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Article

Hyperlocalized Measures of Air Pollution and Preeclampsia in Oakland, California

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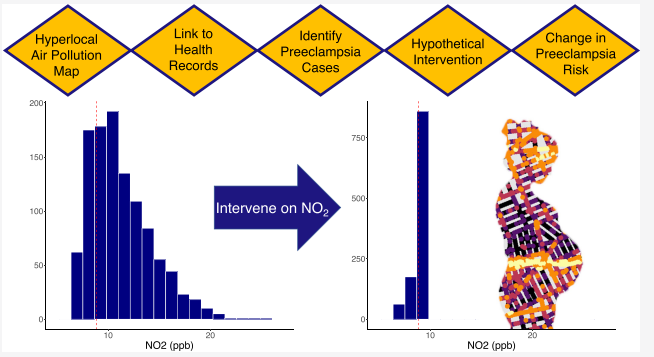
ABSTRACT: Exposure to nitrogen dioxide (NO_2), black carbon (BC), and ultrafine particles (UFPs) during pregnancy may increase the risk of preeclampsia, but previous studies have not assessed hyperlocalized differences in pollutant levels, which may cause exposure misclassification. We used data from Google Street View cars with mobile air monitors that repeatedly sampled NO_2, BC, and UFPs every 30 m in Downtown and West Oakland neighborhoods during 2015−2017. Data were linked to electronic health records of pregnant women in the 2014−2016 Sutter Health population, who resided within 120 m of monitoring data (N = 1095), to identify preeclampsia cases. We used G-computation with log-binomial regression to estimate risk differences (RDs) associated with a hypothetical intervention reducing pollutant levels to the 25th percentile observed in our sample on preeclampsia risk, overall and stratified by race/ethnicity. Prevalence of preeclampsia was 6.8%. Median (interquartile range) levels of NO_2, BC, and UFPs were 10.8 ppb (9.0, 13.0), 0.34 $\mu g/m^3$ (0.27, 0.42), and 29.2 # × $10^3/cm^3$ (26.6, 32.6), respectively. Changes in the risk of preeclampsia achievable by limiting each pollutant to the 25th percentile were NO_2 RD = −1.5 per 100 women (95% confidence interval (CI): −2.5, −0.5); BC RD = −1.0 (95% CI: −2.2, 0.02); and UFP RD = −0.5 (95% CI: −1.8, 0.7). Estimated effects were the largest for non-Latina Black mothers: NO_2 RD = −2.8 (95% CI: −5.2, −0.3) and BC RD = −3.0 (95% CI: −6.4, 0.4).



KEYWORDS: *black carbon, nitrogen dioxide, ultrafine particles, hypertensive disorders of pregnancy, pregnancy complications, maternal health, air pollution*

Preeclampsia and other hypertensive disorders of pregnancy are threats to both maternal and fetal health. A pregnancy complicated by preeclampsia or gestational hypertension is more likely to result in a fetal-growth-restricted or premature newborn,[1,2] and experiencing a hypertensive disorder of pregnancy has been linked to increased risk for cardiovascular disease for mothers later in life.[3,4] Preeclampsia can result in severe complications and maternal death if untreated.[2]

The prior evidence linking air pollution to hypertensive disorders of pregnancy, including preeclampsia and gestational hypertension,[5,6] is limited due to coarse geographic resolution and limited categories of pollutants assessed. The majority of studies of air pollution and maternal health outcomes have relied on methods with low spatial resolution, such as fixed-site air pollution monitors, chemical transport models, satellite remote sensing, and distance to nearby roads.[7] These measurement methods provide spatial exposure estimates of 1 km or more in resolution,[8] while recent studies using mobile monitoring have suggested that on-road pollutant concentrations may vary by factors of 5−8 within a city block.[8] Therefore, previous studies that rely on air pollution measures with low spatial resolution may have significant exposure misclassification that masks important heterogeneity within neighborhoods.

In addition, some pollutants have not been assessed using standard methods. For example, black carbon (BC) and ultrafine particles (UFPs, particles with diameters less than 0.1 μm) have not been measured using satellite remote sensing methods.[8] However, the established links between these pollutants and hypertension, asthma exacerbations, and adverse cardiovascular outcomes[9−11] suggest that they can negatively affect cardiovascular and immune functions in ways that are relevant to maternal health and the risk for preeclampsia, in particular. Land-use regression models can

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provide spatially detailed information[7,12−14] but may fail to capture local emission sources and are inconsistent at predicting pollution hotspots.[8,15] Studies linking air pollution to preeclampsia have focused almost exclusively on particulate matter less than 2.5 μg ($PM_{2.5}$) and nitrogen dioxide (NO_2).[5] Other pollutants relevant to urban areas, like black carbon (BC) and ultrafine particles (UFPs), have only been studied in limited settings.[16−19] To our knowledge, only one prior study has evaluated the association between UFPs and hypertensive disorders of pregnancy.[17]

