. From the entire cohort ( $n = 409,037$ ), we included 304,570 (74.46%) pregnancies from 215,886 individuals with a single pregnancy and 88,684 individuals with multiple pregnancies, respectively; c) We restricted the study population to pregnancies with a gestational age between 20 and 43 weeks (n  $=$  408,975, 99.98%); d) We conducted the analysis based on the original residential information before filling in missing data for all pregnancies ( $n = 429,839$ ); e) We performed co-pollutant models by further adjusting for NO<sub>2</sub> and  $O_3$ ; f) We applied the alternative exposure data of total  $PM_{2,5}$  from the geoscience-derived model and the EBK model. All the analyses were also conducted for non-wildfire  $PM_{2.5}$ , except the analysis using exposure data from other sources.

For trimester-specific associations with total PM<sub>2.5</sub> and PM<sub>2.5</sub> constituents, we fitted a model by including all trimester-specific exposures in a single model (denoted as the all-trimester model) for each pollutant to reduce potential bias as a previous study suggested 6,17.

Next, for the associations with exposure to PM<sub>2.5</sub> constituents during the entire pregnancy, we co-adjusted five constituents to test the robustness of the single-pollutant model.

Furthermore, we examined the effect modification by street view green space, NDVI, and tree canopy exposure in different buffers (i.e., 200 m, 500 m, or 1000 m) in associations between total  $PM_{2.5}$  and sPTB. To test the robustness of our findings, we also categorized the green space exposure into tertile groups (i.e., low, medium, and high exposure groups), another commonly used strategy in the analysis of effect modification 18-22.

To support the causal inference, we applied propensity score matching to examine the risk of sPTB associated with  $PM_{2.5}$  exposure  $^{23-25}$ . We dichotomized PM<sub>2.5</sub> exposure during pregnancy as high vs. low exposures based on the median level. A propensity score was derived to reflect the probability of a participant being exposed to a high level of  $PM_{2.5}$  pollution during pregnancy given an observed set of characteristics. We calculated the propensity score using multivariate logistic regression and included the following variables in our main analysis, i.e., age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index (BMI), season of conception, year of delivery, and county of residency. Participants in two exposure groups were matched 1:1 in random order on the propensity scores using a greedy algorithm and nearest-neighbor approach with a caliper of 0.1 using the PROC PSMATCH Procedure in SAS. The balance of characteristics between matched participants was assessed by standardized mean differences calculated using the R package "Tableone". After obtaining a matched dataset, we estimated the association between PM<sub>2.5</sub> exposure and sPTB based on logistic regression. In addition, to test the robustness of the analysis, we tried different matching strategies and included a different set of variables (including temperature exposure during pregnancy, insurance type, parity, smoking status, diabetes, and chronic hypertension).

### **eResults**

The exposure to total  $PM_{2.5}$  and non-wildfire  $PM_{2.5}$  during pregnancy measured based on the ensemble model were highly correlated with each other and both had low correlations with exposure to wildfire-specific  $PM_{2.5}$  (eTable 1). They were moderately to highly correlated with exposure to  $PM_{2.5}$  constituents (0.36  $\leq$  r  $\leq$  0.71) estimated based on the geoscience-derived model, with the lowest correlation with  $PM_{2.5}$  sulfate and the highest correlation with  $PM_{2.5}$ nitrate. Wildfire-specific PM<sub>2.5</sub> had low correlations with all five PM<sub>2.5</sub> constituents (-0.15  $\leq$  r  $\leq$  0.26).

The total green space exposure showed a high correlation with trees  $(r = 0.83)$  but low correlations with low-lying vegetation ( $r = 0.21$ ) and grass ( $r = 0.17$ ) (eTable 2). The exposure to total PM<sub>2.5</sub> and non-wildfire PM<sub>2.5</sub> during pregnancy had low correlations with total and specific green space exposure, except moderate and negative correlations with exposure to low-lying vegetation. There were little correlations between exposure to wildfirespecific  $PM_{2.5}$  and green space. In addition, we observed little correlation between temperature exposure and other environmental exposures.

eFigure 2 depicts the temporal trend of daily average concentrations of total, non-wildfire, and wildfire-specific  $PM_{2.5}$  across California from 2007 to 2018. The peaks in total and wildfire-specific  $PM_{2.5}$  concentrations were both observed in the years 2008 and 2018. eFigure 3 displays the average exposure to total, non-wildfire, and wildfirespecific  $PM_{2.5}$  of the study population during pregnancy. The maximum values of exposure to total, non-wildfire, and wildfire-specific PM<sub>2.5</sub> were 24.65  $\mu$ g/m<sup>3</sup>, 24.49  $\mu$ g/m<sup>3</sup>, and 3.99  $\mu$ g/m<sup>3</sup>, respectively.

