Association of Ambient Air Pollution with Perceived Stress in Pregnant Women: A Prospective Cohort Study

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Research

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Abstract

Background: Air pollution is associated with perceived stress in the general population, but its influence on maternal perceived stress during pregnancy has not been investigated.We aimed to investigate the relationship between air pollution and non-specific perceived stress among pregnant women.

Methods: Our analysis included2162 pregnant women who had participated in the cohort for childhood origin of asthma and allergic disease study between 2008 and 2015. Maternal exposures to particulate matter with an aerodynamic diameter < 2.5 μm ($PM_{2.5}$) and < 10 μm (PM_{10}), as well as to nitrogen dioxide (NO_2) and ozone (O_3) for each trimesterand the entire pregnancy were determined using land-use regression models. Maternal perceived stress during the third trimester was assessed using the 14-item Perceived Stress Scale (PSS): scores ranged from 0-56 with higher scores indicating increased stress. Linear regression models were applied to estimate associations between PSS scores and each air pollutant, after adjusting for socio-demographic and behavioral covariates.

Results: In single-pollutant models,after adjustment, an IQR increase in the whole pregnancy exposure to $PM_{2.5}$ and PM_{10} and O_3 in the third trimester was related to 0.37 (95% confidence interval [CI]: 0.01, 0.74) and 0.55 (95% CI: 0.12, 0.98) and 0.29 (95% CI: 0.05, 0.52) points increase in the PSS score, respectively.This association was more evident in women with child-bearing age and lower levelofeducation, and the association of $PM_{10}$was stronger in thespring season.In multi-pollutant models, exposures to PM_{10} and O_3 were associated with higher perceived stress.

Conclusion: Our findings suggest that pregnancy exposure to $PM_{2.5}$, $PM_{10}$and O_3 is positively associated with maternal PSS score during the third trimester.

Introduction

Maternal psychosocial stress is relatively common during the prenatal period [1, 2]. Stress perceived by mothers during this period has been associated with adverse outcomes for mothers, including postpartum depression and suicide [3], as well as adverse outcomes for the fetus, including preterm birth [4], low birth weight [5], congenital heart defects [6] and impaired cognitive development of neonate [7]. In the last decades, air pollution has emerged as a potential risk factor for the development of psychosocial stress. Epidemiological studies show associations of air pollution with a range of psychiatric disorders, including cognitive decline [8], anxiety and depression [9, 10] and suicide [11]. Experimental research supports these epidemiological associations [12, 13], indicating that exposure to air pollution leads to depression-like response in mice [13]. So far, few epidemiological studies have investigated the potential effects of air pollution on maternal psychosocial stress, and more specifically perceived stress, which is thought to contribute to the development of psychiatric disorders, including depression, in chronic state [14, 15].

Psychosocial stress can be manifested in many forms, such as perceived stress, anxiety, and depression. Previous studies have shown that air pollution is associated with perceived stress [16], mood [17], depressive symptoms [10], anxiety symptoms [9], psychiatric emergency room visits [18] and mental health disorders as summarized in a meta-analysis [19]. Perceived stress, widely assessed using the Perceived Stress Scale (PSS), is a measure of the degree to which situations in one's life are appraised as stressful and has been suggested as a global stress measure [20]. A longitudinal study of older men reported that exposure to air pollution, including particulate matter with an aerodynamic diameter < 2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2), is linked with higher PSS score, particularly in cold months [16]. However, other study that explored associations between personal exposure to NO_2 and PSS in the healthy elderly persons has reported insignificant results [17].

The pregnant women are especially vulnerable to air pollution due their increased ventilation rate for higher oxygen requirements of the developing fetus and decreased oxygen-binding capability [21]. In addition, brain is susceptible to environmental factors due to high metabolic demands [9]: air pollutants are capable of reaching the brain, potentially by crossing the blood-brain barrier, and can trigger neuroinflammation, leading to pathological changes [22]. To date, only few studies have investigated the relationship between air pollution and maternal psychosocial stress in perinatal period. These studies have mostly focused on depression or emotional stress [23 – 26], while other indicator of psychosocial stress, such as perceived stress, has not been studied on pregnant women. Maternal perceived stress during pregnancy is an important predictor for postpartum depression [27]. Highlighting the relationship between air pollution and the perceived stress will help to understand a possible mechanism that relates air pollution to depression.

The aim of this study was to investigate potential associations between exposure to air pollution during different trimesters and maternal PSS, which was assessed at 36th week of pregnancy, hypothesizing that increased level of air pollution would be associated with higher PSS in our sample of pregnant women.

Methods

Study population

Participants included in this study were enrolled in the Cohort for Childhood Origin of Asthma and Allergic disease (COCOA), a prospective hospital-based birth cohort study conducted in South Korea, details of which have been published previously [28]. Briefly, pregnant women before 26 weeks of gestational age were recruited at five medical centers and eight public health centers in the Seoul metropolitan area between 2008 and 2015. For this analysis, subjects were limited to those with maternal PSS data. Of the 3102 women recruited, 638 women without PSS data and 86 with multiple records were excluded. Women with missing information on residential address and preterm births were not included in the study. Some covariates with missing information were also excluded. Supplementary material (Fig. S1) provides further details of the exclusion criteria. The final study population consisted of 2162 pregnant women. Prior to enrollment, written informed consent was obtained from all study subjects. The study protocol was approved by the institutional review boards (IRBs) of Asan Medical Center (IRB No. 2008 – 0616), Samsung Medical Center (IRB No. 2009- 02-021), Yonsei University (IRB No. 4-2008-0588), the CHA Medical Center (IRB No. 2010-010), and Seoul National University (IRB No. 1401-086-550).