To address the limitations of the prior literature on air pollution and hypertensive disorders of pregnancy, we use data from Sutter Health electronic health records (EHRs) in combination with exposure information collected by Google Street View cars that measured air quality on average 50 times per block in West and Downtown Oakland, California, between 2015 and 2017. This novel assessment of exposure permitted granular characterizations of NO_2, BC, and UFPs in 30 m road segments across neighborhoods in Oakland. We focused on these three pollutants because they are characterized by a high degree of intra-urban and intra-neighborhood spatial variability. Within our study area, black carbon (BC) is generated principally by diesel engines, with an additional contribution from wood combustion during the heating season.[9] Nitrogen dioxide (NO_2) results from traffic and other combustion sources, such as residential and industrial combustion. NO_2 is one of two nitrogen oxide species (NO_x = NO + NO_2) that exist in dynamic equilibrium. Most primary combustion emissions of NO_x are released as NO and are rapidly converted to NO_2 (timescale ∼5−15 min) during daylight hours. Therefore, NO_2 exhibits less sharp spatial gradients than NO but is the NO_x species with clearly identified health effects. Ultrafine particles (UFPs) are produced by both direct emissions and secondary atmospheric formation (nucleation), which occurs most commonly in the summer months. Major primary sources of UFPs include traffic, residential natural gas combustion, meat cooking, and industrial combustion emissions.[20] To evaluate associations with preeclampsia, we linked maternal addresses to these block segments, identified cases of preeclampsia from the Sutter EHRs among these mothers, and evaluated the impact of a hypothetical intervention in which air pollutant levels were reduced.

We focused our analyses on Oakland because it is a city in the San Francisco Bay Area that has documented challenges and activism around high air pollution levels,[21−23] a history of racial residential segregation,[24] and elevated prevalence of adverse birth outcomes. Therefore, based on prior evidence that exposure to environmental hazards and social inequality can explain racial disparities in adverse maternal and infant health outcomes,[25] we hypothesized that exposure to air pollution is associated with increased risk of preeclampsia, and that these associations are stronger for Black women due to the chronic stress experienced as a result of structural and interpersonal racism.[26,27] Additionally, using hyperlocalized measures of air pollution is especially important in a city like Oakland, which has densely populated neighborhoods near multiple industrial and traffic sources of pollution with hills and other complex terrains that traditional methods cannot effectively capture.[28]

METHODS

Study Population. Mothers who lived in West or Downtown Oakland at the time of delivery and had a singleton live birth in a Sutter Hospital between 2014 and 2016 were eligible for inclusion (see Supporting Information for a detailed description of analytic sample creation). Our study population (N = 1095 births to 1059 mothers) includes approximately 70% of the births that occurred to mothers living in these neighborhoods during the study period based on statewide birth certificate data from the California Department of Public Health.

This study was approved by the University of California, Berkeley Committee on Human Subjects and University of California, San Francisco, Sutter Health, and Columbia University Institutional Review Boards.

Air Pollution Measures. We used a fleet of Google Street View cars to repeatedly measure air quality on every street within West and Downtown Oakland from May 2015 to December 2017 during weekdays, with daytime hours balanced among all seasons from approximately 9:00 a.m. to 5:00 p.m.[8] The cars used were gasoline-powered Subaru Impreza equipped with fast-response laboratory-grade air pollution instrumentation to measure NO_2 (a Teledyne T500U via cavity attenuation phase-shift spectroscopy), BC (a Droplet Measurement Technologies PAX photoacoustic spectrometer), and UFPs (a TSI 3788 water-based condensation particle counter) with high accuracy and precision.[8] Instruments were subjected to daily quality control procedures and weekly calibration and zero checks. Testing indicated that the monitors self-sampled exhaust from the Street View cars themselves in rare circumstances, when backing up after idling in low-wind conditions.[8] Oakland neighborhoods comprising approximately 40 km^2 were the focus of the most intensive repeated monitoring, with an average of 50 car visits to each city street over the 2.5-year study. The internal consistency of the data was verified using careful subsampling/bootstrap resampling to demonstrate that spatial patterns were stable and intraclass correlation coefficients of the measurements were high (0.8−0.95), indicating that the majority of variability was across block segments rather than within segments over time.[8] An algorithm was developed to precisely (±10−20%) estimate the median weekday daytime pollution concentrations every 30 m based on repeated observations from the cars.[8] Concentrations were consistent with regulatory monitors where they existed, and a comparison of our approach to other mobile monitoring approaches and fixed-site monitors of pollutants in Oakland indicates that the measurement data is robust.[29,30] Additional information about the exposure measurement approach is available elsewhere.[8] Our main analysis linked maternal address at delivery to the median pollutant level across the approximately 50 repeated measurements at the nearest 30 m block segment. This represents the average long-term exposure to each pollutant within the 30 m segment.

Preeclampsia and Gestational Hypertension Measurement. We identified cases of preeclampsia from mothers' EHR data using International Classification of Diseases (ICD)-9 codes 642.4x−642.5x and 642.7x and ICD-10 codes O11.x, O14.0x, O14.1x, and O14.9x. These include diagnoses of mild or unspecified preeclampsia, severe preeclampsia, and preeclampsia with pre-existing hypertension. As a sensitivity analysis, we created a composite outcome variable that included all mothers who were classified as experiencing either

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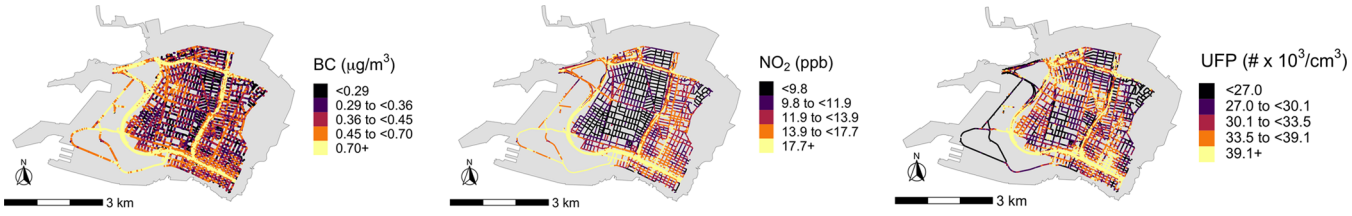

Figure 1. Distribution of black carbon (BC), nitrogen dioxide (NO_2), and ultrafine particles (UFPs) within the study area of Downtown and West Oakland, California.