The ORs of iPTB associated with per IQR increase in total  $PM_{2.5}$  exposure were 0.81 (95% CI, 0.79-0.83;  $P < .001$ ), 0.87 (95% CI, 0.85-0.89; *P* < .001), 0.87 (95% CI, 0.85-0.89; *P* < .001), and 0.87 (95% CI, 0.86-0.89; *P* < .001) during the entire pregnancy, first, second, and third trimester, respectively.

We observed similar but lower associations from the unadjusted models compared to the adjusted models in the main analysis (eTable 3). For the sensitivity analysis of associations with total  $PM_{2.5}$  and non-wildfire  $PM_{2.5}$ exposure during the entire pregnancy, (a) Models further adjusted for different sets of covariates changed the results minimally; (b) We observed similar results before vs. after controlling for multiple deliveries; (c) Restricting the study population to pregnancies with a gestational age of 20-43 weeks did not change the observed associations; (d) The results without filling in missing residential information were similar to those of our main analysis; (e) Coadjustment of  $NO<sub>2</sub>$  and  $O<sub>3</sub>$  did not change our conclusions; (f) By using total PM<sub>2.5</sub> exposure data estimated based on the geoscience-derived model and the EBK model, we observed slightly attenuated associations compared to our main analysis, while our conclusion remained unchanged. The results of non-wildfire  $PM_{2.5}$  exposure were very close to those of the total PM<sub>2.5</sub>.

The all-trimester models indicated that the second trimester might be the most susceptible exposure window, consistent with our main analysis (eTable 4).

The results derived from co-pollutant models fitted for five  $PM_{2.5}$  constituents did not change substantially compared to those of the single-pollutant models (eTable 5). We observed that the association with  $PM_{2.5}$  nitrate was increased after adjusting for  $PM_{2.5}$  ammonium, while the association with  $PM_{2.5}$  ammonium was changed to be negative. This is likely due to the high correlation between those two constituents  $(r = 0.8)$ . In addition, we found the associations with the other four constituents were slightly attenuated after adjusting for  $PM_{2.5}$  black carbon.

We examined the effect modification by street view-based green space, NDVI, and tree canopy exposure in different buffers (e.g., 200 m, 500 m, or 1000 m) around the residential area (eFigures 4 and 5). We found similar results indicating that individuals living in areas with more exposure to total green space or trees tended to have a lower risk of sPTB associated with exposure to total PM2.5. The results regarding effect modification by street-view green space based on tertile groups were similar to the results in the main analysis, indicating that a high level of exposure to total green space and trees can attenuate the association between  $PM_{2.5}$  and exposure, while exposures to lowlying vegetation and grass modified the association in another direction (eFigure 6).

We reported the risk differences (RDs) for exposures to total PM<sub>2.5</sub> and five PM<sub>2.5</sub> constituents during pregnancy. Every interquartile range (IQR) increase in exposures to PM2.5, sulfate, nitrate, ammonium, organic matter, and black carbon was associated with increases in odds of spontaneous preterm birth (sPTB) by 0.74%, 0.27%, 0.49%, 0.18%, 0.27%, and 0.68%, respectively (eTable 6).

By applying the propensity score matching, we found that higher exposure to  $PM<sub>2.5</sub>$  during pregnancy was associated with a 7% increased odds of sPTB, which supports our findings in the main analysis (eTable 7). The results based on different matching strategies were consistent and indicated significantly positive associations between PM2.5 and sPTB.



