# Maternal exposure to ambient air pollution mixture and premature rupture of membranes: Evidence from a large cohort in Southern California (2008–2018)

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## Abstract

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**Background:** There is minimal evidence of relationships between maternal air pollution exposure and spontaneous premature rupture of membranes (SPROM), a critical obstetrical problem that can significantly increase maternal and fetal mortality and morbidity. No prior study has explored the PROM risk related to specific components of particulate matter with aerodynamic diameters of 2.5 μm ($PM_{2.5}$). We examined associations between maternal exposure to nitrogen dioxide ($NO_2$), ozone ($O_3$), $PM_{2.5}$, $PM_{10}$, and $PM_{2.5}$ constituents and SPROM.

**Methods:** A large retrospective cohort study was conducted and included 427,870 singleton live births from Kaiser Permanente Southern California during 2008–2018. Monthly averages of $NO_2$, $O_3$ (8-h daily maximum), $PM_{2.5}$, and $PM_{10}$ were measured using empirical Bayesian kriging based on measurements from monitoring stations. Data on $PM_{2.5}$ sulfate, nitrate, ammonium, organic matter, and black carbon were obtained from a fine-resolution model. A discrete time approach with pooled logistic regressions was used to estimate associations throughout the pregnancy and based on trimesters and gestational months. The quantile-based g-computation models were fitted to examine the effects of 1) the air pollution mixture of four pollutants of interest and 2) the mixture of $PM_{2.5}$ components.

**Results:** There were 37,857 SPROM cases (8.8%) in our study population. We observed relationships between SPROM and maternal exposure to $NO_2$, $O_3$, and $PM_{2.5}$. $PM_{2.5}$ sulfate, nitrate, ammonium, and organic matter were associated with higher SPROM risks in the single-pollutant model. Mixture analyses demonstrated that the overall effects of the air pollution mixture and $PM_{2.5}$ mixture in this study were mainly driven by $O_3$ and $PM_{2.5}$ nitrate, respectively. Underweight mothers had a significantly higher risk of SPROM associated with $NO_2$.

**Conclusion:** Our findings add to the literature on associations between air pollution exposure and SPROM. This is the first study reporting the impact of $PM_{2.5}$ constituents on SPROM.

## 1. Introduction

Premature rupture of membranes (PROM) is a critical obstetrical event complicating approximately 7–8% of pregnancies (Esteves, 2022) and has been associated with considerable risks of poor maternal and fetal outcomes. Specifically, mothers with PROM have higher risks of intra-amniotic infections, placental abruption, cord prolapse, sepsis, and death (Assefa et al., 2018; Gonzalez-Mesa et al., 2021; Mercer, 2003). For offspring, PROM can result in elevated neonatal mortality and morbidity (Tchirikov et al., 2018; Yagur et al., 2019). Umbilical cord compression or placental abruption following PROM can result in serious fetal complications such as respiratory distress syndrome (Caughey et al., 2008). Of all cases, 30–40% of PROMs can occur before 37 gestational weeks (preterm PROM) and trigger preterm births (Menon and Richardson, 2017). The etiology of PROM remains unclear, but a variety of factors, including apoptosis, oxidative stress, and altered membrane morphology triggered by infection and inflammation, have been suggested (Menon and Richardson, 2017; Tchirikov et al., 2018). Potential risk factors for PROM may include some maternal characteristics, such as cervical incompetence, low body

mass index (BMI), low socioeconomic status, and smoking (Caughey et al., 2008; Esteves, 2022; Lyons and McLaughlin, 2020). Environmental factors, such as air pollution, have also been suggested to participate in the pathogenesis of PROM (Dadvand et al., 2014; Yackerson et al., 2008). However, the evidence for different air pollutants remains limited and inconclusive (Dadvand et al., 2014; Pereira et al., 2014; Pereira et al., 2016; Wallace et al., 2016; Wang et al., 2019); these pollutants include nitrogen dioxide ($NO_2$), nitrogen oxides ($NO_x$), ozone ($O_3$), and particulate matter with aerodynamic diameters of 2.5 μm ($PM_{2.5}$) and 10 μm ($PM_{10}$).

The first investigation regarding air pollution and PROM was conducted in Barcelona using matched case-control analyses and showed that entire-pregnancy exposure to $NO_2$, $NO_x$, and $PM_{2.5}$ light absorbance (a marker of black carbon aerosol) increased the risk of preterm PROM, while no relationships were found for $PM_{2.5}$, $PM_{2.5-10}$, and $PM_{10}$ (Dadvand et al., 2014). This study was partly in line with another study in the United States where exposure to $NO_x$, $PM_{2.5}$, and $PM_{10}$ was not associated with PROM risks (Wallace et al., 2016). Nevertheless, a Chinese cohort study linked $PM_{2.5}$ exposure to increased risks of PROM regardless of the trimester of exposure (Wang et al., 2019), while a longitudinal study on an Australian cohort only reported $PM_{2.5}$-related associations in the second trimester (Pereira et al., 2014). Understanding susceptible windows for air pollution can help reveal underlying mechanisms and provide targeted clinical interventions or guidance on behavioral changes to reduce health risks (Warren et al., 2018). Previous epidemiological findings are inconsistent, especially for $PM_{2.5}$, $PM_{10}$, and $NO_2$, with some studies observing no association (Dadvand et al., 2014; Pereira et al., 2016; Wallace et al., 2016) and others finding varying critical trimesters (Pereira et al., 2014; Wang et al., 2019). As the biological response to adverse exposure may not be exactly trimester-specific, it is meaningful to capture shorter exposure periods (e.g., months or weeks) that might help identify more specific windows of susceptibility (Sheridan et al., 2019; Sun et al., 2020; Wang et al., 2018).

Ambient $PM_{2.5}$ pollution has been regarded as the leading environmental risk factor for various health issues globally and contributes to significantly increased premature deaths as well as adverse pregnancy outcomes (Li et al., 2017; Liu et al., 2019). However, research has not reached a clear conclusion on associations between prenatal $PM_{2.5}$ exposure and PROM (Dadvand et al., 2014; Li et al., 2021; Pereira et al., 2014, 2016; Wallace et al., 2016; Wang et al., 2019; Wu et al., 2023; Zhang et al., 2021). In addition to different study populations and study designs, the difference in study conclusions may be partially explained by the heterogeneity in $PM_{2.5}$ chemical compositions due to regional differences in types of sources and climatic conditions (Cai et al., 2020; Ebisu and Bell, 2012; Qiao et al., 2014; Sun et al., 2021). Identification of specific impacts of $PM_{2.5}$ components can assist in effective targeted emission control of particle pollution from a public health viewpoint. However, to our best knowledge, no previous study on PROM looked at the $PM_{2.5}$ components. Though measuring the $PM_{2.5}$ elements can be expensive, there have been some models estimating ambient levels of $PM_{2.5}$ components from high-resolution satellite data and other data sources. Statistical models have also been improved to analyze the effects of air pollution mixtures. Recently, a quantile-based g-computation (QGC) method was developed to evaluate the joint effects of all exposures within a mixture

(Keil et al., 2020). This innovative method can estimate the effects of a specific subset of components controlling for possible confounding from other chemicals in the mixture (van den Dries et al., 2021) and would be an appropriate approach to assess the effect of the mixture containing different air pollutants on PROM.