Table 1. Descriptive Statistics of Participant Exposure to Pollutant Levels across 30 m Segments in the Study Area of Downtown and West Oakland, California

	mean	minimum	25th percentile	median	75th percentile	maximum
nitrogen dioxide (ppb)	11.5	6.7	9.0	10.8	13.0	24.0
black carbon ($\mu g/m^3$)	0.37	0	0.27	0.34	0.42	1.32
ultrafine particles (# × $10^3/cm^3$)	30.1	17.0	26.6	29.2	32.6	67.3

preeclampsia and/or gestational hypertension. The latter were characterized by the ICD-9 code 642.3x and the ICD-10 code O13.x, which identify transient hypertension of pregnancy.

Area-Level Socioeconomic Factors. We calculated the percentage of people with less than high school education and below the federal poverty threshold at the block group level using the 2011−2015 American Community Survey. The distribution of educational attainment and poverty varied across the study area (Supplemental Figure 1).

Statistical Analysis. We estimated the correlations between pollutants and community covariates using Pearson's correlation coefficient. We examined the linearity of the relationship between each pollutant and the odds of preeclampsia using penalized splines. We then estimated the effect of a potential intervention in which pollution levels were reduced to the 25th percentile of levels observed across the study participants. Therefore, we used G-computation with log-binomial regression to estimate risk differences (RDs) if all mothers with pollutant levels above the 25th percentile were set to the 25th percentile level, while those with pollutant levels below the 25th percentile were left as observed.[31] G-computation is a substitution estimator of the average treatment effect;[32] it is also a form of standardization that produces a marginal effect estimate,[33] which, in this case, represents the expected change in the risk of the outcome (i.e., the change in the expected number of cases per 100 women) if the hypothetical intervention had occurred. For these estimates to be interpreted causally, the models must be correctly specified, and exchangeability, positivity, and consistency must be satisfied.[34]

We estimated log-binomial regression models of pollutant levels on preeclampsia, controlling for maternal race/ethnicity, health insurance type, maternal age at delivery, maternal age squared, smoking history, parity, season of conception, the block group percentage with less than high school education, and the block group percentage below the federal poverty level. Supplemental Figure 2 shows a directed acyclic graph that illustrates why we elected to control for these variables. We modeled pollution levels continuously and included squared terms to account for potential nonlinearities in their effect on the outcome; we did not coadjust for the other pollutants. We stratified by maternal race/ethnicity and season of conception to assess whether there were differential effects by these potential effect modifiers. In stratified analyses, the 25th percentile of air pollutants across all participants was used as the intervention threshold, not the 25th percentile within the strata. For inference, we calculated Wald-type confidence intervals using a clustered bootstrap by the block group with 250 iterations. The cluster bootstrap helps account for spatial autocorrelation in exposure and outcome. All analyses were conducted using R version 3.6.0.[35]

Sensitivity Analyses. We conducted several sensitivity analyses. First, we repeated our main analyses using the average value of all 30 m segments within a 120 m radius of the maternal residence to capture larger areas of potential exposure, which is approximately the length of one city block in West and Downtown Oakland and could be more representative of mothers' actual exposures due to wind patterns or if they traveled within their neighborhoods often during pregnancy. Second, to assess whether more extreme levels of pollutants had stronger impacts on mothers' cardiovascular health during pregnancy, we used the 75th percentile, rather than the median, of the pollutant measurements across the approximately 50 repeated measurements for each 30 m segment. Third, we also estimated the risk difference for a hypothetical intervention setting with the pollution levels above the median to the median, rather than the 25th percentile. In the Supporting Information, we also show results for NO_x, which is the combination of NO and NO_2. We also include in the Supporting Information a sensitivity analysis limiting the study years to 2015 and 2016 so that the outcome measurements overlap with the exposure measurements. Finally, we present results for a joint evaluation of the pollutants as a mixture using quantile G-computation,[36] which estimates the expected change in the risk of preeclampsia if all pollutant levels increased by one quartile.

RESULTS

Our data on NO_2, BC, and UFPs in Oakland, California neighborhoods during 2015−2017 demonstrate pollution patterns that are remarkably variable in space (Figure 1), including across the 30 m segments we included in our analyses. The median levels of NO_2, BC, and UFP exposure among our study participants were 10.8 ppb, 0.34 $\mu g/m^3$, and 29.2 # × $10^3/cm^3$, respectively (Table 1), and pollutant levels were moderately correlated across participants (Table 2). NO_2

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Table 2. Correlation of Participant Pollutant Exposure Levels across 30 m Segments and Socioeconomic Factors by Census Block Groups within the Study Area of Downtown and West Oakland, California[a]

	NO_2	BC	UFPs	percentage below poverty	percentage with less than high school education
NO_2	1.00	0.65	0.56	−0.19	−0.05
BC		1.00	0.49	0.03	−0.09
UFPs			1.00	0.07	0.18
percentage below poverty				1.00	0.50
percentage with less than high school education					1.00

[a]BC, black carbon; NO_2, nitrogen dioxide; UFPs, ultrafine particles.

and BC had the highest correlation with one another (Pearson's ρ = 0.65), and ρ = 0.56 for NO_2 and UFPs (Table 2). The area-level socioeconomic factors, percentage with less than a high school education and percentage with household income below the poverty line, had a correlation of 0.50. The socioeconomic factors were not as strongly or, in all cases, positively correlated with the pollution levels.