Exposure assessment

Land use regression (LUR) model was applied to predict maternal exposures to $PM_{2.5}$, particulate matter with an aerodynamic diameter < 10 μm (PM_{10}), NO_2 and ozone (O_3). Ambient air monitoring data were obtained from the Korean Ministry of Environment (http://www.airkorea.or.kr/web) measured at a maximum of 40 regulatory air pollution monitoring sites in Seoul from 2007 to 2015. Daily 24-h average concentrations of $PM_{2.5}$, PM_{10}, NO_2, and O_3 were measured in each monitoring station. Monthly exposures to particulate matter ($PM_{2.5}$ and PM_{10}), NO_2 and O_3 at maternal residential addresses were estimated using LUR model, as previously described [29, 30]. The LUR model used several geographical variables, such as traffic indicators, surrounding-land use, topography and spatial trends, and the final LUR model included lengths of roads, traffic intensities on nearest roads, total heavy-duty traffic on all roads and a variable representing spatial trends. Model performance was assessed using leave-one-out cross-validation (LOOCV). The models explained 66 – 81% of the variability in the measured $PM_{2.5}$, PM_{10}, NO_2 and O_3 levels, and the predicted values fitted well with the measured values, as reported in our previous studies [31, 32]. The model-adjusted R^2 and LOOCV R^2 for $PM_{2.5}$, PM_{10}, NO_2 and O_3 were 0.66 and 0.56, 0.69 and 0.60, 0.79 and 0.73 and 0.81 and 0.77, respectively.

To examine potential critical exposures during pregnancy, we calculated the average concentrations of $PM_{2.5}$, PM_{10}, NO_2 and O_3 for three trimesters and the entire pregnancy: the first trimester (from 1 to 13 weeks), the second trimester (from 14 to 27 weeks), and the third trimester (from 28 weeks to until birth).

Assessment of maternal perceived stress

Maternal perceived stress was evaluated during the third trimester of pregnancy using the 14-item PSS [20, 33], which is a validated measure of stress appraisal and was used to assess the extent to which respondents think their lives have been unpredictable, uncontrollable and overloaded during the previous month. The PSS is a widely used stress appraisal measure and has been verified among pregnant women at risk for mental stress (Cronbach's alpha = 0.88) [34]. Each item was rated using a Likert-type five-point scale that ranges from "never" (0) to "very often" (4). The scores for seven positively stated items in the 14-items scale were reversed, and a total score was obtained by summing all items. The total score ranges from 0 to 56, a high score indicates a high perception of stress. In the current study, the PSS was normal in distribution and had excellent reliability (Cronbach's alpha = 0.884).

Covariates

Potential confounding variables, including maternal age at delivery, maternal education, occupation during pregnancy (yes vs. no), parity (nulliparous vs. parous), smoking history (ever vs. never), family income and drinking during pregnancy (yes vs. no), were ascertained at baseline. The maternal age was divided into two groups: child-bearing age (< 35 years old) and advanced age (≥ 35 years old). Mother's education was categorized into three levels: secondary school, college or university and graduate school. Family income was dichotomized as high (≥ 4 million Korean won per month) or low (< 4 million Korean won per month) [35]. The data on gestational age in weeks was obtained from medical records at delivery. We also obtained medical history of participants according to physicians' diagnoses, including hypertension or diabetes mellitus, asthma, thyroid diseases, malignant tumor and liver diseases. We used children's birth season to indicate a seasonal variation in the perceived stress during the third trimester. The season at delivery was classified into spring (March to May), summer (June to August), autumn (September to November) and winter (December to February) according to the climate characteristics in South Korea. Previous studies indicated that these variables were related to psychosocial stress and may affect the estimated association between exposure to air pollution and perceived stress [2, 16, 36].

Statistical analysis

Descriptive statistics were presented as mean, standard deviation (SD), and frequency (%). Spearman's correlation coefficient was used to estimate the correlations among air pollutants during pregnancy. Linear regression models were used to assess the association between air pollutants averaged over each trimester and the whole pregnancy and PSS score. Point estimate was estimated by interquartile range (IQR) increase in the exposure level for each air pollutant. Model 1 examined the bivariate associations between PSS score and air pollutants measured during the pregnancy. Model 2 adjusted for age, education, occupation and income only, whereas model 3 additionally adjusted for a number of lifestyle and maternal characteristics, including gestational age, smoking, drinking during pregnancy, parity and season at delivery. In model 4, as our primary model, we added an additional control for chronic health conditions, including asthma, thyroid disease, malignant tumor, liver disease and hypertension or diabetes. In addition to continuous variable, we modeled air pollution as categorical variables (quartiles of air pollution exposure) using linear regression for the model 4. Tests for linear trend across quartiles were conducted by using the median value of air pollutant to each quartile and modeling this variable as a continuous variable in separate regression models.

To further explore the potential nonlinear association between maternal air pollution exposure and PSS score, we performed a restricted cubic spline analysis based on linear regression model [37]. The optimal number of knots for the spline analysis was determined by Akaike information criterion (AIC). Nonlinearity was assessed by testing the regression coefficient of nonlinear term, with p for nonlinearity < 0.05 indicating a nonlinear association: the overall association indicated that the regression coefficients of both linear and non-linear terms of the factor were equal to zero.