**eFigure 1. The composition of the Kaiser Permanente Southern California pregnancy cohort from 2008 to 2018 and the population selection process.**



**eFigure 2. The temporal trend of daily average concentrations of total, nonwildfire, and wildfire-specific PM2.5 across California from 2007 to 2018 based on the census tract level data. The 75th, 90th, and 95th percentiles of the total PM2.5** were 11.83, 14.43, and 16.19 µg/m<sup>3</sup>, respectively. The 95th percentiles of non**wildfire and wildfire-specific PM2.5 were 15.72 and 1.17 µg/m3, respectively.** 



**eFigure 3. The average exposure to total PM2.5, non-wildfire PM2.5, and wildfirespecific PM2.5 during pregnancy for the study population.**

![](_page_9_Picture_42.jpeg)

**eFigure 4. The adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of spontaneous preterm birth (sPTB) associated with exposure to total PM2.5 during pregnancy among subgroups stratified by street-view green space exposure in 200 m and 500 m buffers. Models adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, county of residence, and the respective effect modifier. The** *P* **value is for the interaction term between PM2.5 exposure and each effect modifier.**

![](_page_10_Figure_0.jpeg)

Lower odds of sPTB Higher odds of sPTB

**eFigure 5. The adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of spontaneous preterm birth (sPTB) associated with exposure to total PM2.5 during pregnancy among subgroups stratified by the Normalized Difference Vegetation Index (NDVI) and tree canopy exposure in 200 m, 500 m, and 1000 m buffers. Models adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, county of residence, and the respective effect modifier. The** *P* **value is for the interaction term between PM2.5 exposure and each effect modifier.**

![](_page_11_Figure_0.jpeg)

Lower odds of sPTB Higher odds of sPTB

**eFigure 6. The adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of spontaneous preterm birth (sPTB) associated with exposure to total PM2.5 during pregnancy among subgroups stratified by street-view green space exposure in the 1000 m buffer (tertile groups). Models adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, county of residence, and the respective effect modifier. The** *P* **value is for the interaction term between PM2.5 exposure and each effect modifier.**

### **eTable 1. Pearson correlation coefficients between exposure to air pollutants throughout pregnancy for the study population.**

![](_page_12_Picture_258.jpeg)

<sup>a</sup> The PM<sub>2.5</sub> data were obtained from the ensemble model that incorporated multiple machine-learning algorithms at the census tract level.

 $^{\rm b}$  The PM $_{2.5}$  constituents data were from the geoscience-derived model at a spatial resolution of 1 km.

<sup>c</sup> The correlation with a *P* value <.001.

![](_page_13_Picture_269.jpeg)

# **eTable 2. Pearson correlation among different environmental exposures during pregnancy.**

 $^{\text{a}}$  The PM<sub>2.5</sub> data were obtained from the ensemble model that incorporated multiple machine-learning algorithms at the census tract level.

 $^{\circ}$  The green space data were estimated based on street view images.

 $^\mathrm{c}$  The temperature exposure was estimated based on daily maximum temperature data.

<sup>d</sup> The correlation with a *P* value <.001.

**eTable 3. The adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of sPTB associated with total PM2.5 and non-wildfire PM2.5 during pregnancy examined in the sensitivity analysis.**

	Total $PM2.5$	Non-wildfire $PM2.5$
Main model <sup>a</sup>	$1.15(1.12 - 1.18)$	$1.15(1.13-1.18)$
Unadjusted model <sup>b</sup>	$1.09(1.07 - 1.10)$	$1.09(1.07 - 1.11)$
Model with more covariates		
Model 1 <sup>c</sup>	$1.15(1.12 - 1.18)$	$1.15(1.13-1.18)$
Model 2 <sup>d</sup>	$1.15(1.12 - 1.17)$	$1.15(1.12 - 1.18)$
Model $3e$	$1.15(1.12 - 1.17)$	$1.15(1.12 - 1.18)$
Model accounting for multiple deliveries <sup>f</sup>	$1.15(1.12 - 1.18)$	$1.15(1.12 - 1.19)$
Model with restricted gestational age <= 43 9	$1.15(1.12 - 1.18)$	$1.15(1.13-1.18)$
Model before filling in missing residential data h	$1.14(1.12 - 1.17)$	$1.15(1.12 - 1.18)$
Co-pollutant model <sup>i</sup>		
$+ NO2$	$1.15(1.12 - 1.19)$	$1.16(1.13-1.19)$
$+$ O <sub>3</sub>	$1.16(1.13-1.18)$	$1.16(1.13-1.19)$
Model using PM <sub>2.5</sub> exposure from other data sources		
Geoscience model j	$1.11(1.07 - 1.14)$	-
Kriging model <sup>k</sup>	1.12 (1.09-1.16)	

Abbreviations: NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>2.5</sub>, particulate matter less than or equal to 2.5 µm; sPTB, spontaneous preterm birth.

a Main model: model in the main analysis adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, and county of residence.