The sample comprised 31.1% Black, 17.9% Latina, 18.6% Asian, and 18.1% White women (Table 3). Women were, on average, 29.8 years old at delivery, and the majority had private health insurance (79.1%). The prevalence of preeclampsia during the study period by the block group varied spatially across the study area (Figure 2). The overall prevalence of

Table 3. Descriptive Statistics of the Study Area and Participants

	N (%)
total block groups	55 (100)
percentage with less than high school education, mean (IQR)	14.3 (7.8, 21.4)
percentage with family income below the poverty level, mean (IQR)	24.6 (14.0, 34.1)
total population[a]	1095 (100)
race/ethnicity	
Latina	196 (17.9)
non-Latina White	198 (18.1)
non-Latina Black	340 (31.1)
non-Latina Asian	204 (18.6)
other[b]	157 (14.3)
parity	
1	524 (47.9)
2	308 (28.1)
3	134 (12.2)
4+	129 (11.8)
insurance	
private	866 (79.1)
Medicaid	229 (20.9)
ever smoked	
no	775 (70.8)
yes	221 (20.2)
unknown	99 (9.0)
preeclampsia	75 (6.8)
either preeclampsia or gestational hypertension	151 (13.8)

[a]Total number of births to 1059 mothers. [b]Includes others, missing or unknown, or multiple race/ethnicity.

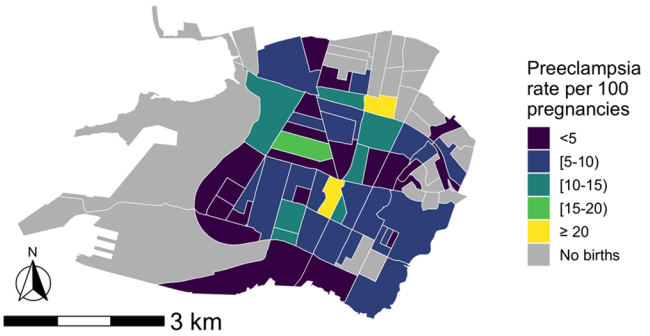

Figure 2. Distribution of preeclampsia among participants across the study area of Downtown and West Oakland, California.

preeclampsia during the study period was 6.8%, and the prevalence of gestational hypertension and/or preeclampsia was 13.8%. The prevalence of both conditions was highest among Black mothers (10.6 and 14.4%, respectively) and lowest among Asian mothers (3.9 and 3.9%, respectively) (Supplemental Table 1). No large differences in exposure by race/ethnicity were observed (Supplemental Table 2). The relationships between all pollutants and the odds of preeclampsia were linear (Supplemental Figure 3).

When estimating the effect of reducing pollutant levels to the 25th percentile (using the closest 30 m segment to characterize exposure), compared to the observed distribution, we estimated reductions in the risk of preeclampsia for both NO_2 (RD = −1.5 cases per 100 women, 95% CI: −2.5, −0.5) and BC (RD = −1.0 cases per 100 women, 95% CI: −2.2, 0.02) (Figure 3). The findings using the average of 30 m segments within 120 m of the maternal residence, representing a larger exposure area, were slightly stronger (NO_2 RD = −1.8, 95% CI: −3.1, −0.5 and BC RD = −1.4, 95% CI: −2.5, −0.3). Associations for UFPs were identified but were smaller in magnitude than for either NO_2 or BC with both the 30 m (RD

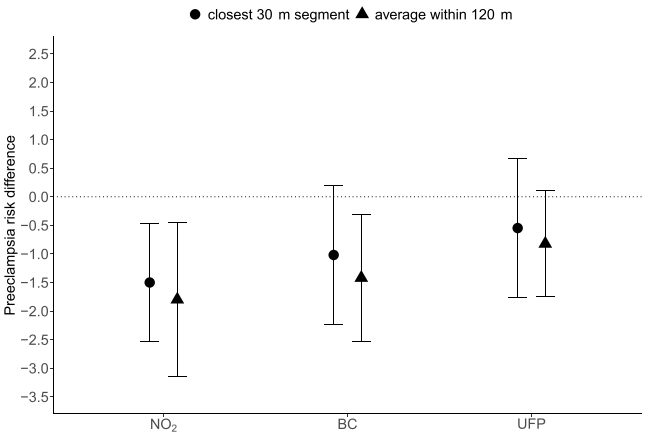

Figure 3. Estimated preeclampsia risk differences per 100 women and 95% CI associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance. Note: Estimates are shown for each pollutant averaged within 120 m and within 30 m of maternal residence at delivery. Models are adjusted for maternal race/ethnicity, insurance type, age at delivery, age squared, smoking history, parity, season of conception, proportion of census block with educational attainment less than high school, and proportion of census block living below the poverty line. The 25th percentile was 9.0 ppb for NO_2, 0.27 $\mu g/m^3$ for BC, and 26.6 # × $10^3/cm^3$ for UFPs.