In addition, stratified analyses were conducted to examine the effect modification by maternal age, parity, education, income and season at delivery. To evaluate the significance of effect modification on the multiplicative scale, we included an interaction (product) term between air pollution exposure and each of these characteristics in our primary model.

Then several sensitivity analyses were conducted. First, to test the stability of the effects after controlling for other pollutants, we built multi-pollutant models for pregnancy exposure to all pollutants except for $PM_{2.5}$ due to its high correlation with PM_{10} (Table S1). Second, we reanalyzed the primary model after excluding women with chronic health condition. Third, we reanalyzed the primary model using multiple imputation technique. Finally, we evaluated the robustness of our results to unmeasured cofounding by calculating the E-value [38], which indicates the minimum strength of association that an unmeasured confounder must have to explain away associations between exposure (air pollution) and outcome (PSS score). We reported the E-value for relative risk estimate for air pollution using our primary model.

Statistical analyses were conducted using STATA (version 16.0; Stata Corporation). $P < 0.05$ was considered statistically significant.

Results

Table 1 presents the summary statistics of the study population. The mean age of pregnant women was approximately 33 years, and the mean PSS score was 20.2 with a standard deviation of 7.2. Among mothers, 1315 (60.8%) were primiparous, 2063 (95.6%) had higher educational level (college or above) and 32 (1.5%) were diagnosed with diabetes or hypertension in pregnancy. Most participants had high income (62.2%), with the majority of women reported to be never smokers (92.2%).

Table 1
Characteristics of participants

Characteristics	Mean ± SD or n (%)
Age (years)	33.1 ± 3.5
Age group	
< 35	1458 (67.4)
≥ 35	704 (32.6)
Parity	
Nulliparous	1315 (60.8)
Parous	663 (30.7)
Missing	184 (8.5)
History of smoking	
Never	1994 (92.2)
Ever	168 (7.8)
Drinking during pregnancy	
No	1996 (92.3)
Yes	166 (7.7)
Occupation	
No	729 (33.7)
Yes	1433 (66.3)
Education	
Secondary school	99 (4.6)
College or university	1587 (73.4)
Graduate school	476 (22.0)
Gestational age (weeks)	39.3 ± 1.1
Family income	
High (≥ 4 million per month)	1357 (62.8)
Low (< 4 million per month)	805 (37.2)
Asthma	

Note: SD, standard deviation. n = 2162.

Characteristics	Mean ± SD or n (%)
No	2090 (96.7)
Yes	72 (3.3)
Thyroid disease	
No	2020 (93.4)
Yes	142 (6.6)
Malignant tumor	
No	2132 (98.6)
Yes	30 (1.4)
Liver disease	
No	2093 (96.8)
Yes	69 (3.2)
Hypertension or Diabetes mellitus	
No	2130 (98.5)
Yes	32 (1.5)
Season at delivery	
Spring	465 (21.5)
Summer	435 (20.1)
Autumn	492 (22.8)
Winter	593 (27.4)
Missing	177 (8.2)
PSS score	20.2 ± 7.2
Note: SD, standard deviation. n = 2162.	

The distributions of the air pollutant concentrations during the entire pregnancy and across the three trimesters are displayed in Table 2. The mean concentrations of air pollutants during the first, second, and third trimesters were 27.66, 26.69 and 27.37 μg/m^3 for $PM_{2.5}$, 51.19, 49.42 and 50.71 μg/m^3 for PM_{10}, 35.08, 34.61 and 35.35 ppb for NO_2, and 44.48, 43.44 and 41.48 ppb for O_3, respectively. The correlation of pollutants by trimesters is provided in the supplementary material (Table S1). Spearman's correlation coefficients between $PM_{2.5}$ and PM_{10} during pregnancy were strong (Spearman's correlation coefficient $r = 0.82$ to 0.91). PM_{10} showed a moderate positive correlation with NO_2 ($r = 0.30$ to 0.54), whereas NO_2 showed a moderate negative correlation with O_3 ($r = -0.46$ to -0.53). Spearman correlations of each air pollutant with itself across three trimesters are presented in Table S2. The levels of air pollution for second trimester were strongly correlated with the levels for the entire pregnancy ($r =$ 0.80 to 0.88).

Table 2
Distributions of maternal air pollution exposure levels for different pregnancy periods

Air pollutants	Mean ± SD	Min	25th	50th	75th	Max
$PM_{2.5}$ (μg/m^3)						
1st trimester	27.66 ± 8.13	11.41	21.19	27.31	32.90	57.46
2nd trimester	26.69 ± 7.68	12.18	20.54	25.98	31.54	61.99
3rd trimester	27.37 ± 7.87	11.71	21.24	26.78	32.33	57.86
Whole pregnancy	27.21 ± 5.67	14.83	23.22	26.07	30.14	53.73
PM_{10} (μg/m^3)						
1st trimester	51.19 ± 12.41	24.25	40.98	51.79	61.24	88.82
2nd trimester	49.42 ± 11.59	25.73	39.37	49.12	58.62	81.48
3rd trimester	50.71 ± 12.04	24.48	40.78	51.19	59.91	85.67
Whole pregnancy	50.37 ± 6.47	34.60	45.80	50.19	54.69	73.93
NO_2 (ppb)						
1st trimester	35.08 ± 9.67	2.00	29.00	35.00	41.00	76.00
2nd trimester	34.61 ± 9.15	2.00	29.00	34.00	40.00	84.00
3rd trimester	35.32 ± 32	3.00	29.00	35.00	41.00	81.00
Whole pregnancy	34.98 ± 7.98	2.00	30.00	35.00	39.00	75.00
O_3 (ppb)						

Note: SD, standard deviation; ppb, parts per billion.

