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Association of ambient air pollution with depressive and anxiety symptoms in pregnant women: A prospective cohort study

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ABSTRACT

Background: Air pollution is associated with depressive and anxiety symptoms in the general population. However, this relationship among pregnant women remains largely unknown.
Objective: To evaluate the association between pregnancy air pollution exposure and maternal depressive and anxiety symptoms during the third trimester assessed using the Center for Epidemiologic Studies-Depression and State-Trait Anxiety Inventory scales, respectively.
Methods: We analyzed 1481 pregnant women from a cohort study in Seoul. Maternal exposure 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 trimester and the entire pregnancy was assessed at participant's residential address by land use regression models. We estimated the relative risk (RR) and corresponding confidence interval (CI) of the depressive and anxiety symptoms associated with an interquartile range (IQR) increase in $PM_{2.5}$, PM_{10}, NO_2, and O_3 using modified Poisson regression.
Results: In single-pollutant models, an IQR increase in $PM_{2.5}$, PM_{10}, and NO_2 during the second trimester was associated with an increased risk of depressive symptoms ($PM_{2.5}$ RR = 1.15, 95% CI: 1.04, 1.27; PM_{10} RR = 1.13, 95% CI: 1.04, 1.23; NO_2 RR = 1.15, 95% CI: 1.03, 1.29) after adjusting for relevant covariates. Similarly, an IQR increase in O_3 during the third trimester was associated with an increased risk of depressive symptoms (RR = 1.09, 95% CI: 1.01, 1.18), while the IQR increase in O_3 during the first trimester was associated with a decreased risk (RR = 0.89, 95% CI: 0.82, 0.96). Exposure to $PM_{2.5}$, PM_{10}, and NO_2 during the second trimester was significantly associated with anxiety symptoms. The associations with $PM_{2.5}$ and O_3 in single-and multi-pollutant models were consistent.
Conclusions: Our findings indicate that increased levels of particulate matter, NO_2, and O_3 during pregnancy may elevate the risk of depression or anxiety in pregnant women.

1. Introduction

Depression and anxiety are the most common mental disorders (Lim

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et al., 2018; Steel et al., 2014) and are significant contributors to the global disease burden, accounting for 43.0 million and 27.1 million years lived with disability, respectively, in 2017 (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Mental disorder rates are substantial during pregnancy, with 12–18% of women are reported to experience prenatal depression and 13–21% experience prenatal anxiety (Toscano et al., 2021; Woody et al., 2017). Mental disorders during pregnancy could have profound consequences for mother and child in terms of adverse pregnancy outcomes (Accortt et al., 2015; Mannisto et al., 2016) and neurodevelopment in infants, including cognitive deficits and changes in temperamental traits (Kinsella and Monk, 2009). Therefore, to reduce these health burdens, it is crucial to identify modifiable risk factors for prenatal depression and anxiety.

Abbreviations

BMI	body mass index
CES-D	center for epidemiologic studies-depression
CI	confidence interval
COCOA	cohort for childhood origin of asthma and allergic disease
EPDS	Edinburgh postnatal depression scale
ICD	international classification of diseases
IQR	interquartile range
LOOCV	leave-one-out cross-validation
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
RR	relative risk
STAI	State-Trait Anxiety Inventory

The development of depression and anxiety can be attributed to genetic (Lawrence et al., 2019; Kang et al., 2020), socio-demographic (Dulaney et al., 2018; Gur et al., 2019; Park et al., 2015), and physical environmental factors (Pun et al., 2017; van den Bosch and Meyer-Lindenberg, 2019). Specifically, exposure to ambient air pollution is hypothesized to induce depression and anxiety (Altuğ et al., 2020; Pun et al., 2017; Zhao et al., 2020). Recent meta-analyses of observational studies are consistent with their findings of a positive association of depression with particulate matter of <2.5 μm ($PM_{2.5}$) (Braithwaite et al., 2019; Gu et al., 2019; Zeng et al., 2019). Further, particulate matter <10 μm (PM_{10}) and nitrogen dioxide (NO_2) are associated with depression in the meta-analysis reported by Zeng et al. (2019). However, the latest systematic review and meta-analysis with the sophisticated inverse variance heterogeneity model reported that exposure to $PM_{2.5}$, PM_{10}, and ozone (O_3) is not associated with depression (Fan et al., 2020). Therefore, current evidence for the impact of air pollution on depression is inconclusive. In addition, only the small number of studies explored the relationship between air pollution and anxiety (Pun et al., 2017; Shin et al., 2018; Vert et al., 2017; Zhao et al., 2020), which warrants further research.