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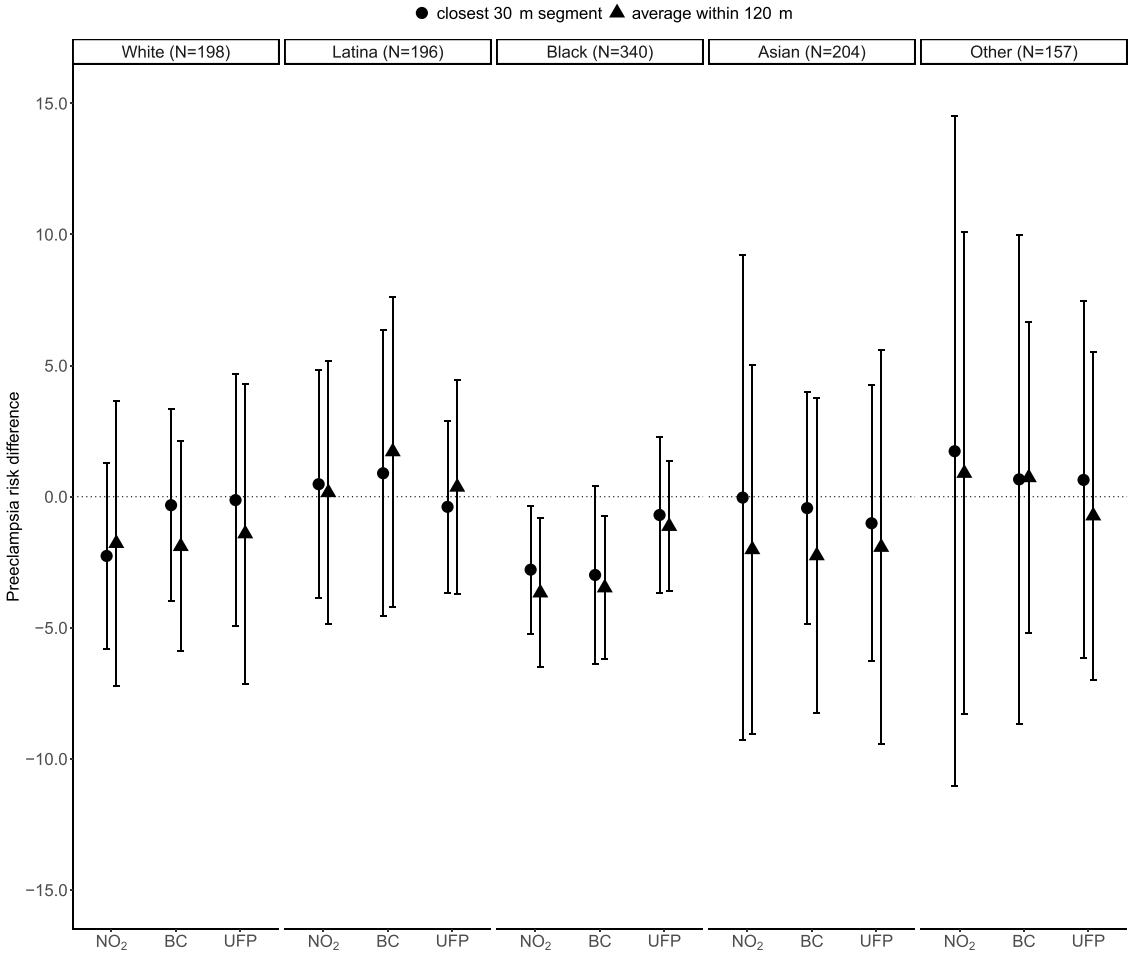

Figure 4. Estimated preeclampsia risk differences per 100 women and 95% CI by race/ethnicity associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance. Note: Estimates are shown for each pollutant averaged within 120 m and within 30 m of maternal residence at delivery. Models are adjusted for maternal insurance type, age at delivery, age squared, smoking history, parity, season of conception, proportion of census block with educational attainment less than high school, and proportion of census block living below the poverty line. The 25th percentile was 9.0 ppb for NO_2, 0.27 $\mu g/m^3$ for BC, and 26.6 # $\times 10^3/cm^3$ for UFPs.

= −0.5, 95% CI: −1.8, 0.7) and 120 m approaches (RD = −0.8, 95% CI: −1.7, 0.1). The associations for NO_x were similar to those observed for NO_2 for both the 30 m (RD = −1.8, 95% CI: −2.9, −0.7) and 120 m approaches (RD = −1.8, 95% CI: −3.1, −0.6) (Supplemental Figure 4). Limiting the outcome years to 2015−2016 resulted in similar findings, although the confidence intervals were wider due to the reduced sample size (Supplemental Figure 5). Estimating the joint effects of pollutants using quantile G-computation showed similar associations (Supplemental Figure 6). For example, using the 30 m exposure metric, we estimated a risk difference of 1.6 cases per 100 women, 95% CI (−0.2, 3.4) when the exposure levels increased by one quartile simultaneously. For the 120 m metric, the findings were slightly stronger (RD = 2.0, 95% CI: 0.3, 3.7). For both exposure metrics, the results were driven equally by BC and NO_2, with UFPs contributing little to the overall association.

We observed stronger associations for Black mothers compared to mothers of other races/ethnicities (Figure 4). For instance, among Black women, we estimated that the hypothetical intervention for NO_2 would result in a preeclampsia risk difference of −2.8 (95% CI: −5.2, −0.3) and −3.0 (95% CI: −6.4, 0.4) for BC, using the 30 m exposure characterization. Using the 120 m exposure characterization resulted in even larger estimates (NO_2 RD = −3.7, 95% CI: −6.5, −0.8; BC RD = −3.5, 95% CI: −6.2, −0.8). Findings were similar when using the 75th percentile of the exposure to characterize more extreme exposure patterns (Supplemental Figures 7 and 8).