Air pollutants	Mean ± SD	Min	25th	50th	75th	Max
1st trimester	44.48 ± 15.13	5.00	31.00	44.00	57.00	88.00
2nd trimester	43.44 ± 14.51	9.00	31.00	42.00	55.00	83.00
3rd trimester	41.48 ± 14.99	8.00	28.00	40.00	53.00	85.00
Whole pregnancy	43.19 ± 7.90	9.00	38.00	43.00	49.00	69.00
Note: SD, standard deviation; ppb, parts per billion.						

Association between maternal air pollution exposure and PSS score is presented in Table 3. Our analyses revealed a statistically significant association between PM_{10} during second trimester and the whole pregnancy and O_3 during third trimester and PSS score before as well as after adjustment of relevant covariates. In the primary model, we observed significant positive associations of an IQR increase in $PM_{2.5}$ and PM_{10} in the first and second trimesters and the entire pregnancy and O_3 in the third trimester with PSS score. For example, an IQR increase in exposure to $PM_{2.5}$ and PM_{10} in the whole pregnancy was associated with 0.37 (95% confidence interval [CI]: 0.01, 0.74) and 0.55 (95% CI: 0.12, 0.98) points higher PSS score, respectively. An IQR increase in exposure to O_3 in the third trimester was related to 0.29 (95% CI: 0.05, 0.52) point higher PSS score. No significant association was found for PSS score and NO_2 exposure. Regression coefficients were generally higher in the model 4, where health behaviors and chronic disease variables were additionally adjusted, compared to those in the model 2 including demographic factors only. We also explored the relationships between quartiles of maternal air pollution exposure and PSS score (Table S3). Compared with those in the lowest quartile, maternal exposure to PM_{10} during the second trimester and O_3 during the third trimester in the highest quartile were related to 1.09 (95% CI: 0.12, 2.06) and 1.36 (0.45, 2.28) points increase in PSS score, respectively (p for trend = 0.023 and 0.002, respectively). The highest quartile of $PM_{2.5}$ in the entire pregnancy showed significant association (p for trend = 0.059), whereas the highest quartile of NO_2 exposure during the first trimester was only a marginal level of significance (p for trend = 0.059).

Table 3
Association between air pollution exposure and PSS score among pregnant women in single-pollutant models

Air pollutants	Trimester	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
$PM_{2.5}$ (IQR: 6.92 μg/m^3)	First	0.12 (− 0.14, 0.38)	0.14 (− 0.12, 0.39)	0.27 (− 0.01, 0.55) +	0.29 (0.02, 0.57) *
	Second	0.26 (− 0.02, 0.53) +	0.30 (0.02, 0.57) *	0.32 (0.03, 0.61) *	0.36 (0.07, 0.65) *
	Third	0.04 (− 0.22, 0.31)	0.05 (− 0.21, 0.32)	−0.02 (− 0.30, 0.25)	−0.01 (− 0.29, 0.26)
	Pregnancy	0.29 (− 0.08, 0.66)	0.33 (− 0.04, 0.70) +	0.33 (− 0.04, 0.69) +	0.37 (0.01, 0.74) *
PM_{10} (IQR: 8.89 μg/m^3)	First	0.12 (− 0.09, 0.34)	0.14 (− 0.08, 0.35)	0.26 (0.02, 0.51) *	0.29 (0.04, 0.53) *
	Second	0.25 (0.01, 0.48) *	0.28 (0.05, 0.51) *	0.31 (0.04, 0.58) *	0.35 (0.08, 0.63) *
	Third	0.02 (− 0.21, 0.24)	0.02 (− 0.20, 0.25)	−0.10 (− 0.34, 0.15)	−0.09 (− 0.33, 0.15)
	Pregnancy	0.48 (0.06, 0.90) *	0.54 (0.13, 0.96) *	0.48 (0.05, 0.90) *	0.55 (0.12, 0.98) *
NO_2 (9.0 ppb)	First	0.00 (− 0.28, 0.29)	0.08 (− 0.20, 0.36)	0.18 (− 0.10, 0.46)	0.18 (− 0.10, 0.46)
	Second	0.03 (− 0.27, 0.33)	0.13 (− 0.17, 0.43)	0.14 (− 0.18, 0.45)	0.14 (− 0.18, 0.45)
	Third	−0.22 (− 0.51, 0.07)	−0.15 (− 0.44, 0.14)	−0.14 (− 0.42, 0.15)	−0.15 (− 0.44, 0.13)
	Pregnancy	−0.07 (− 0.41, 0.27)	0.04 (− 0.30, 0.38)	0.08 (− 0.26, 0.42)	0.08 (− 0.26, 0.41)
O_3 (11.0 ppb)	First	−0.11 (− 0.33, 0.11)	−0.13 (− 0.35, 0.08)	−0.14 (− 0.36, 0.09)	−0.15 (− 0.38, 0.08)
	Second	0.03 (− 0.20, 0.26)	−0.00 (− 0.23, 0.23)	0.16 (− 0.13, 0.45)	0.17 (− 0.12, 0.46)
	Third	0.28 (0.06, 0.51) *	0.29 (0.07, 0.51) *	0.29 (0.05, 0.52) *	0.29 (0.05, 0.52) *
	Pregnancy	0.21 (− 0.21, 0.63)	0.15 (− 0.27, 0.57)	0.28 (− 0.17, 0.73)	0.28 (− 0.18, 0.73)

Air pollutants	Trimester	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Note: CI, confidence interval; IQR, interquartile range; ppb, parts per billion; PPS, perceived stress scale.					
[a] Model 1: unadjusted.					
[b] Model 2: Model 1 + maternal age, education, occupation and income.					
[c] Model 3: Model 2 + gestational age, maternal smoking, drinking during pregnancy, parity and season at delivery.					
[d] Model 4: Model 3 + asthma, thyroid disease, malignant tumor, liver disease and hypertension or diabetes.					
+ p-value < 0.1. *p-value < 0.05.					