Although pregnancy has been identified as a vulnerable window for the detrimental impacts of air pollution (Hannam et al., 2013), the majority of previous studies focused on non-pregnant populations, and increased exposure to air pollution had been linked to depressive and anxiety symptoms among adults in South Korea (Shin et al., 2018), general population in Germany (Zhao et al., 2020), elderly population in the United States (Pun et al., 2017), and in women in the Nurses' Health Study in the United States (Kioumourtzoglou et al., 2017; Power et al., 2015). Pregnant women may be especially vulnerable to air pollution due to their increased ventilation rate for the higher oxygen requirements of the developing fetus and a decreased oxygen-binding capability (Kannan et al., 2006). However, few studies have investigated the association between air pollution and mental disorders in pregnant women (Ahlers and Weiss, 2021; Kanner et al., 2021; Lin et al., 2017); no studies have examined the effect of air pollution on prenatal anxiety. Further, for ambient ozone, an air pollutant and potent oxidant, the relationship between exposure to O_3 in different trimesters of pregnancy and prenatal depression or anxiety has not been examined.

This study aimed to investigate the effect of prenatal exposure to air pollution during different trimesters on maternal depressive and anxiety symptoms, which were evaluated at 36th week of pregnancy using the Center for Epidemiologic Studies-Depression (CES-D) and State-Trait Anxiety Inventory (STAI) scales, respectively, hypothesizing that increased level of air pollution would be associated with higher risk for depression and anxiety in our sample of pregnant women.

2. Materials and methods

2.1. Study population

This study was conducted as part of the Cohort for Childhood Origin of Asthma and Allergic disease (COCOA), a prospective hospital-based birth cohort study conducted in South Korea. Details of the COCOA study have been previously published (Shin et al., 2013; Yang et al., 2014). In this study, 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 depression and anxiety data. Of the 3102 women recruited, 870 women without depression and anxiety data and 83 with multiple records were excluded. Women with missing information on residential address, preterm births, and chronic diseases (thyroid diseases, cardiovascular disease, cancer, and tuberculosis) were not included in the study. Those with missing covariate information were also excluded. Supplementary material (Fig. S1) provides further details of the exclusion criteria. The final study population consisted of 1481 pregnant women. In general, there were no significant differences in general characteristics of pregnant women between the included and excluded participants, except for gestational age (Table S1). 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).

2.2. Exposure assessment

We obtained hourly air pollution data 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. Monthly exposures to particulate matter ($PM_{2.5}$ and PM_{10}), NO_2, and O_3 at residential addresses were estimated using a land use regression (LUR) model, as previously described (Lee et al., 2012; Yang et al., 2020). The LUR model contains several geographical variables, such as traffic indicators, surrounding-land use, topography, and spatial trends, and the final LUR model includes 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 elsewhere (Lamichhane et al., 2017). 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. We calculated average particulate matter exposures over pregnancy using clinically defined trimesters (1st trimester: 1–13 weeks, 2nd trimester: 14–27 weeks, 3rd trimester: 28 weeks until birth) using gestational age, calculated from the last menstrual period, and birth dates.

2.3. Outcomes assessment

Maternal depressive symptoms were evaluated during the third trimester of pregnancy using the CES-D-10 scale, which is a brief screening tool for depressive symptoms (Andersen et al., 1994). The CES-D-10 has been shown to be acceptable for screening depression during pregnancy (Chang et al., 2016). Items were rated using a 4-point Likert scale (0, 1, 2, 3). A sample question from the scale is as follows: "I was bothered by the things that usually do not bother me." We calculated the sum of all question-specific scores as the CES-D-10 score to indicate the general depression status of each subject. The score ranges from 0 to 30, with a higher score indicating a higher severity of depression. Maternal depressive symptoms were defined as a dichotomous measure using an optimal threshold of CES-D-10 score (CES-D-10 $\geq$ 12), as this cutoff generated most balance sensitivity and specificity for the detection of depressive symptoms (Baron et al., 2017). In the current study, the internal consistency of CES-D-10 indicated excellent reliability (Cronbach's alpha = 0.882).