Therefore, we carried out a retrospective cohort study in Southern California to investigate: (1) the associations between maternal exposure to $NO_2$, $O_3$, $PM_{2.5}$, $PM_{10}$, and $PM_{2.5}$ constituents and spontaneous PROM (SPROM) in various exposure windows (i.e., entire pregnancy, trimesters, and gestational months); (2) the joint effects of air pollution mixture on SPROM; and (3) the joint effects of $PM_{2.5}$ components on SPROM.

## 2. Methods

### 2.1. Study population

From 2008 to 2018, over 340,000 mothers who were members of Kaiser Permanente Southern California (KPSC), a large integrated healthcare system, with gestational ages from 20 to 47 weeks were included in this large pregnancy cohort (Fig. S1). More information about the study population can be found elsewhere (Sun et al., 2021). We included mothers who had singleton live births from this cohort for the study on SPROM. Electronic health records (EHRs) provide detailed information including maternal demographic factors, residential histories, medical and obstetrical records, as well as individual health-related behaviors. In total, 429,839 pregnancies were preliminarily identified after excluding multiple births (n = 7,454) and stillbirths (n = 1,961).

### 2.2. Outcome: SPROM

SPROM is defined as the spontaneous ROM without the onset of labor regardless of gestational age. PROMs due to iatrogenic interventions (non-spontaneous PROM, n = 1,651, 4.1% of all PROM cases) were excluded from our study as the main trigger of those cases would be human factors that may not be attributable to air pollution. More diagnosis information has been provided in our prior study (Jiao et al., 2023). The pregnancy period for our study started from the date of the last menstrual period confirmed by ultrasonography (Sun et al., 2021) and ended at the ROM date (Dadvand et al., 2014; Jiao et al., 2023).

### 2.3. Exposure assessment

Monthly averages of $NO_2$, $O_{3-8h}$ (daily maximum from 10 AM to 6 PM), $PM_{2.5}$, and $PM_{10}$ were estimated using empirical Bayesian kriging (EBK) based on daily measurements from monitoring stations of the U.S. Environmental Protection Agency during 2007–2018. The EBK method showed a cross-validation $R^2$ ranging from 0.65 to 0.75 for different air pollutants (Wu et al., 2016). Our previous studies have extensively described the used EBK model (Laurent et al., 2016a; Wu et al., 2016). Monthly data on $PM_{2.5}$ total mass and components at a 1 km resolution, including sulfate, nitrate, ammonium, organic matter, and black carbon, were obtained from a geoscience-derived model from 2007 to 2017 (Meng et al., 2019; van Donkelaar et al., 2019). This model incorporated information from chemical transport modeling, satellites, and ground monitoring stations to provide validated measurements of $PM_{2.5}$ composition over North America (Meng et al., 2019;

van Donkelaar et al., 2019). In the Southwestern United States, the model showed the highest cross-validated agreement for nitrate ($R^2 = 0.78$) and ammonium ($R^2 = 0.75$), followed by sulfate ($R^2 = 0.59$), organic matter ($R^2 = 0.52$), and black carbon ($R^2 = 0.42$). Maternal addresses of residence incorporating detailed information about residential mobility during the entire pregnancy were geocoded. Monthly air pollution data were temporally interpolated to obtain gestational month- and trimester-specific exposure for each participant based on geocoded residential addresses (Sun et al., 2021). Mainly to simplify the monthly analysis, a gestational month was calculated on 30 days, and rough cutoff points for trimesters were applied (i.e., first: gestational months 1–3 [1–90 days]; second: gestational months 4–6 [91–180 days]; third: gestational months 7–9 [181–270 days]). More details for exposure measurement have been provided in our previous work (Sun et al., 2021; Sun et al., 2020).

### 2.4. Statistical analysis

We summarized the study population characteristics and the exposure to air pollution. The correlation between exposure to each pollutant throughout the pregnancy was measured by Pearson's correlation. To identify windows of susceptibility, a discrete time approach with the logit function was fitted to estimate associations between air pollution exposure and SPROM during each period, including the entire pregnancy, trimesters, and gestational months. Like the Cox proportional hazard model, the discrete time approach is a method for survival analysis, which is particularly useful for handling large datasets with many ties and time-dependent variables without assuming proportional hazards. As time should be included as a covariate in this approach, in the present study, we included time (i.e., the gestational month) in a flexible manner (i.e. polynomials) as suggested by prior research (Murray et al., 2020). We included the county of residence as a random effect in the model (Sun et al., 2021). Covariates were selected a priori based on existing literature, including maternal age, self-reported race/ethnicity, educational level, neighborhood household income, pre-pregnancy BMI ($kg/m^2$), smoking status, parity, year of infant birth, and season of conception (Dadvand et al., 2014; Jiao et al., 2023; Pereira et al., 2016; Wallace et al., 2016; Wang et al., 2019). To align better with the analysis using monthly exposure data, we included pregnancies with gestational months ≥ 5 (n = 427,870, 99.9%) from the entire pregnancy cohort as the minimum gestational age of mothers in our cohort was 20 weeks.

The trimester-specific associations were jointly examined in a single model by including exposures in three trimesters simultaneously (denoted as the all-trimester model) to provide more accurate estimates (Wilson et al., 2017). We further performed a sensitivity analysis by running single-trimester models to estimate the association for each trimester without controlling for exposures in the other two trimesters. To account for potential correlations between associations across different gestational months, the distributed lag model (DLM) was used to provide less biased results. A natural cubic spline function with 4 degrees of freedom was applied in the DLMs to model the lag structure of associations from gestational month 1 to month 8 (Wang et al., 2018; Wilson et al., 2017). As about 37.2% of mothers giving birth before month 9 did not have exposure data in this month, we did not estimate the association in month 9 to avoid a large decrease in the sample size for the DLM analysis.

The results for krigged $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$ based on the EBK model and $PM_{2.5}$ total mass and components from the geoscience-statistical model were reported as odds ratios (ORs) and 95% confidence intervals (CIs) per interquartile range (IQR) increase in average exposure during the pregnancy. To evaluate the impact of physical condition before pregnancy on the susceptibility of pregnant women to SPROM, subgroup analysis stratified by pre-pregnancy BMI was conducted to identify its potential effect modification (Esteves, 2022). We measured the heterogeneity among BMI subgroups using Cochran's Q test.

The mixture effects were measured by a novel method QGC from the "qgcomp" package in R. This method combines aspects of weighted quantile sum (WQS), a widely used statistical method for mixture analysis, with a causal inference method known as g-computation (Schmidt, 2020). WQS regression measured the combined effects of components in a mixture under two assumptions that associations between each component and the outcome are (1) in the same direction (or null), and (2) linear and additive, while QGC relaxes both assumptions and provides unbiased estimates when its assumptions are violated (Keil et al., 2020; Liu et al., 2021; Sun et al., 2021). We included air pollutants and $PM_{2.5}$ components associated with SPROM in the single-pollutant model in the mixture analysis.