Table 4
Multi-pollutant model of associations between exposure to air pollutants and PSS score among pregnant women

Trimester	+ PM_{10}	+ NO_2	+ O_3	+ PM_{10} + NO_2 + O_3
	β (95% CI) [b]	β (95% CI) [b]	β (95% CI) [b]	β (95% CI) [b]
First				
PM_{10}	-	0.29 (− 0.01, 0.58) [+]	0.27 (− 0.01, 0.55) [+]	0.28 (− 0.02, 0.58) [+]
NO_2	0.00 (− 0.33, 0.34)	-	0.11 (− 0.22, 0.45)	−0.01 (− 0.37, 0.35)
O_3	−0.03 (− 0.29,0.23)	−0.10 (− 0.37, 0.17)	-	−0.03 (− 0.31, 0.25)
Second				
PM_{10}	-	0.35 (0.06, 0.64) *	0.34 (0.06, 0.61) *	0.31 (0.01, 0.62) *
NO_2	−0.00 (− 0.34, 0.34)	-	0.23 (− 0.11, 0.57)	0.07 (− 0.30, 0.44)
O_3	0.12 (− 0.18, 0.41)	0.25 (− 0.06, 0.56)	-	0.14 (− 0.18, 0.47)
Third				
PM_{10}	-	−0.04 (− 0.31, 0.24)	0.06 (− 0.21, 0.34)	0.05 (− 0.24, 0.34)
NO_2	−0.13 (− 0.46, 0.20)	-	0.06 (− 0.28, 0.41)	0.04 (− 0.32, 0.41)
O_3	0.32 (0.05, 0.59) *	0.32 (0.03, 0.61) *	-	0.33 (0.03, 0.63) *
Pregnancy				
PM_{10}	-	0.57 (0.12, 1.02) *	0.55 (0.12, 0.98) *	0.53 (0.08, 0.99) *
NO_2	−0.06 (− 0.41, 0.30)	-	0.21 (− 0.17, 0.59)	0.06 (− 0.34, 0.46)
O_3	0.29 (− 0.17, 0.74)	0.40 (− 0.11, 0.91)	-	0.32 (− 0.19, 0.83)

[b] Multi-pollutant model was further adjusted for the effects of other air pollutants in the same time window on the adjusted single-pollutant model 4 in Table 3.

[+] p-value < 0.1. *p-value < 0.05.

Spline analyses showed that increase in the mean PM_{10} concentration during the second trimester and O_3 concentration during the third trimester were associated with higher PSS score (p for overall association = 0.039 and 0.006, respectively) (Fig. 1B and D): $PM_{2.5}$ during the second trimester showed only marginal level of significance for overall association (p for overall association = 0.053) (Fig. 1A). Spline analyses showed linear dose-response function of $PM_{2.5}$ and PM_{10} concentrations during the second trimester (p for nonlinear = 0.743 and 0.999, respectively). In contrast, the association between maternal O_3 exposure during the third trimester and PSS score was nonlinear (p for nonlinear = 0.024). The overall association between NO_2 during the first trimester and PSS score was insignificant (p for overall = 0.364) and did not significantly deviate from linearity (p for nonlinear = 0.519) (Fig. 1C), which was consistent with estimates from the other models (Fig. S2).

Figure 2 shows evidence of effect modification for the relationship between air pollution and PSS by season. Significant interactions were observed between spring and exposure to PM_{10} during the first trimester and the entire pregnancy (p for interaction < 0.01); positive associations between PSS score and PM_{10} were significant in spring, but not in other seasons. Inverse association between NO_2 exposure during the third trimester and PSS was observed in autumn, but the interaction term was not significant. Analyses of effect modification by maternal age, parity, education and income are reported in the supplementary material (Fig. S3). In age-stratified models, we found a significant association between PM_{10} exposure during the first and second trimesters and the entire pregnancy and O_3 exposure during the third trimester and PSS score in pregnant women with child-bearing age, but not in women with advanced age. There was a significant interaction between O_3 exposure during the third trimester and age group on the PSS score (p for interaction < 0.05), while the interaction for PM_{10} exposure in the second trimester and the entire pregnancy was marginal level of significance (p for interaction < 0.1). For education, significant positive associations between PSS score and exposure to $PM_{2.5}$ during the second trimester and the entire pregnancy were only observed for women with less than graduate education (p for interaction < 0.05). For parity and income, the associations of $PM_{2.5}$, PM_{10} and O_3 with PSS were greater for primiparous women and women with low income, but p-values for interaction terms were not significant (p > 0.05).

In sensitivity analyses, the relationships between maternal exposure to PM_{10} during the second trimester and the entire pregnancy and O_3 during the third trimester and PSS score remained significant after adding other pollutants into the primary models (multi-pollutant models). The positive relationships between maternal exposure to air pollution and PSS score were not materially changed after excluding mothers with chronic health condition (Table S4). The findings were also similar when examining the association using the multiple imputation technique (Table S5). The E-values with lower 65% CI and relative risks for the primary model are reported in the supplementary material (Table S6). The results suggest that our conclusions are overall robust to unmeasured confounding bias.