There was no strong patterning by season of conception, although the associations for NO_2, BC, and UFPs were slightly stronger among women who conceived in the winter and spring compared to those who conceived in the summer and fall (Supplemental Figure 9).

Secondary analyses that conducted a hypothetical intervention by setting the pollutants to the median, rather than the 25th percentile, resulted in attenuated estimates. For example, the expected difference in preeclampsia risk was −0.5 (95% CI: −1.4, 0.5) for NO_2 and −0.4 (95% CI: −1.1, 0.2) for BC when using the 30 m exposure characterization (Supplemental Figure 10). The 120 m characterization of exposure resulted in larger estimated effects compared to the 30 m exposure for this hypothetical intervention as well: RD = −0.8 (95% CI: −1.6, 0.0) for NO_2 and RD = −0.9 (95% CI: −1.7, −0.2) for BC. The race-stratified results for this scenario followed a

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similar pattern, with the strongest results observed among Black women (Supplemental Figure 11).

When we analyzed the impact of our hypothetical intervention on gestational hypertension and/or preeclampsia, our results were attenuated (Supplemental Figure 12). For example, the estimated changes in the risk of gestational hypertension and/or preeclampsia were NO_2 RD: −0.3 (95% CI: −1.9, 1.2) and BC RD: −0.2 (95% CI: −1.8, 1.5). The race-stratified results for gestational hypertension and/or preeclampsia were stronger for both Black and Asian mothers, with slightly stronger associations observed for Asian mothers for NO_2 and UFPs (Supplemental Figure 13).

DISCUSSION

Using hyperlocalized measures of air pollution in Oakland, California, we estimated the effect of a potential intervention reducing pollutants to the first quartile of their observed distribution. Results showed that reducing NO_2 and BC to the 25th percentile would substantially reduce the risk of preeclampsia among pregnant women, especially among non-Latina Black women, but reducing UFPs had little effect. Associations using the 120 m exposure metric were slightly stronger than those using the 30 m metric, suggesting that a larger geographic resolution of BC and NO_2 exposure measurements, which are nonetheless an order of magnitude smaller than the traditional measurements, may better represent actual exposures people experience in their neighborhoods. It is also possible the larger exposure metrics may have less sampling uncertainty, given the greater number of measurements that are averaged, or they may be more strongly correlated with unmeasured neighborhood-level factors associated with preeclampsia risk. Preeclampsia is a severe maternal complication of pregnancy that often leads to preterm birth, fetal growth restriction, and if untreated, can lead to maternal death, and these findings indicate that NO_2 and BC exposure during pregnancy likely contributes to adverse maternal health outcomes. Further, the prevalence of preeclampsia was 40% higher in non-Latina Black versus White women in our sample (Supplemental Table 1). Air pollution exposures, therefore, may contribute to disparities in both preeclampsia and the fetal and maternal health sequelae of preeclampsia by race/ethnicity.

Studies evaluating the mechanisms underlying the relationships between traffic-related air pollutants and hypertensive disorders of pregnancy indicate that different pollutants likely operate via distinct pathways. For example, $PM_{2.5}$ appears to increase vascular inflammation, whereas NO_2 likely operates via oxidative stress,[5] although both result in higher blood pressure. Mechanistic understanding of the roles of BC and UFPs in hypertensive disorders of pregnancy is not well-developed, however. Studies of potential toxicity associated with BC have focused on diesel exhaust or woodsmoke but have not isolated BC from other components of the particulate matter produced by these combustion processes.[9] However, existing evidence suggests that BC carries other toxic components of combustion-related particulate matter, such as semivolatile organics, to the pulmonary or cardiovascular tissue.[9] Recent evidence has suggested that UFP exposure may have adverse health effects that exceed those produced by larger particles like $PM_{2.5}$ because of their small size (which means they travel through the body via diffusion and systemic circulation and penetrate deeper into the tissue), large surface-area-to-mass ratio, high retention rate (their small size allows them to evade clearance by phagocytosis), and ability to generate reactive oxygen species and oxidative stress.[37] While there is evidence that short-term UFP exposure can adversely affect the respiratory, cardiovascular, and nervous systems,[38] the mechanisms linking UFP exposure to possible adverse health effects, especially among pregnant women, are poorly understood.[37,38] Future studies that are sufficiently powered to examine the potential interactive effects of BC, NO_2, and UFPs would be helpful to better understand how these pollutants may jointly affect pregnancy outcomes.

Two prior studies examined the relationships between BC and either preeclampsia or hypertensive disorders of pregnancy using land-use regression models to characterize exposure. One did not find associations,[16] while the other found small, nonstatistically significant positive associations.[17] The average level of BC exposure in the study by Choe et al 16 was higher than what we observed, with an average of 0.5 versus 0.34 $\mu g/m^3$ in our study. Differences in results between this study and ours could therefore be due to differences in exposure levels or could be explained by our hyperlocalized exposure measurements or different study populations. In addition, including gestational hypertension with preeclampsia largely attenuated our results; these smaller findings were consistent with the previous study that focused exclusively on hypertensive disorders of pregnancy.[17] Assibey-Mensah et al.[17] focused on identifying critical windows of exposure for each month of pregnancy and found small associations of an IQR increase of BC (0.67−1.52) with gestational hypertension during months 3 and 7. Our study was unable to assess critical windows of exposure, which may also explain the inconsistent results.