In sensitivity analyses: (a) We examined the relatively short-term associations in the last one and the last three gestational months (Dadvand et al., 2014). (b) The zip code of residence was used as a random effect for $PM_{2.5}$ total mass and components to account for smaller spatial clustering. Given that kriging interpolation based on monitoring station data was too coarse to capture within-zip code variability due to relatively sparse stations (Sun et al., 2021), we did not include zip codes in the single-pollutant model for krigged $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$. (c) We further included the history of PROM in the analysis as a potential confounder. (d) To check the robustness of our model, we removed the restriction on the time effect in the model by adding a monomial of time as a covariate instead of the polynomials. (e) We examined the associations using the Cox proportional hazards model with the gestational month as the temporal unit. (f) We also conducted a sensitivity analysis using WQS regression as an alternative method to the QGC model. (g) For the $PM_{2.5}$ mixture, we added $PM_{2.5}$ total mass in QGC and WQS models to control for any potential effects of other $PM_{2.5}$ components. (h) We further performed co-pollutant models for entire-pregnancy associations with four krigged air pollutants and five $PM_{2.5}$ components, respectively, to evaluate the robustness of single-pollutant models. (i) We tested the effect modification by performing models with the interaction term between air pollution exposure and pre-pregnancy BMI. All analyses were conducted with SAS version 9.4 and R 4.1.3.

## 3. Results

Table 1 summarizes the study population characteristics. A total of 427,870 pregnancies with 37,857 (8.8%) SPROM cases from 2008 to 2018 were included. Approximately 60% of the total population were mothers aged 25–34. Hispanic and non-Hispanic White mothers accounted for approximately 50% and 25% of all subjects, respectively. Among non-SPROM cases, about 60% of them have two or more deliveries, while only about 46%

of SPROM cases gave birth two or more times. More SPROM cases had a history of PROM (3.08%) compared with non-SPROM cases (2.13%).

Table 2 shows the distribution of exposure levels during pregnancy for the study population. The average levels of entire-pregnancy exposure to $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$ were 15.62 ppb, 44.12 ppb, 11.63 μg/m$^3$, and 28.65 μg/m$^3$, respectively. Table S1 describes Pearson correlation coefficients between air pollution exposure throughout pregnancy. $NO_2$ was negatively correlated with $O_3$ (correlation coefficient r = −0.39) and moderately correlated with $PM_{2.5}$ and its components (0.55　r　0.66), except for $PM_{2.5}$ sulfate (r = 0.08). $O_3$ was moderately correlated with $PM_{2.5}$ sulfate (r = 0.38), while other correlations were relatively weaker. $PM_{2.5}$ exposure measurements based on the EBK model and the geoscience-derived model were highly correlated with each other (r = 0.83) and both were moderately to highly correlated with $PM_{2.5}$ components (0.43　r　0.91). Those correlations were similar to our previous findings for the same population (Sun et al., 2021).

Adjusted pooled ORs and corresponding 95% CIs of SPROM associated with air pollution exposure in trimesters and entire pregnancy based on the single-pollutant model are shown in Table 3. Throughout pregnancy, 2–7% higher risks of SPROM were related to per IQR increase in exposure to krigged $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$. The strongest associations were found for $O_3$ and $PM_{2.5}$, followed by $NO_2$ and $PM_{10}$. In terms of trimester-specific results, associations with $NO_2$ and $O_3$ were observed in the first and third trimesters, while associations with $PM_{2.5}$ were observed in the second and third trimesters. The trimester-specific estimates for $PM_{10}$ exposure were not statistically precise. Results for $PM_{2.5}$ components showed similar trends with $PM_{2.5}$ exposure (Table 3). Every IQR increase in sulfate, nitrate, ammonium, and organic matter throughout the pregnancy was associated with 6%–8% higher risks of SPROM in the single-constituent model, except black carbon (1%, 95% CI: − 2%, 4%). Trimester-specific results showed relatively stronger associations in the second trimester for all $PM_{2.5}$ components.

Fig. 1 shows the monthly associations between air pollution estimated by the EBK model and SPROM based on the DLMs. In general, the monthly associations and the trimester-specific results showed consistent critical exposure windows. Windows of increased risks associated with $NO_2$ occurred at the beginning and the end of pregnancy (gestational months 1–2 and 7–8). The highest risk of SPROM was associated with $O_3$ exposure in gestational month 1. For $PM_{2.5}$, the period of increased risks was mainly identified from month 4 to month 7. For $PM_{10}$, being consistent with the trimester-specific results, we did not observe any associations. Details on the effect sizes are provided in Table S2.

The results of mixture analyses based on the QGC model are shown in Table 4. Krigged $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$ as well as $PM_{2.5}$ sulfate, nitrate, ammonium, and organic matter were included in the mixture analysis. Positive associations of SPROM were observed for both the krigged air pollution mixture and the $PM_{2.5}$ mixture during the pregnancy. Each quartile increase in the mixture containing four krigged air pollutants was associated with 15% (95% CI: 12%, 18%) higher odds of SPROM. Increasing all four air pollutants at once by a quartile, the positive weights of associations with SPROM were mainly driven by $O_3$ (49.6%), followed by $PM_{2.5}$ (25.4%) and NO2 (25.0%), while $PM_{10}$ was the only

pollutant negatively and weakly associated with SPROM. Each quartile increase in the mixture containing four $PM_{2.5}$ components was associated with 7% (95% CI: 5%, 9%) higher odds of SPROM. The positive weights of contributions for sulfate, nitrate, and organic matter were similar to each other, while ammonium was negatively associated with SPROM in this model.

We conducted subgroup analyses stratified by pre-pregnancy BMI (Fig. 2 and Table S3). Significant associations were observed in most of the subgroups for different air pollutants, except $PM_{10}$. The mothers with the lowest pre-pregnancy BMI ($< 18.5$ kg/m$^2$) tended to have higher risks of SPROM associated with $NO_2$ and $PM_{2.5}$, compared with higher pre-pregnancy BMI subgroups. Each IQR increase in exposure to $NO_2$ and $PM_{2.5}$ in underweight mothers was associated with 36% (95% CI: 17%, 58%) and 15% (95% CI: 1%, 30%) higher odds of SPROM during the pregnancy, respectively. Significant heterogeneity in associations with $NO_2$ exposure was detected across different BMI subgroups ($p$-value = 0.005).

Sensitivity analyses are shown in Tables S4–S10. Trimester-specific associations based on the single-trimester models are shown in Table S4. Associations with exposure to each air pollutant and $PM_{2.5}$ components in the last one and three gestational months (Table S5) were similar to estimates for the third trimester shown in Table 3. Associations with $NO_2$ and $PM_{2.5}$ in later pregnancy were slightly higher compared to associations with $O_3$. The associations for entire pregnancy exposure were robust among different models in the sensitivity analyses (Table S5). The WQS and QGC analyses showed similar results (Table S6). A quartile increment in the air pollution mixture of $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$ resulted in 13% (95% CI: 10%, 17%) higher risk of SPROM in the WQS model and the highest weighted pollutant was $O_3$ (weight: 51%). For $PM_{2.5}$ components, the OR for each quartile increase in the mixture of nitrate, sulfate, ammonium, and organic matter was 1.08 (95% CI: 1.05, 1.11) and sulfate contributed most to the association (weight: 46%). Adding the $PM_{2.5}$ total mass in the model for the mixture analyses of $PM_{2.5}$ components did not change our conclusions (Table S7). The results of entire-pregnancy associations changed minimally by performing co-pollutant models (Table S8-S9), while the associations with $NO_2$ and with $PM_{2.5}$ nitrate were attenuated to be insignificant after adjusting for $PM_{2.5}$ and $PM_{2.5}$ ammonium, respectively. This was likely due to moderate to high correlations between $PM_{2.5}$ and $NO_2$ (r = 0.61) and between $PM_{2.5}$ nitrate and $PM_{2.5}$ ammonium (r = 0.80). For effect modification by pre-pregnancy BMI evaluated in the interaction model, underweight mothers were at higher risks of $NO_2$- and $PM_{2.5}$-related SPROM (Table S10).