Discussion

In this prospective cohort study of pregnant women, we investigated the association of exposure to air pollution with maternal PSS. We found that maternal exposures to $PM_{2.5}$ and PM_{10} during the first and second trimesters and the entire pregnancy and to O_3 during the third trimester were significantly associated with higher perceived stress rating, as measured during the third trimester, in the single-pollutant models. The associations between PM_{10} exposure during the second trimester and the entire pregnancy and O_3 during the third trimester and PSS remained significant in the multi-pollutant models. In addition, we found the evidence of effect modification for the air pollution-perceived stress associations by season, maternal age and education.

Experimental research provides biological plausibility for potential associations of air pollution with stress [39]. Yokota et al. showed that exposure to diesel exhaust particles during pregnancy decreased serotonin in mouse, which may lead to depressive behaviors [13]. Furthermore, epidemiological studies reported the association of air pollution with specific perceived stress, such as perceived air quality [40], as well as with non-specific perceived stress [16], where perceptions of air quality were unlikely to change due to the range of air pollution levels. In our study, we aimed to detect changes in non-specific perceived stress levels, as intermediate steps in the associations observed between exposure to air pollution and depressive symptoms. We focused on pregnant women as there is evidence of high susceptibility for the effects of air pollution among pregnant women. So far, only four studies have investigated the effects of air pollution on psychosocial stress during the perinatal period in a pregnant population [23 – 26]. One of these studies investigated the relationship between air pollution and maternal stress, and found that maternal exposures to $PM_{2.5}$, sulphur dioxide (SO_2), and NO_2 were associated with higher scores on Global Severity-Indices, indicating higher levels of emotional stress [26].

In stratified analyses, we found a significant positive effect of PM_{10} on PSS score in the spring season, while the effects were not statistically significant in other seasons. This finding is consistent with a previous study reporting a higher risk estimate of the link between PM_{10} and suicide in the spring season in Korea [11]. The average PM_{10} concentration is relatively high in Seoul during the spring season [41], so pregnant women may be more likely to perceive the effect of air pollution in the spring season and the effect may be more apparent in this season. However, some studies reported a stronger association between particulate air pollution and maternal perceived stress or emotional stress in the cold season [16, 26], which is inconsistent with our results. The inconsistency is possibly due to the seasonal and geographical variations of air pollutants and different weather conditions and lifestyles [42].

Furthermore, we estimated a stronger positive association of $PM_{2.5}$ and PM_{10} with PSS score in pregnant women with a lower socio-economic status indicator, particularly in women with lower level of education. In Korea, air pollution is known to be spatially associated with lower socio-economic status, including low income and lower educational attainment [43, 44]. Additionally, individuals with lower socio-economic status may be more likely to have higher perceived stress [45] and may be more susceptible to the effects of air pollution. Thus, a combination of greater pollution exposure and larger influence of lower socio-economic status on perceived stress may explain the stronger associations between particulate air pollution and PSS score among pregnant women in our study. In addition, in our study, women with child-bearing age showed a significant association between air pollution exposure and perceived stress, but not women with advanced age. Young pregnant women are more likely to develop stress-related disorders than those with advanced age [46] that may contribute to the increased vulnerability to air pollution.

Although the underlying biological mechanisms by which air pollution exposure may lead to altered perceptions of stress are yet to be elucidated, our findings are biologically plausible. Research has demonstrated that exposure to particulate matter increased inflammation in the brains of mice [47]. Chronic inflammation in the brain leads to the formation of reactive oxygen species and oxidative stress, which are reported among the hypothesized biological pathways of mental disorders [48, 49]. Pregnant women are reported to be more vulnerable to oxidative stress than the general population due to their altered physiology and increased energy requirements [50]. Maternal air pollution exposure may also lead to stress through the activation of the hypothalamic-pituitary-adrenal axis [51], which is associated with stress and stress-related disorders [52, 53].

The major strengths of this study were the prospective design to investigate the role of air pollution on the maternal perceived stress, use of validated models for assessment of exposure to air pollution and adjustment for multiple confounders. In addition, we showed effect modification of the association between air pollution and PSS by participant's characteristics, providing insight into susceptibility. Our findings were robust to multiple sensitivity analyses. Multi-pollutant models enabled us to conclude that both PM_{10} and O_3 exposure are associated with higher perceived stress independently from each other. We believe that our study is the first to investigate the relationship between air pollution and maternal perceived stress during pregnancy. However, this study had several limitations. First, air pollution estimates were based on maternal residential address, and geospatial data on maternal residential history, movement patterns, and time spent indoors and outdoors were unavailable. This may bias the model of air pollution exposure, particularly if women with perceived stress have different local mobility patterns. Previous research indicated that maternal mobility during pregnancy is usually limited and generally restricted to residential areas [54]. Air pollution tends to be more homogenous across the local areas, which may have little effect on our exposure estimates and was unlikely to have changed our findings. Second, although we controlled for several important potential confounders, it is possible that other factors may confound the relationship between air pollution exposure and PSS scores, such as noise pollution, meteorologic conditions and exposure to indoor pollutants. However, we evaluated E-values to see the strength of the relationship a hypothetical unmeasured confounder would have with the air pollution and PSS score to fully account for our results, suggesting that unmeasured confounders might not have a major influence on the association. Third, perceived stress was measured using self-reports and was assessed only once during pregnancy, a single measurement of the perceived stress might not present maternal stress status throughout pregnancy. Finally, while the homogenous makeup of the COCOA study in the Korean population provided excellent internal validity, its generalizability in other populations may be limited.