Our results for both NO_2 and UFPs were largely consistent with prior evidence. The National Toxicology Program's Systematic Review of Traffic-Related Air Pollution and Hypertensive Disorders of Pregnancy determined that there was evidence to support a small positive relationship between increasing NO_2 exposure and the risk of preeclampsia based on nine studies.[5] These studies used air dispersion or land-use regression models to characterize exposure, and the meta-analysis indicated a pooled relative risk for preeclampsia of 1.04 (95% CI: 0.91, 1.10) associated with a 10 $\mu g/m^3$ increase in NO_2. We estimated a risk difference of −1.5 (95% CI: −2.5, −0.5) associated with setting all mothers with NO_2 exposure above 9 $\mu g/m^3$ (range = 9.1−24 $\mu g/m^3$) to 9 $\mu g/m^3$. Furthermore, another study in southern California that also used local monitoring to inform their air quality estimates examined the relationship between UFPs and hypertensive disorders of pregnancy and did not find a relationship between them.[17] We found a reduced risk associated with reduced UFP exposure, but the magnitude was smaller than those observed for NO_2 and BC and the estimate was imprecise. Two studies, however, found increased odds of preterm birth associated with elevated UFP exposure during pregnancy,[39,40] and preeclampsia is a major risk factor for preterm birth. The most recent study took place in Los Angeles and reported a modeled mean UFP level of 12.0 # $\times 10^3/cm^3$.[39] This is less than half of the average exposure level we observed in Oakland (30.1 # $\times 10^3/cm^3$).

While our study improved upon prior work in important ways, it had limitations. The air pollution measurements were averaged from observations that took place between May 2015 and December 2017, while the births occurred between 2014 and 2016. Therefore, we do not have strict temporality between our exposures and outcomes. Given that the annual

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averages were consistent over time, exposure measurements are good proxies for exposure during the times during which our participants were pregnant. Furthermore, while seasonality exists in the levels of air pollutants in Oakland, we did not have enough measurements to create season-specific exposures, although we did control for season of conception and evaluated whether it modified the findings. In addition, while prior evidence indicates that there are critical windows during which air pollution may impact the risk of hypertensive disorders of pregnancy,[41] we were not able to assess trimester-specific effects.

On the whole, the mobile monitoring approach used to measure exposure had several strengths and weaknesses. Mobile monitoring captures greater spatial variation compared to fixed-site monitoring or land-use regression models. Another advantage over land-use regression models is that mobile monitoring is a direct measurement of ambient air quality that does not require prediction based on associations with a limited set of spatial covariates. Therefore, it can capture idiosyncratic pollution hotspots missed by land-use regression models.[15] However, mobile monitoring has limitations. Traffic patterns and atmospheric dispersion differ between daytime and nighttime, and we collected measurements only during daytime hours. For the years of mobile monitoring (2015−2017), the average weekday 9 a.m.−5 p.m. NO_2 concentrations at the Oakland West fixed-site monitor (which was located at the center of the mobile monitoring road network) were ∼5% (0.7 ppb) lower than the corresponding annual average concentrations. This temporal pattern is consistent with other Bay Area monitors, suggesting that the temporal bias of our measurements imposed minimal bias on the average conditions represented. Additionally, the concentration surfaces that result from mobile measurements are inherently time-averaged, so this exposure measurement approach is better suited for capturing spatial variation than seasonal variation that may be important when assessing susceptibility windows.

We also geocoded women based on the address they provided at delivery, which may have resulted in exposure misclassification if they moved during pregnancy. Several previous studies have evaluated the extent of bias from exposure misclassification due to maternal mobility during pregnancy and have found the bias to be small and generally toward the null, although with differential patterns by maternal characteristics.[42−45] However, given the hyperlocal nature of our exposure measurements, it is possible that the misclassification due to mobility may be larger in our study population. It is also possible that on-road concentrations of pollutants overestimate the exposure levels at residential addresses. In the parts of Oakland included in this analysis, however, housing units are generally close to the street and lack large front yards. The potential for exposure mismeasurement may vary by block socioeconomic characteristics. We controlled for area-level socioeconomic factors to mitigate this potential bias. Furthermore, a recent study has compared the mobile monitoring approach we use in this study to a fixed-site network of monitors for BC among homes, businesses, and industrial sites in West Oakland.[30] The fixed-site monitors were attached to fences and porches at a height of 1.5 m with a median distance to the nearest road of 15 m,[46] and 97 of the 100 sites were located within 30 m of the mobile monitoring road network. There was also overlap in the time of sampling—of the 100 days the fixed-site monitors were deployed, 57 days were simultaneously covered by the Google Street View mobile monitoring.[30] The comparison found no systematic overestimation of pollution using mobile monitoring compared to fixed-site monitors at residences and businesses; median levels of BC were 0.48 $\mu g/m^3$ across the fixed-site monitors and 0.44 $\mu g/m^3$ using the mobile monitoring on residential roads. While this study only examined levels of BC, and not NO_2 or UFPs, the findings suggest that the differential between on-road versus residential exposure in these areas may be minimal.