We assessed the level of anxiety of pregnant women by using the Korean version of STAI (K-STAI) (Kim and Shin, 1978; Spielberger, 1972). COCOA participants were asked to complete a 20-item trait anxiety subscale of K-STAI to indicate a general tendency to perceive situations as threatening (Yang et al., 2014). Each item of subscale scored on a 4-point Likert scale ("not at all", "somewhat", "moderately so" and "very much so"), and total possible scores range from 20 to 80 points, with higher scores indicating more anxiety. We used a cutoff score of $\geq$40 to identify clinically significant symptoms of anxiety, which was validated in pregnant women and was reported as a predictor of postpartum anxiety and mood states (Grant et al., 2009; Kimmel et al., 2021). In the current study, the Cronbach's alpha of the trait anxiety subscale of K-STAI was 0.937.

2.4. Other variables

Potential confounding variables, including mother's age ($\geq$35 vs. <35 years), maternal education, occupation during pregnancy (yes vs. no), pre-pregnancy body mass index (BMI) (kg/m^2: $\geq$25 vs. <25), birth order (first-born vs. second or later-born), smoking history (ever vs. never), family income, and drinking during pregnancy (yes vs. no), were ascertained at baseline. Mother's education was categorized into three levels: secondary school, college or university, and graduate school. Family income was dichotomized as high ($\geq$4 million Korean won per month) or low (<4 million Korean won per month) (Cho et al., 2018). The data on gestational age in weeks was obtained from medical records at delivery. We used children's birth season to indicate a seasonal variation in the depressive and anxiety symptoms. The birth season was defined according to weather patterns in Korea as warm (April to September) and cold (October to March). Residential-related variable included pets keeping during pregnancy and the past years. Previous studies indicated that these variables were related to mental disorders and may affect the estimated association between exposure to air pollution and depressive and anxiety symptoms (Biggai et al., 2016; Brooks et al., 2018; Lee et al., 2007).

2.5. Statistical analysis

Descriptive statistics are presented as mean, standard deviation (SD), interquartile range (IQR), and frequency (%). Modified Poisson regression with robust error variance approach of Zou (2004), which provides estimates of relative risk (RR), was used to investigate the association between air pollutants averaged over the full gestational period and depressive and anxiety symptoms. RR was estimated by an interquartile range (IQR) increases in pollutant concentrations averaged over the pregnancy. To facilitate comparison of results, we were consistent in the use of a whole-pregnancy IQR across the analyses. A p-value of less than 0.05 was considered statistically significant.

We adjusted for a priori-specified factors that could potentially confound the association between air pollution and depression and anxiety. Models were adjusted for maternal age, pre-pregnancy BMI, birth order, history of smoking, drinking during pregnancy, maternal education, maternal occupation, gestational age, birth season, family income, and pet ownership. The potential nonlinear relationship of air pollutants with the depressive symptoms was examined by utilizing restricted cubic splines with knots at the fifth, 35th, 65th' and 95th percentiles of the distribution of air pollution concentrations (Desquilbet and Mariotti, 2010). A test for nonlinearity was conducted by testing the regression coefficient of nonlinear term, with p for nonlinearity <0.05 indicating a non-linear association. The p-value for overall association indicated that the regression coefficients of both linear and non-linear terms of the factor were equal to zero. We also conducted stratified analyses to assess potential effect modification by selected maternal characteristics. Stratum-specific RRs were obtained by modified Poisson regression. We evaluated the significance of effect modification on the multiplicative scale by including an interaction (product) term between air pollution exposure and each characteristic. Statistical analyses were conducted using STATA (version 16.0; Stata Corporation).