Conclusions

Our findings suggested that maternal exposures to $PM_{2.5}$, PM_{10}, and O_3 were related to higher levels of perceived stress among pregnant women. Pregnant women with child-bearing age and lower level of education may be more susceptible to air pollution. In addition, the association of PM_{10} with PSS was stronger in spring. Future studies are warranted on how air pollution may lead to higher perceived stress, and the potential role of perceived stress for the association between air pollution and affective disorder.

Abbreviations

CI: Confidence interval; COCOA: Cohort for childhood origin of asthma and allergic disease; IQR: Interquartile range; LUR: Land use regression; NO_2: Nitrogen dioxide; O_3: Ozone; $PM_{2.5}$: Particulate matter with an aerodynamic diameter < 2.5 μm; PM_{10}: Particulate matter with an aerodynamic diameter < 10 μm; ppb: parts per billion; PPS: Perceived stress score; SO_2: Sulphur dioxide

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review boards (IRBs) of Asan Medical Center (IRB No. 2008-0616), Samsung Medical Center (IRB No. 2009- 02-021), Yonsei University (IRB No. 4-2008-0588), the CHA Medical Center (IRB No. 2010-010), and Seoul National University (IRB No. 1401-086-550).

Consent for publication

Not applicable.

Competing interests

The authors have nothing to disclose.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Authors’ contributions

Authors YJS, KSL, KA, KWK, YHS, SJH and HCK made substantial contributions to conception and design of COCOA study. Authors DYJ and HCK were involved in the development or application of exposure modeling. Authors DKL performed the statistical analysis and drafted the manuscript. Authors SYL, DIS and HCK helped supervise the statistical analysis. Authors SJH and HCK reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