## 4.  Discussion

In a large retrospective cohort of 427,870 births with detailed individual-level EHRs in the KPSC healthcare system from 2008 to 2018, our results suggested that maternal exposure to $NO_2$, $O_3$, and $PM_{2.5}$ was consistently associated with increased risks of SPROM, and the critical exposure windows varied for each air pollutant: the first and third trimesters for $NO_2$ and $O_3$ and the latter two trimesters for $PM_{2.5}$. The mixture analysis showed that, among air pollutants examined in this study, the overall adverse effect on SPROM was mostly driven by $O_3$, followed by $PM_{2.5}$ and $NO_2$. In terms of $PM_{2.5}$ components, sulfate, nitrate, and

organic matter contributed to the most SPROM risk. Mothers with lower pre-pregnancy BMI were more susceptible to SPROM related to air pollution, especially to $NO_2$.

PROM is a common pregnancy complication arising from complicated pathophysiological factors and it has attracted growing interest for its association with elevated levels of ambient air pollution (Esteves, 2022; Goldenberg et al., 2008). To date, evidence of air pollution effects is still very limited and remains inconclusive to a large extent, with five studies conducted in China (Li et al., 2021; Song et al., 2019; Wang et al., 2019; Wu et al., 2023; Zhang et al., 2021), two in the United States (Pereira et al., 2016; Wallace et al., 2016), one in Spain (Dadvand et al., 2014), and another one in Australia (Pereira et al., 2014). Dadvand et al. first linked air pollution exposure and preterm PROM risks (Dadvand et al., 2014). They performed a matched case-control study on a hospital-based cohort with 5,555 singleton births in Spain and observed adverse effects of $NO_2$ and $NO_x$ during the entire pregnancy. $NO_2$ often serves as a widely used marker of complex traffic pollution (Durant et al., 2014). Similarly, our study identified significant associations for $NO_2$, especially at the beginning and the end of pregnancy, based on a larger cohort in Southern California. There is only one other study examining long-term exposure to $NO_x$, but that retrospective cohort study did not replicate findings regarding $NO_x$ exposure during the whole pregnancy (Wallace et al., 2016). The authors suggested that different levels of $NO_x$ pollution might be a possible explanation for the inconsistency, as the median $NO_x$ concentration was 28.9 $\mu g/m^3$ in their study, while the median level was much higher in the study from Spain (i.e., 102.6 $\mu g/m^3$) (Dadvand et al., 2014; Wallace et al., 2016). However, our study offered evidence in the context of lower pollution. The different characteristics of study populations, such as the population composition and susceptibility, might lead to possible discrepancies. As few studies analyzing these relationships have been reported, further investigations are necessary to confirm our findings.

Prior studies mainly examined the short-term effects of $O_3$ on PROM. Song et al. carried out a time series study in Xinxiang, China, and included 3,255 PROM admissions from 2015 to 2017 (Song et al., 2019). They found that higher exposure to $O_3$ at lag 1, 2, 0–1, 0–2, 0–3, and 0–4 significantly increased PROM admissions, and the strongest effect was observed at lag 0–2 (5.42% [95% CI: 1.45%, 9.39%] changes in hospitalization per 10 $\mu g/m^3$ increase in daily $O_{3-8h}$ concentration). Following this study, Zhang et al. reported a similar but slightly smaller effect of $O_3$ in their time series research conducted in Hefei, China (Zhang et al., 2021). In addition, a retrospective cohort study in the United States observed very acute effects of $O_3$ exposure several hours (1–5) before the delivery, while no association related to entire-pregnancy exposure was observed (Wallace et al., 2016). However, they used the delivery admission time as a proxy for the time that PROM occurred due to data unavailability. Even though most of the women would deliver their babies soon after the PROM, some mothers will experience a prolonged PROM (PROM greater than 24 h) (about 14% in our study population) and deliver their babies even after several weeks from PROM occurrence (Caughey et al., 2008). Neglecting the time interval between the PROM event and delivery may lead to bias, especially for the study on acute effects focusing on hourly or daily associations. Based on the rich clinical database from the KPSC healthcare system, we were able to obtain the accurate dates of PROM diagnosis and exclude non-spontaneous PROMs in our study and first observed long-term associations for $O_3$ during the whole

pregnancy, especially in the first trimester. According to the results from the QGC model, $O_3$ was the highest positively weighted air pollutant associated with SPROM in the present study, indicating that $O_3$ might be the most harmful component when the concentration level of four air pollutants increased simultaneously. Some previous studies also reported long- or short-term relationships between maternal exposure to carbon monoxide and sulfur dioxide and PROM (Li et al., 2021; Wallace et al., 2016; Wu et al., 2023; Zhang et al., 2021). The contribution to positive associations with PROM may vary accordingly for their study populations due to different exposure profiles. Thus, more studies from different regions or countries are warranted to identify the most important air pollutants for corresponding public interventions.

$PM_{2.5}$ is the criteria pollutant of the greatest public concern in California due to its high emission level and great health impacts (Anderson et al., 2018). There have been several papers examining the long-(Dadvand et al., 2014; Pereira et al., 2014, 2016; Wallace et al., 2016; Wang et al., 2019; Wu et al., 2023) or short-term (Li et al., 2021; Zhang et al., 2021) relationships between $PM_{2.5}$ and PROM, and conclusions remain mixed possibly due to differential study designs, populations, or $PM_{2.5}$ chemical compositions. Pereira et al. conducted a longitudinal study in an Australian cohort and reported a 3% (95% CI: 0%, 6%) higher risk of PROM per 1 μg/m$^3$ increase in the second-trimester exposure (Pereira et al., 2014), while they did not replicate the results in another study in New York (Pereira et al., 2016). Dadvand et al. and Wallace et al. also did not find associations for $PM_{2.5}$ or $PM_{10}$ (Dadvand et al., 2014; Wallace et al., 2016). By contrast, a study in Wuhan, China, demonstrated more conclusive associations across trimesters in the context of more severe $PM_{2.5}$ pollution and reported a 9%–35% higher risk of PROM per 10 μg/m$^3$ increase in $PM_{2.5}$ exposure (Wang et al., 2019). However, their study may suffer from a relatively smaller sample size and underlying measurement error, since it included only about 5,000 singleton births from a single hospital and used air pollution measurement from a single ground-based monitoring station as a proxy for personal exposure without considering maternal residential changes in the study period. In our study, we included mothers from a large pregnancy cohort spanning 10 counties that covers 146,350 km$^2$ area of California. Based on air pollution data with a higher spatial resolution, higher SPROM risks were observed with increased $PM_{2.5}$ exposure in the second and third trimesters and throughout the pregnancy, further strengthening the existing evidence of associations for $PM_{2.5}$.