To confirm the robustness of our findings, several sensitivity analyses were performed. First, we ran multi-pollutant models for pregnancy exposure to all pollutants except for PM_{10} due to its high correlation with $PM_{2.5}$ (Table S1). Second, we considered different cutoffs for depressive (CES-D-10 $\geq$ 10, CES-D-10 $\geq$ 11, and CES-D-10 $\geq$ 13) and anxiety (K-STAI $\geq$ 39, K-STAI $\geq$ 41, and K-STAI $\geq$ 44) symptoms. Third, we considered depression and anxiety as a continuous rather than binary measure. Negative binomial regression was used to examine the association between the air pollutants and continuous scale of CES-D-10 and K-STAI scores due to evidence of overdispersion. Fourth, we reanalyzed the models using multiple imputation technique. Fifth, the associations between air pollution and depressive and anxiety symptoms were investigated for trimester-specific exposure, where exposure during the three trimesters were simultaneously included (multi-trimester model). Finally, we calculated E-values to determine the degree to which potential unmeasured confounding could explain away associations between air pollution and depressive and anxiety symptoms (VanderWeele and Ding, 2017).

3. Results

Table 1 presents the summary statistics of the study population. Among the 1481 pregnant women, 221 (14.9%) and 827 (55.8%) had depressive (CES-D-10 $\geq$ 12) and anxiety (K-STAI $\geq$ 40) symptoms, respectively: none of them were being medically treated by physicians or used any antidepressants. The mean age was 32.9 years and the mean BMI was 20.7 kg/m^2. Most participants had high income (62.9%), with the majority of women reported to be never smokers (92.7%).

The mean trimester-specific air pollutant concentrations for the study period are reported in Table 2. The average concentrations of exposure during pregnancy were 26.9 μg/m^3, 49.8 μg/m^3, 34.6 ppb, and 43.2 ppb for $PM_{2.5}$, PM_{10}, NO_2, and O_3, respectively. The correlation of pollutants is provided in supplementary material (Table S2). The trimester-specific mean concentrations of pollutants in subjects showed very weak to strong correlations (Pearson's correlation coefficient r = −0.17 to 0.89), with the highest Pearson's correlation coefficient between $PM_{2.5}$ and PM_{10} at the first trimester. PM_{10} showed a moderate positive correlation with NO_2 (r = 0.46 to 0.51), whereas NO_2 showed a moderate negative correlation with O_3 (r = −0.48 to −0.53).

Table 1
Descriptive statistics for the study population (n = 1481).

Characteristics	n (%) or mean (SD)
Age (years)	32.9 (3.6)
Age group	
<35	1033 (69.7)
≥35	448 (30.3)
Pre-pregnancy BMI (kg/m^2)	20.7 (2.5)
BMI group	
<25	1387 (93.6)
≥25	94(6.4
Birth order	
First-born	984 (66.4)
Second or later-born	497 (33.6)
History of smoking	
Never	1373 (92.7)
Ever	108 (7.3)
Drinking during pregnancy	
No	1382 (93.3)
Yes	99 (6.7)
Occupation	
No	498 (33.6)
Yes	983 (66.4)
Education	
Secondary school	109 (7.4)
College or university	1039 (70.2)
Graduate school	333 (22.5)
Gestational age (weeks)	39.3 (1.1)
Family income	
High (≥4 million per month)	932 (62.9)
Low (<4 million per month)	549 (37.1)
Pet ownership	
No	1393 (94.1)
Yes	88 (5.9)
Birth season	
Warm	635 (42.9)
Cold	846 (57.1)
CES-D-10 score	6.6 (4.7)
CES-D-10 ≥ 12	221 (14.9)
K-STAI score	40.6 (9.0)
K-STAI ≥ 40	827 (55.8)

BMI, body mass index; CES-D-10, center for epidemiologic studies depression scale-10; K-STAI, Korean version of state-trait anxiety inventory. Numbers in the table are mean (standard deviation) or n (%).

Table 2
Mean air pollution exposures during pregnancy.