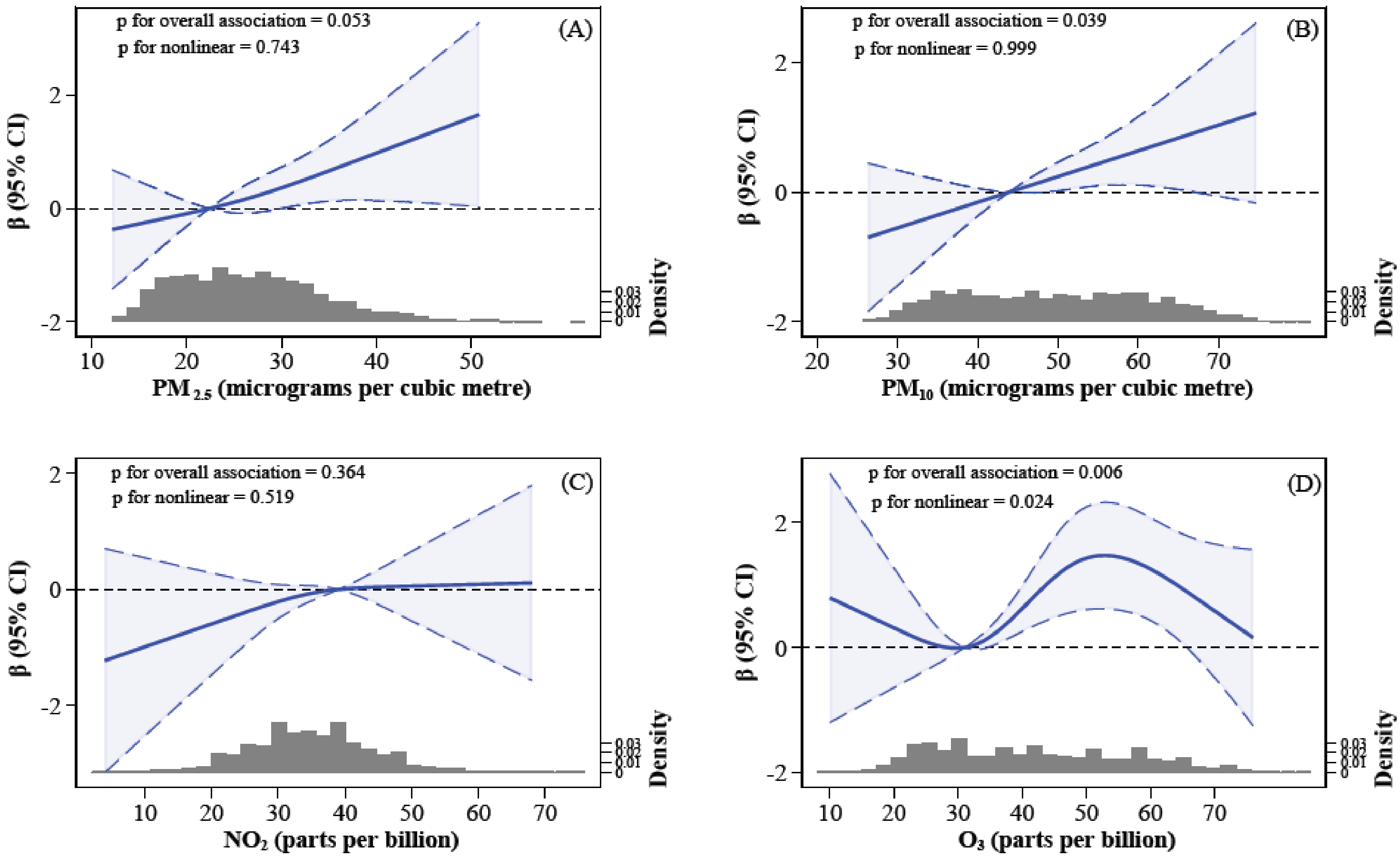

Figure 1

Nonlinear effects ofPM2.5 (A), PM10 (B), NO2 (C)and O3 (D) on the PSS score. Point estimates (solid line) and 95% confidence intervals (long dashed lines) were obtained by restricted cubic splines with three knots at the 10th, 50thand 90th percentiles of PM2.5, PM10and NO2 and four knots at the 5th, 35th, 65thand 95th percentile of O3 distributions. PM2.5 and PM10 during the second trimester, NO2 during the first trimesterand O3 during the third trimester were used for spline analyses.The reference exposure level was set at the 10th percentile of the distribution of PM10 (52.3 μg/m3) and O3 (30.0 ppb) concentrations. The modelsadjusted for maternal age, education, occupation, gestational age, maternal smoking, drinking during pregnancy, parity, season at delivery,income, asthma, thyroid disease, malignant tumor, liver diseaseand hypertension or diabetes.The histograms show the distribution of PM2.5 (A), PM10 (B), NO2 (C)and O3 (D) exposures.

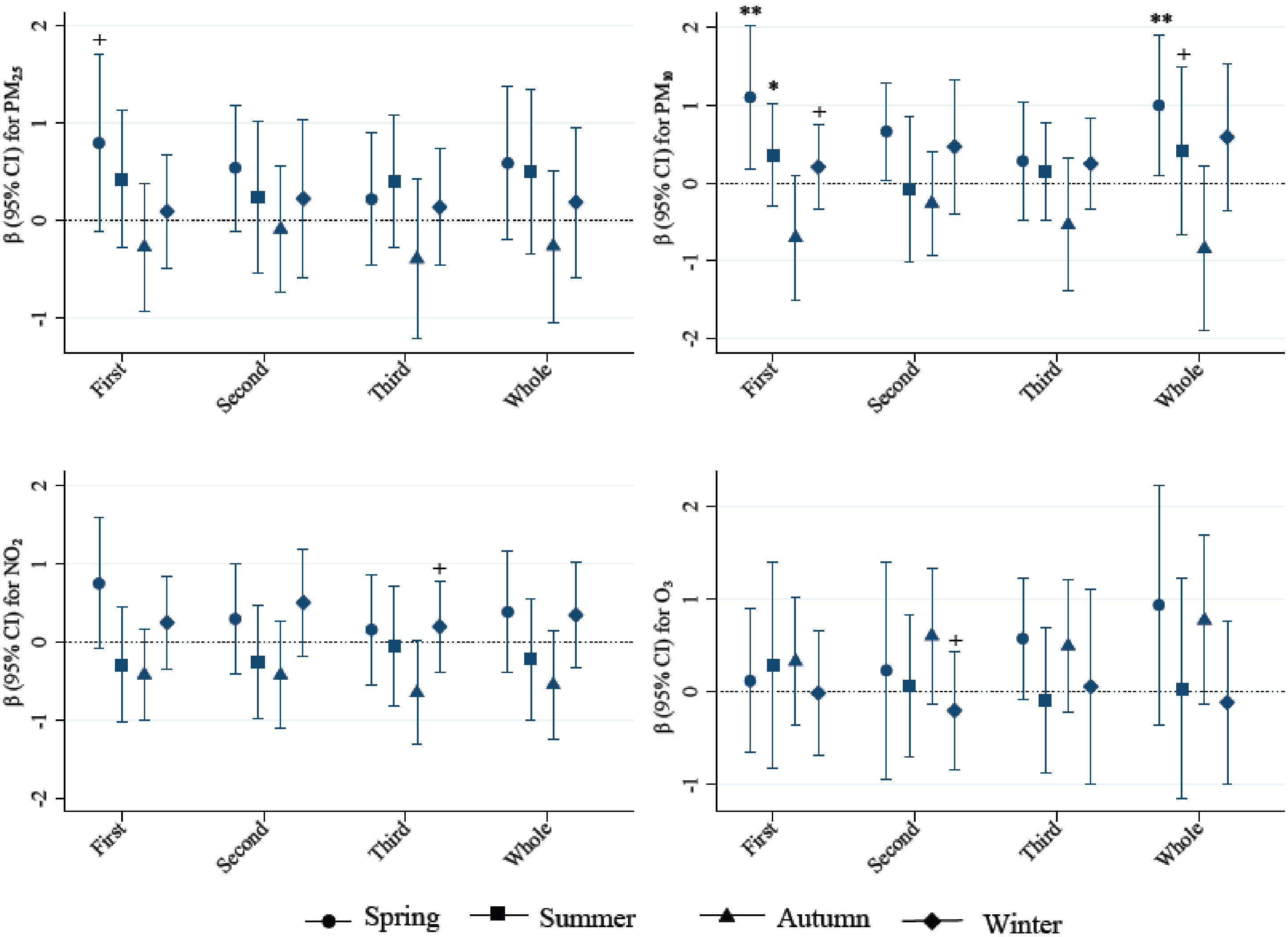

Figure 2

Adjusted difference in PSS score per IQR increase in air pollutants stratified by season. Analyses were adjusted for maternal age, education, smoking, occupation, drinking during pregnancy, parity, gestational age, income, asthma, thyroid disease, malignant tumor, liver diseasesand hypertension or diabetes. + p for interaction < 0.1. *p for interaction < 0.05. **p for interaction < 0.01.

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