To have a further understanding of the $PM_{2.5}$ effect, we estimated the associations for some $PM_{2.5}$ components. In the single-component model, sulfate, nitrate, ammonium, and organic matter showed comparable estimates with the result of $PM_{2.5}$ total mass. Considering any potential interaction of the intake of $PM_{2.5}$ components (Li et al., 2022), we applied the QGC model for multiple components and noticed that the effect of the $PM_{2.5}$ mixture was mainly dominated by nitrate, sulfate, and organic matter. Although ammonium was positively associated with SPROM in the single-pollutant model, it did not show a similar effect in the mixture analysis. As the levels of nitrate and ammonium were highly correlated (r = 0.80), we were unable to determine the independent impact for each of them by only conducting the single-pollutant analysis. The QGC approach can leverage the correlation among exposures (Keil et al., 2020). The positive association of SPROM with nitrate but a negative association with ammonium in the QGC model indicates that nitrate may play a

more crucial role in the SPROM risk, while ammonium is likely a surrogate of nitrate in the single-pollutant model (Dadvand et al., 2014). Interestingly, we did not find a relationship between black carbon and SPROM during any exposure windows in our study, which is inconsistent with the study conducted in Barcelona, Spain, that found an association between $PM_{2.5}$ light absorbance and preterm PROM (Dadvand et al., 2014). Sulfate, nitrate, and ammonium are soluble ions and constitute the secondary inorganic aerosols formed by the photochemical transformation of precursor pollutants mainly produced by coal burning and vehicle exhaust (Cai et al., 2020; Cyrys et al., 2003; Weagle et al., 2018; Zhang et al., 2015). Black carbon is a typical primary pollutant and usually serves as an important indicator of traffic-related particles, as its emission has been strongly associated with diesel engines (Andrew Gray and Cass, 1998; Cyrys et al., 2003; Zhang et al., 2017). Those ingredients of $PM_{2.5}$ have been linked to systematic inflammation, oxidative stress, and coagulation in previous studies (Chuang et al., 2007; Lei et al., 2019; Liu et al., 2017; Wu et al., 2012). A recent experimental study found evidence of particle translocation and reported black carbon accumulating on the fetal side of the placenta (Bove et al., 2019). Black carbon exposure has also been linked to preterm births. (Basu et al., 2017; Cai et al., 2020; Laurent et al., 2016b; Wilhelm et al., 2011). As PROM is an important contributor to preterm births (Esteves, 2022; Goldenberg et al., 2008), understanding the relationships between $PM_{2.5}$ components and PROM to identify the most hazardous constituents may help to further clarify their effects on preterm births. Our findings may be informative for future research to identify the critical sources of ambient $PM_{2.5}$ pollution and thus to provide some references for emission controls and mitigation strategies.

Trimester- and gestational month-specific results demonstrated the susceptible windows depending on exposure to different air pollutants. We observed a more important role for $O_3$ in early pregnancy, for $PM_{2.5}$ in mid to late pregnancy, and for $NO_2$ in early and late pregnancy. Researchers have suggested that amniotic membranes grow rapidly with the production of collagen during the first half of pregnancy and stretch in the rest of the pregnancy period to provide more space for fetal growth. The pathogenesis of membrane ruptures has been reported to be associated with the reduction, degradation, damage, or deficiency of chorioamniotic collagen (MacDermott and Landon, 2000; Stuart et al., 2005). Previous studies have linked reactive oxygen species (ROS) to the biological changes in the chorionic and amniotic membranes (Wall et al., 2002; Woods, 2001). Subsequent oxidative stress induced by excessive ROS can cause tearing in membranes by impairing the integrity of collagen (i.e., strength and elasticity) and lead to PROM as a result of collagen damage (Aponte and Agarwal, 2013; Huang et al., 2018; Longini et al., 2007). As a reactive form of oxygen gas, $O_3$ can cause serious oxidative stress damage, induce inflammation responses and cell apoptosis, then disturb the production of collagen or affect the fluidity of membranes, thereby leading to PROM (Gervasi et al., 2002; Huang et al., 2018; Kataoka et al., 2002; Parry and Strauss, 1998; Song et al., 2019; Wallace et al., 2016). Exposure to $PM_{2.5}$ or $NO_2$ can also promote oxidative stress or inflammation to weaken the structure of membranes or impair placental functions (Li et al., 2017; Li et al., 2019; Shah and Balkhair, 2011).

Our stratified analysis indicates that mothers with the lowest pre-pregnancy BMI can be more vulnerable to the effect of air pollution, especially for $NO_2$, even though the results for

those underweight mothers might be less precise (e.g., with wider CIs) compared to results of other subgroups due to a smaller sample size (10,453 underweight mothers, 2.44% of the entire study population). With the interaction term, the heterogeneity of SPROM risk among different BMI groups for $NO_2$ exposure was attenuated to be marginally significant (*p*-value = 0.108). Pre-pregnancy BMI is a potential risk factor for SPROM, and lower BMI may be associated with a lack of micro and macronutrients that may amplify the vulnerability to air pollution exposure during pregnancy (Caughey et al., 2008; Esteves, 2022). Women who are planning for a pregnancy should pay more attention to their living environment (e.g., taking measures to prevent adverse air pollution) as well as pre-conception conditions (e.g., keeping BMI ≥ 18.5 $kg/m^2$) to avoid higher risks of adverse pregnancy outcomes.

Our study had some unique strengths. First, to the best of our knowledge, this is the first study examining associations between $PM_{2.5}$ chemical components and SPROM, which may have important intervention implications in source-specific emission control of particulate matter pollution. Second, we collected important characteristics and high-quality medical and obstetrical information on mothers from the large and diverse pregnancy cohort of the KPSC healthcare system, including exact dates of PROM occurrence with its types (spontaneous/non-spontaneous) and maternal residential changes with the accurate address history. More than 40% of participants moved during their pregnancies and exposure assessment irrespective of such changes may result in more bias (Sun et al., 2021). Third, we investigated the effect modification of pre-pregnancy BMI to provide a reference for pre-pregnancy care.

Limitations in this study must be acknowledged. First, although residential mobility was considered in this study, using ambient pollutant levels as a proxy for personal exposure may lead to exposure misclassification. We were unable to take indoor air pollution and maternal time-activity patterns into account due to data unavailability. Besides, residual confounding resulting from other factors that were not controlled may exist in this study. Second, we used rough definitions of gestational months and trimesters and did not examine narrower exposure windows or any acute effects of air pollution exposure, including weekly or daily associations, as we obtained only monthly air pollution data. Our trimester-specific results may not be accurate enough based on monthly exposure data. Given the acute effects of air pollution detected in earlier research, both chronic and acute associations merit further examination with the air pollution data in a finer temporal resolution (e.g., daily air pollutant concentrations). Moreover, as only five $PM_{2.5}$ components were included in this study, potential associations between other components (i.e., heavy metals in $PM_{2.5}$) and SPROM merit further investigations.

## 5. Conclusions

The findings of this retrospective cohort study in Southern California add to the literature on associations between maternal exposure to $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$ and spontaneous PROM and corresponding critical susceptible windows. $O_3$ appeared to be more harmful among the four air pollutants of interest and the effects of $PM_{2.5}$ were mainly driven by nitrate, sulfate, and organic matter in this study. As air pollution mixture varies regionally,

more studies are warranted in different locations to replicate previous findings and explore more air pollutants or PM$_{2.5}$ components.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

## Data availability

The data that has been used is confidential.