We were not able to account for fetal loss or still births, which may have created live birth bias in our analysis.[47] However, we expect that this would bias our findings toward the null. The study population of births at Sutter Hospitals included approximately 70% of all births in West and Downtown Oakland that occurred during the study period, and therefore it is possible that our results were affected by selection bias. To evaluate this, we considered the predictors of giving birth at a Sutter Hospital compared to other facilities in the Bay Area. In a comparison of demographics, the only differences we observed were that Sutter births were more likely to be covered by private insurance. Since we have controlled for insurance type in the analysis, for selection bias to be induced, there would need to at least two other factors that are uncontrolled for in the analysis that (1) both independently influence the likelihood of having private insurance and (2) one must be associated with exposure to air pollutants and the other must be associated with preeclampsia (or they are associated with both air pollutants and preeclampsia). An example of two such factors could be educational attainment and occupation, factors for which we were not able to control. However, we expect the majority of the effects of education and occupation on selection into the Sutter population to operate through insurance type. Furthermore, we have controlled for other markers of socioeconomic status, including maternal age at delivery, race/ethnicity, smoking history, parity, and the block group percentage with less than high school education, and the percentage below the federal poverty level. Given the number of socioeconomic variables we controlled for and the small magnitudes of bias that are common with this type of bias structure,[48] we do not expect selection bias to substantially affect our findings. However, the potential remains for bias from residual confounding, as we lacked data on potentially important confounders and effect modifiers including maternal body mass index, marital status, education, and occupational exposures. We were also unable to assess potential confounding or effect modification by pre-existing hypertension as there was too much missingness in this variable to conduct stratified analyses. We were also not able to include information on use of antihypertensive medication during pregnancy.

The levels of pollutants we observed in Oakland were below the EPA's standards for health and welfare, where those standards exist. For instance, the annual standard for NO_2 is 53 ppb,[49] while the maximum level observed in this study was 24 ppb. Nevertheless, we found associations of NO_2 with preeclampsia at annual levels below half the standard. This suggests that air pollutants may have detrimental effects on the health of pregnant women, even in places where the air quality is better than the standard. While there are no current standards for UFPs or BC, levels of BC in California have been declining over the past few decades, averaging 0.14 $\mu g/m^3$

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since 2010.[50,51] The average BC exposure levels we observed in Oakland (0.34 $\mu g/m^3$), however, were more than double the state average.

Preeclampsia is a pregnancy complication with potentially life-threatening implications, for both mother and fetus, and prevention is an important public health goal. Nationally, preeclampsia affects 3.4% of pregnancies,[52] but we observed a risk twice as high in our sample overall (6.8%) and 3 times as high for non-Latina Black women in our sample (10.6%). We estimated reductions in the risk of preeclampsia overall, and even larger benefits for Black women could be achieved with hypothetical interventions reducing the levels of BC and NO_2. Since we did not observe differences in the average pollutant levels across racial/ethnic groups in our study (Supplemental Table 2), it may be that the larger estimated effects of pollution reduction we observed among Black women may be a result of interaction between the air pollutants we measured here and other chemical or nonchemical stressors. For example, these stressors could increase the likelihood among Black women of having pre-existing hypertension, which could interact with air pollution exposure to influence the risk of preeclampsia. This study provides evidence that reducing air pollutants even far below regulatory standards may reduce the risk of preeclampsia and alleviate disparities in maternal and infant health in Oakland, California. The Clean Air Act stipulates a duty for the EPA to protect at-risk populations with an adequate margin of safety. Our findings support previous recommendations to consider pregnant women an at-risk group under the Clean Air Act National Ambient Air Quality Standards.[53]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c02151.

Description of creation of analytic sample; counts and prevalence of preeclampsia and preeclampsia and/or gestational hypertension overall and by race/ethnicity in Downtown and West Oakland, California (Supplemental Table 1); median (IQR) of pollutant exposure levels by race/ethnicity of participants in Downtown and West Oakland, California (Supplemental Table 2); distributions of educational attainment and poverty rate by block group in West and Downtown Oakland (Supplemental Figure 1); directed acyclic graph of variables and their hypothesized relationships with exposure and outcome (Supplemental Figure 2); estimated odds ratios and 95% confidence intervals for preeclampsia across the distribution of each pollutant (Supplemental Figure 3); estimated preeclampsia risk differences per 100 women and 95% CI associated with the hypothetical intervention reducing NO_x to the 25th percentile versus the observed levels by exposure characterization distance (Supplemental Figure 4); estimated preeclampsia risk differences associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance, limited to study years 2015−2016 (Supplemental Figure 5); estimated preeclampsia risk differences associated with jointly increasing all exposures by one quartile, by exposure characterization distance (Supplemental Figure 6); estimated preeclampsia risk differences associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance, using the 75th percentile of exposure (Supplemental Figure 7); estimated preeclampsia risk differences by race/ethnicity associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance, using the 75th percentile of exposure (Supplemental Figure 8); estimated preeclampsia risk differences per 100 women and 95% CI by season of conception associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance (Supplemental Figure 9); estimated preeclampsia risk differences associated with the hypothetical intervention reducing the pollutant levels to the 50th percentile versus the observed levels by exposure characterization distance (Supplemental Figure 10); estimated preeclampsia risk differences by race/ethnicity associated with the hypothetical intervention reducing the pollutant levels to the 50th percentile versus the observed levels by exposure characterization distance (Supplemental Figure 11); estimated gestational hypertension and/or preeclampsia risk differences associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance (Supplemental Figure 12); and estimated gestational hypertension and/or preeclampsia risk differences by race/ethnicity associated with the hypothetical intervention reducing the pollutant levels to the 25th percentile versus the observed levels by exposure characterization distance (Supplemental Figure 13) (PDF)

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Notes

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