**b Unadjusted model: the model including only the exposure variable.** 

c Model 1: the main model further adjusted for average exposure to temperature during pregnancy.

d Model 2: the main model further adjusted for average exposure to temperature during pregnancy, insurance type, parity, and smoking status.

e Model 3: the main model further adjusted for average exposure to temperature during pregnancy, insurance type, parity, smoking status, pre-existing diabetes, and chronic hypertension.

<sup>f</sup> The model including only the first delivery for each participant during the study period.

<sup>9</sup> The model excluding extremely post-term pregnancies > 43 weeks of gestation.

h The model with exposure data before filling in missing residential information.

<sup>i</sup> The main model was further adjusted for average exposure to  $NO<sub>2</sub>$  and  $O<sub>3</sub>$  during the entire pregnancy, respectively.

 $\mu$  The PM<sub>2.5</sub> exposure data were obtained from the geoscience-derived model.

 $k$  The PM<sub>2.5</sub> exposure data were obtained from the empirical Bayesian Kriging model.

**eTable 4. The adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of sPTB associated with total PM2.5 and PM2.5 constituents during each trimester examined in all-trimester models.**

	Exposure window <sup>a</sup>		
	First trimester	Second trimester	Third trimester
Total $PM2.5$	$1.03(1.01-1.05)$	$1.06(1.04-1.08)$	$1.05(1.03-1.07)$
$PM2.5$ sulfate	$1.03(1.01-1.05)$	$1.01(1.00-1.03)$	$1.02(1.01-1.04)$
$PM2.5$ nitrate	1.02 (1.00-1.04)	$1.05(1.02 - 1.07)$	$1.02(1.00-1.04)$
$PM2.5$ ammonium	$1.01(0.99-1.03)$	$1.03(1.00-1.05)$	$1.00(0.98-1.02)$
PM <sub>2.5</sub> organic matter	$1.00(0.97-1.02)$	$1.06(1.03-1.09)$	$1.00(0.98-1.03)$
$PM2.5$ black carbon	$1.04(1.00-1.07)$	$1.12(1.08-1.17)$	$0.99(0.96-1.03)$

Abbreviations: PM $_{2.5}$ , particulate matter less than or equal to 2.5 µm; sPTB, spontaneous preterm birth. a Models adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, and county of residence.

### **eTable 5. The adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of sPTB associated with PM2.5 constituents during pregnancy examined in co-pollutant models.**

![](_page_16_Picture_148.jpeg)

Abbreviations: PM $_{2.5}$ , particulate matter less than or equal to 2.5 µm; sPTB, spontaneous preterm birth.

a Models adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, and county of residence.

# **eTable 6. The adjusted odds ratios (ORs) and risk differences (RDs) with 95% confidence intervals (CIs) of sPTB associated with per interquartile range (IQR) increase in exposures to total PM2.5 and five PM2.5 constituents during pregnancy.**

![](_page_17_Picture_96.jpeg)

Abbreviations: PM<sub>2.5</sub>, particulate matter less than or equal to 2.5 µm; sPTB, spontaneous preterm birth.<br><sup>a</sup> Models adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body season of conception, year of delivery, and county of residence. Since the model with a random effect of residence county cannot converge when calculating risk differences using an identity link, we included the county as a fixed effect in these models. The results were comparable with our main analysis where the county was included as a random effect.

![](_page_18_Picture_290.jpeg)

### **eTable 7. The results of associations between PM2.5 exposure during pregnancy and sPTB based on the propensity score matching.**

Abbreviations:  $PM_{2.5}$ , particulate matter less than or equal to 2.5  $\mu$ m; sPTB, spontaneous preterm birth.<br><sup>a</sup> Main model, adjusted for age, race and ethnicity, educational attainment, median household income, pre-preg index, season of conception, year of delivery, and county of residence.

**b The model was adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass** index, season of conception, year of delivery, and county of residence. The logit of the propensity score was used in computing differences between pairs of observations.

<sup>c</sup> The model was adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, and county of residence. The caliper was 0.2.

<sup>d</sup> The model was adjusted for age, race and ethnicity, educational attainment, median household income, pre-pregnancy body mass index, season of conception, year of delivery, county of residence, temperature, insurance type, parity, smoking status, diabetes, and chronic hypertension.

<sup>e</sup> The results were represented by odds ratios with 95% confidence intervals.

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