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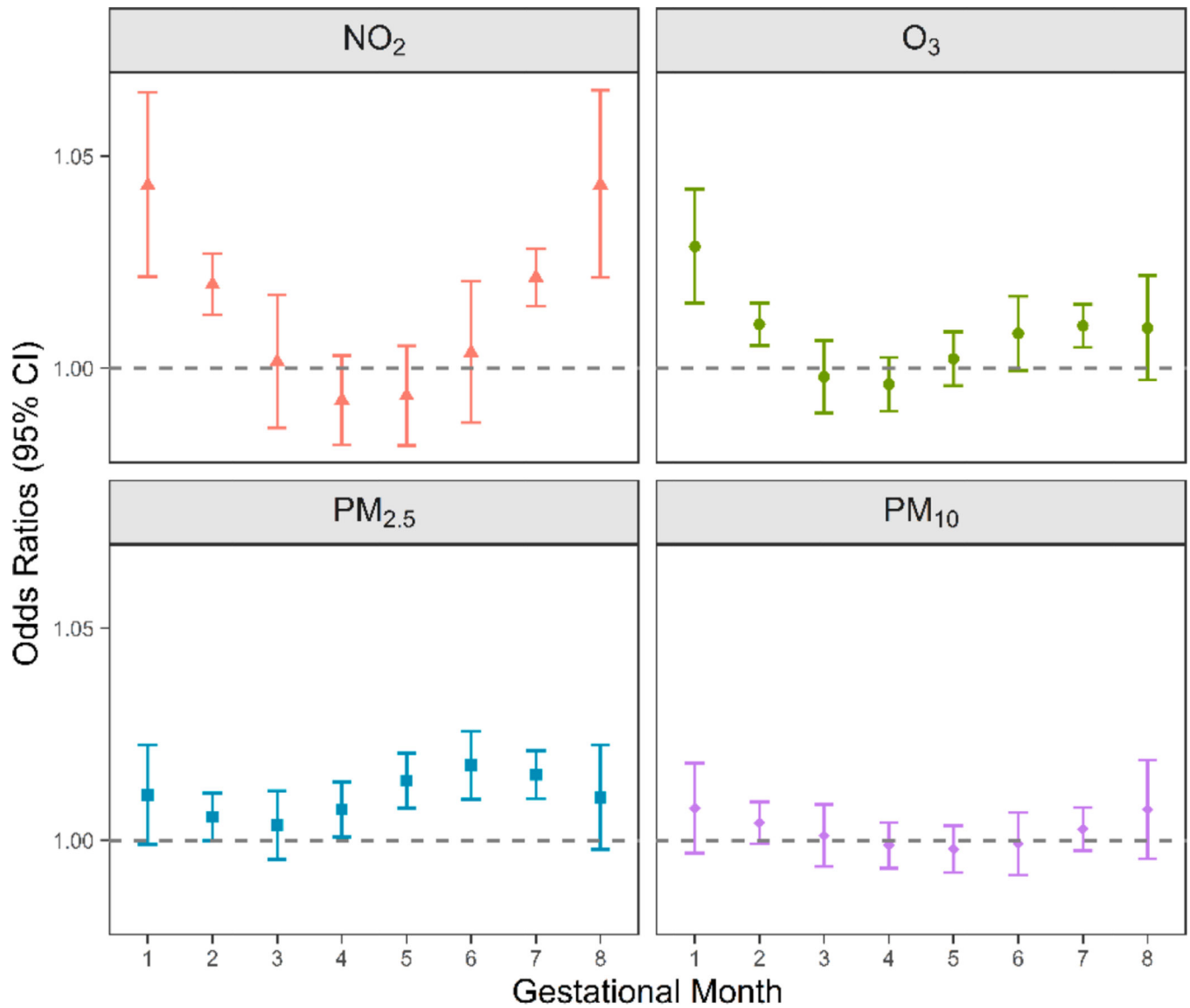
**Fig. 1.**
Monthly associations between maternal exposure to $NO_2$, $O_3$, $PM_{2.5}$, and $PM_{10}$ and spontaneous premature rupture of membranes in the distributed lag models (odds ratios [ORs] with 95% confidence intervals [CIs]). Exposure data were obtained from the empirical Bayesian kriging model. Models were adjusted for maternal age, race/ethnicity, education level, income level, pre-pregnancy body mass index, smoking status, parity, year of infant birth, and season of conception.

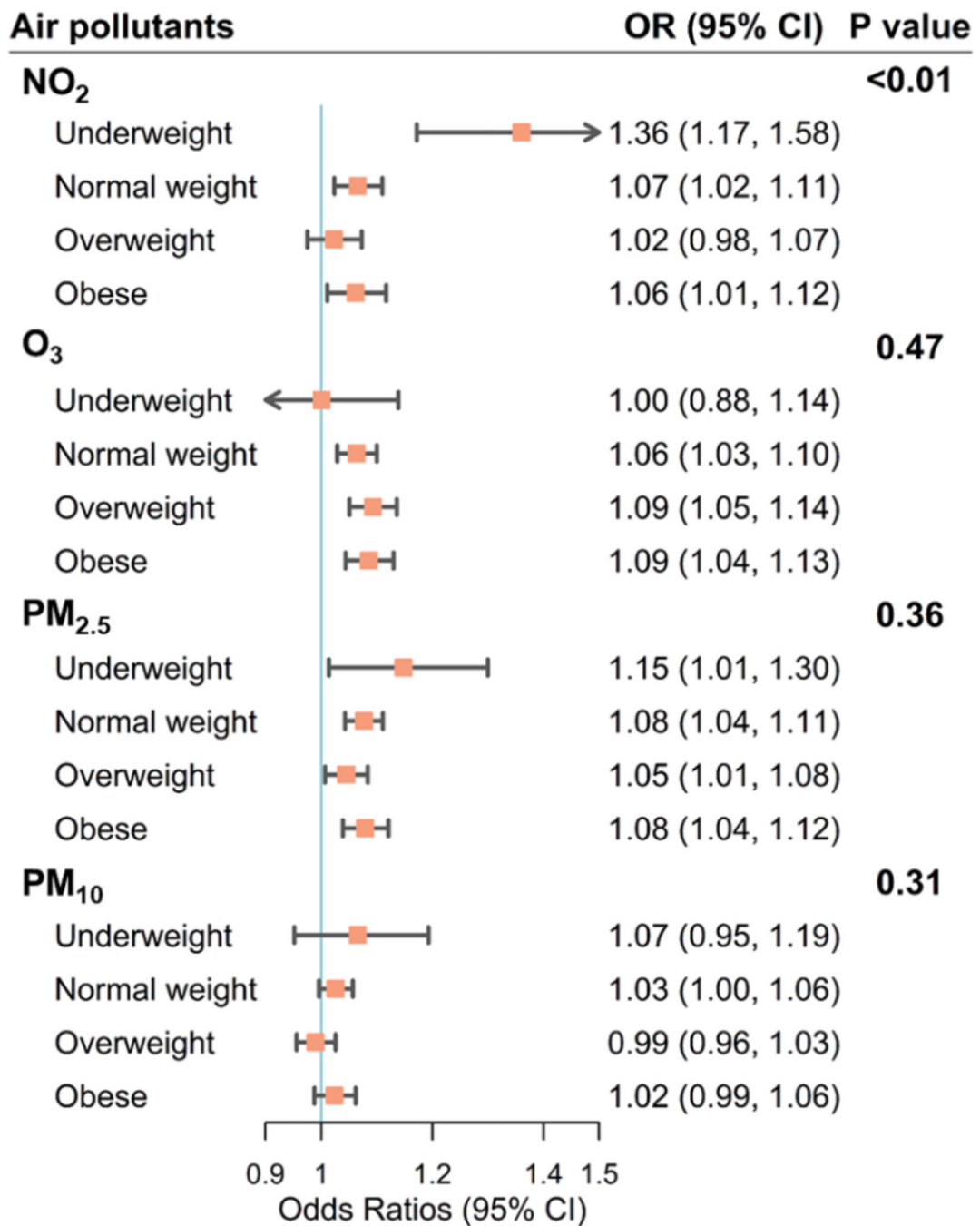| Air pollutants | OR (95% CI) | P value |
| --- | --- | --- |
| NO$_2$ | | <0.01 |
| Underweight | 1.36 (1.17, 1.58) | |
| Normal weight | 1.07 (1.02, 1.11) | |
| Overweight | 1.02 (0.98, 1.07) | |
| Obese | 1.06 (1.01, 1.12) | |
| O$_3$ | | 0.47 |
| Underweight | 1.00 (0.88, 1.14) | |
| Normal weight | 1.06 (1.03, 1.10) | |
| Overweight | 1.09 (1.05, 1.14) | |
| Obese | 1.09 (1.04, 1.13) | |
| PM$_{2.5}$ | | 0.36 |
| Underweight | 1.15 (1.01, 1.30) | |
| Normal weight | 1.08 (1.04, 1.11) | |
| Overweight | 1.05 (1.01, 1.08) | |
| Obese | 1.08 (1.04, 1.12) | |
| PM$_{10}$ | | 0.31 |
| Underweight | 1.07 (0.95, 1.19) | |
| Normal weight | 1.03 (1.00, 1.06) | |
| Overweight | 0.99 (0.96, 1.03) | |
| Obese | 1.02 (0.99, 1.06) | |

Odds Ratios (95% CI)

**Fig. 2.**
Subgroup analyses of associations (odds ratios [ORs] with 95% confidence intervals [CIs]) between air pollution exposure throughout the pregnancy and spontaneous premature rupture of membranes stratified by pre-pregnancy body mass index (BMI), kg/m$^2$, where underweight refers to pre-pregnancy BMI < 18.5, normal weight refers to 18.5 ≤ pre-pregnancy BMI ≤ 24.9, overweight refers to 25.0 ≤ pre-pregnancy BMI ≤ 29.9, and obese refers to pre-pregnancy BMI ≥ 30.0. Exposure data were obtained from the empirical Bayesian kriging model. Models are adjusted for maternal age, race/ethnicity, education

level, income level, smoking status, parity, year of infant birth, and season of conception. The $p$-value refers to the comparison among BMI subgroups and is obtained from Cochran's Q test.

**Table 1**

Descriptive statistics of the study population (2008–2018).

| Characteristics | Total pregnancies (n = 427,870) | Non-SPROMs (n = 390,013) | SPROMs (n = 37,857) |
|---|---|---|---|
| Maternal age (n, %) | | | |
| < 25 | 83,170 (19.44) | 75,880 (19.46) | 7,290 (19.26) |
| 25–34 | 253,755 (59.31) | 231,148 (59.27) | 22,607 (59.72) |
| 35 | 90,945 (21.26) | 82,985 (21.28) | 7,960 (21.03) |
| Race/Ethnicity (n, %) | | | |
| African American | 32,275 (7.54) | 29,580 (7.58) | 2,695 (7.12) |
| Asian | 53,829 (12.58) | 48,578 (12.46) | 5,251 (13.87) |
| Hispanic | 218,804 (51.14) | 199,269 (51.09) | 19,535 (51.60) |
| Non-Hispanic White | 111,717 (26.11) | 102,338 (26.24) | 9,379 (24.77) |
| Multiple/Others | 11,199 (2.62) | 10,203 (2.62) | 996 (2.63) |
| Missing | 46 (0.01) | 45 (0.01) | 1 (0.00) |
| Education level (n, %) | | | |
| Less than college | 133,596 (31.22) | 123,063 (32.55) | 10,533 (27.82) |
| College | 229,984 (53.75) | 208,955 (53.58) | 21,029 (55.55) |
| Higher than college | 55,879 (13.06) | 50,352 (12.91) | 5,527 (14.60) |
| Missing | | | |
| BMI, kg/m$^2$ (n, %) | 8,411 (1.97) | 7,643 (1.96) | 768 (2.03) |
| Underweight (<18.5) | 10,453 (2.44) | 9,538 (2.45) | 915 (2.42) |
| Normal weight (18.5–24.9) | 181,905 (42.51) | 165,909 (42.54) | 15,996 (42.25) |
| Overweight (25.0–29.9) | 119,181 (27.85) | 108,336 (27.78) | 10,845 (28.65) |
| Obese ( 30.0) | 112,859 (26.38) | 103,009 (26.41) | 9,850 (26.02) |
| Missing | 3,472 (0.81) | 3,221 (0.83) | 251 (0.66) |
| Smoking status (n, %) | | | |
| Never smoker | 357,244 (83.49) | 325,650 (83.50) | 31,594 (83.46) |
| Past smoker | 48,813 (11.41) | 44,488 (11.41) | 4,325 (11.42) |
| Smoker during pregnancy | 21,769 (5.09) | 19,833 (5.09) | 1,936 (5.11) |
| Missing | 44 (0.01) | 42 (0.01) | 2 (0.01) |
| Parity (n, %) | | | |
| Primiparous | 176,862 (41.34) | 156,316 (40.08) | 20,546 (54.27) |
| Multiparous | 250,444 (58.53) | 233,172 (59.79) | 17,272 (45.62) |
| Missing | 564 (0.13) | 525 (0.13) | 39 (0.10) |
| Season of conception Cool (November-April) | 216,761 (50.66) | 197,169 (50.55) | 19,592 (51.75) |
| Warm (May-October) | 211,109 (49.34) | 192,844 (49.45) | 18,265 (48.25) |
| History of PROM | | | |
| Never having PROM | 418,384 (97.78) | 381,693 (97.87) | 36,691 (96.92) |
| Having PROM before | 9,486 (2.22) | 8,320 (2.13) | 1,166 (3.08) |
| Income level, US Dollars (mean ± SD) | 59,664 (21,801) | 59,652 (21,804) | 59,784 (21,766) |

Note: There were 1,359 (0.32%), 1,279 (0.33%), and 80 (0.21%) pregnancies with missing data on the income level among total pregnancies, non-SPROM cases, and SPROM cases, respectively. Abbreviation: BMI, body mass index; SD, standard deviation; SPROM, spontaneous premature rupture of membranes.

**Table 2**

Summary statistics (Mean ± SD) of the average exposure to air pollutants and $PM_{2.5}$ total mass and components throughout pregnancy for the study population.

| Air pollutants | Total pregnancies | Non-SPROMs | SPROMs |
| --- | --- | --- | --- |
| Krigged $NO_2$, ppb | 15.62 ± 4.21 | 15.64 ± 4.23 | 15.46 ± 4.06 |
| Krigged $O_3$, ppb | 44.12 ± 6.80 | 44.04 ± 6.79 | 44.94 ± 6.88 |
| Krigged $PM_{2.5}$, μg/m$^3$ | 11.63 ± 2.37 | 11.64 ± 2.38 | 11.48 ± 2.21 |
| Krigged $PM_{10}$, μg/m$^3$ | 28.65 ± 5.64 | 28.69 ± 5.69 | 28.31 ± 5.13 |
| $PM_{2.5}$ total mass, μg/m$^3$ | 12.88 ± 2.64 | 12.88 ± 2.65 | 12.81 ± 2.53 |
| $PM_{2.5}$ sulfate, μg/m$^3$ | 1.28 ± 0.30 | 1.28 ± 0.30 | 1.27 ± 0.32 |
| $PM_{2.5}$ nitrate, μg/m$^3$ | 2.41 ± 0.66 | 2.41 ± 0.66 | 2.44 ± 0.63 |
| $PM_{2.5}$ ammonium, μg/m$^3$ | 0.95 ± 0.32 | 0.95 ± 0.32 | 0.93 ± 0.30 |
| $PM_{2.5}$ organic matter, μg/m$^3$ | 5.39 ± 1.34 | 5.40 ± 1.34 | 5.30 ± 1.29 |
| $PM_{2.5}$ black carbon, μg/m$^3$ | 1.49 ± 0.62 | 1.49 ± 0.62 | 1.42 ± 0.64 |

Note: The exposure to four krigged air pollutants was measured based on empirical Bayesian kriging. The exposure to $PM_{2.5}$ total mass and components was measured based on a fine-resolution geoscience-derived model. Abbreviation: ppb, parts per billion; SD, standard deviation; SPROM, spontaneous premature rupture of membranes.

**Table 3**

Adjusted pooled odds ratios (95% confidence intervals) of spontaneous premature rupture of membranes associated with air pollution exposure during trimesters and throughout the pregnancy in the single-pollutant model.

| Air pollutants | Exposure windows | | | |
|---|---|---|---|---|
| | 1st trimester | 2nd trimester | 3rd trimester | Entire pregnancy |
| Krigged $NO_2$ | 1.05 (1.03, 1.08) | 0.98 (0.95, 1.01) | 1.07 (1.05, 1.09) | 1.06 (1.03, 1.09) |
| Krigged $O_3$ | 1.04 (1.02, 1.05) | 1.00 (0.99, 1.02) | 1.02 (1.01, 1.04) | 1.07 (1.05, 1.10) |
| Krigged $PM_{2.5}$ | 1.01 (0.99, 1.03) | 1.04 (1.02, 1.06) | 1.02 (1.01, 1.04) | 1.07 (1.05, 1.09) |
| Krigged $PM_{10}$ | 1.01 (1.00, 1.02) | 1.00 (0.99, 1.01) | 1.00 (0.99, 1.02) | 1.02 (1.00, 1.04) |
| $PM_{2.5}$ total mass | 0.99 (0.97, 1.02) | 1.07 (1.04, 1.09) | 1.02 (1.00, 1.05) | 1.09 (1.06, 1.11) |
| $PM_{2.5}$ sulfate | 1.03 (1.01, 1.05) | 1.04 (1.01, 1.06) | 1.04 (1.02, 1.06) | 1.08 (1.05, 1.12) |
| $PM_{2.5}$ nitrate | 1.00 (0.99, 1.02) | 1.04 (1.03, 1.06) | 1.02 (1.00, 1.03) | 1.06 (1.04, 1.08) |
| PM2.5 ammonium | 1.01 (1.00, 1.03) | 1.04 (1.03, 1.06) | 1.01 (1.00, 1.03) | 1.07 (1.05, 1.09) |
| $PM_{2.5}$ organic matter | 0.98 (0.96, 1.00) | 1.07 (1.04, 1.10) | 1.01 (0.99, 1.03) | 1.06 (1.04, 1.09) |
| $PM_{2.5}$ black carbon | 1.00 (0.98, 1.03) | 1.01 (0.98, 1.05) | 1.01 (0.98, 1.04) | 1.01 (0.98, 1.04) |

Note: The exposure to four krigged air pollutants was measured based on empirical Bayesian kriging. The exposure to $PM_{2.5}$ total mass and components was measured based on a fine-resolution geoscience-derived model. IQR increments are 6.69 ppb for $NO_2$, 9.89 ppb for $O_3$, 3.26 $\mu g/m^3$ for $PM_{2.5}$, 6.82 $\mu g/m^3$ for $PM_{10}$, 3.91 $\mu g/m^3$ for $PM_{2.5}$ total mass, 0.627 $\mu g/m^3$ for $PM_{2.5}$ sulfate, 0.946 $\mu g/m^3$ for $PM_{2.5}$ nitrate, 0.421 $\mu g/m^3$ for $PM_{2.5}$ ammonium, 1.99 $\mu g/m^3$ for $PM_{2.5}$ organic matter, and 1.05 $\mu g/m^3$ for $PM_{2.5}$ black carbon. All models were adjusted for maternal age, race/ethnicity, education level, income level, pre-pregnancy body mass index, smoking status, parity, year of infant birth, and season of conception.

**Table 4**

Mixture effects on spontaneous premature rupture of membranes for one quartile increase in the air pollution mixture and PM$_{2.5}$ mixture throughout the pregnancy based on quantile-based g computation.

| Mode | Contribution to positive/negative effect (%) | Positive/Negative coefficient (β)[a] | Overall mixture coefficient (β [95% CI])[b] | Overall mixture effect (OR [95% CI]) |
|---|---|---|---|---|
| *Model 1: Krigged air pollutants* | | | | |
| Positive mixture[c] | | | 0.14 (0.12, 0.17) | 1.15 (1.12, 1.18) |
| NO$_2$ | 25.0 | 0.16 | ($p$<.001) | ($p$<.001) |
| O$_3$ | 49.6 | | | |
| PM$_{2.5}$ | 25.4 | | | |
| Negative mixture[d] | | | | |
| PM$_{10}$ | 100.0[e] | −0.02 | | |
| *Model 2: PM$_{2.5}$ components* | | | | |
| Positive mixture[c] | | | 0.07 (0.05, 0.09) | 1.07 (1.05, 1.09) |
| PM$_{2.5}$ sulfate | 34.1 | 0.10 | ($p$<.001) | ($p$<.001) |
| PM$_{2.5}$ nitrate | 43.3 | | | |
| PM$_{2.5}$ organic matter | 22.6 | | | |
| Negative mixture[d] | | | | |
| PM$_{2.5}$ ammonium | 100.0[e] | −0.03 | | |

Note: The exposure to four krigged air pollutants was measured based on empirical Bayesian kriging. The exposure to PM$_{2.5}$ components was measured based on a fine-resolution geoscience-derived model. Models were adjusted for maternal age, race/ethnicity, education level, income level, pre-pregnancy body mass index, smoking status, parity, year of infant birth, and season of conception. Abbreviation: CI, confidence interval; OR, odds ratio.

[a]The coefficient for the positive or negative mixture.

[b]The overall mixture coefficient is the sum of coefficients of the positive mixture and negative mixture.

[c]The positive mixture includes pollutants positively associated with the outcome in the model.

[d]The negative mixture includes pollutants negatively associated with the outcome in the model.

[e]The contribution of the pollutant is 100.0% as it is the only pollutant negatively associated with the outcome in the model.