Pollutant and trimester	Mean	IQR	Min - Max
$PM_{2.5}$(μg/m^3)			
First	26.9	11.3	11.4–57.5
Second	26.6	11.2	12.2–62.0
Third	27.2	10.8	11.7–57.9
Pregnancy	26.9	6.9	14.8–52.5
PM_{10} (μg/m^3)			
First	49.8	19.6	24.3–77.9
Second	49.2	19.6	25.6–81.5
Third	50.4	19.1	24.5–85.6
Pregnancy	49.8	8.5	34.6–68.9
NO_2 (ppb)			
First	34.5	12.0	2.0–74.0
Second	34.4	12.0	2.0–70.0
Third	35.0	12.0	3.0–81.0
Pregnancy	34.6	9.0	2.0–65.0
O_3 (ppb)			
First	44.6	26.0	5.0–79.0
Second	43.1	25.0	9.0–83.0
Third	41.9	25.0	8.0–85.0
Pregnancy	43.2	10.0	9.0–69.0

IQR, interquartile range; PM_{10}, particulate matter with aerodynamic diameters ≤ 2.5 μm; $PM_{2.5}$, particulate matter with aerodynamic diameters ≤ 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone.

Table 3
Single-pollutant model of associations between air pollution and depressive and anxiety symptoms among pregnant women.[a]

Air pollutants	Trimester	Depression (CES-D-10 ≥ 12)		Anxiety (K-STAI ≥ 40)	
		Unadjusted model	Adjusted model[b]	Unadjusted model	Adjusted model[b]
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
$PM_{2.5}$ (IQR: 6.9 μg/m^3)	First	1.01 (0.91, 1.12)	1.03 (0.91, 1.17)	1.05 (1.01, 1.08) **	1.04 (0.99, 1.09) +
	Second	1.13 (1.02, 1.24) *	1.15 (1.04, 1.27) **	1.04 (1.00, 1.07) *	1.07 (1.02, 1.12) **
	Third	1.00 (0.89, 1.13)	1.00 (0.88, 1.13)	1.01 (0.97, 1.04)	1.03 (0.98, 1.08)
	Pregnancy	1.09 (0.95, 1.26)	1.12 (0.97, 1.28)	1.07 (1.01, 1.11) *	1.07 (1.01, 1.13) *
PM_{10} (IQR: 8.5 μg/m^3)	First	0.99 (0.92, 1.08)	1.00 (0.90, 1.12)	1.03 (1.00, 1.06) *	1.03 (0.98, 1.07)
	Second	1.11 (1.02, 1.21) **	1.13 (1.04, 1.23) **	1.02 (0.99, 1.05)	1.07 (1.02, 1.12) **
	Third	0.98 (0.89, 1.08)	0.96 (0.87, 1.07)	0.99 (0.97, 1.02)	1.02 (0.97, 1.06)
	Pregnancy	1.11 (0.95, 1.30)	1.13 (0.96, 1.31)	1.05 (0.99, 1.11)	1.08 (1.01, 1.16) *
NO_2 (IQR: 9.0 ppb)	First	1.05 (0.94, 1.17)	1.14 (1.01, 1.28) *	1.02 (0.99, 1.06)	1.05 (1.00, 1.10) *
	Second	1.08 (0.96, 1.20)	1.15 (1.03, 1.29) *	1.02 (0.98, 1.06)	1.07 (1.02, 1.12) **
	Third	0.91 (0.81, 1.03)	0.95 (0.85, 1.07)	0.99 (0.95, 1.03)	1.01 (0.96, 1.06)
	Pregnancy	1.03 (0.90, 1.17)	1.11 (0.97, 1.27)	1.02 (0.97, 1.06)	1.05 (1.00, 1.11) *
O_3 (IQR: 10.0 ppb)	First	0.91 (0.84, 0.99) *	0.89 (0.82, 0.96) **	0.99 (0.97, 1.02)	0.97 (0.93, 1.01)
	Second	0.97 (0.89, 1.05)	0.95 (0.86, 1.06)	1.01 (0.98, 1.04)	0.97 (0.93, 1.02)
	Third	1.10 (1.02, 1.19) *	1.09 (1.01, 1.18) *	1.01 (0.98, 1.03)	1.04 (0.99, 1.09) +
	Pregnancy	0.95 (0.82, 1.10)	0.91 (0.78, 1.06)	1.01 (0.96, 1.06)	0.98 (0.92, 1.05)

$^+p < 0.10$, $^*p < 0.05$, $^{**}p < 0.01$.

[a] Relative risk (RR) estimated from modified Poisson regression models with robust error variance, representing RRs for prenatal depression and anxiety as dichotomous outcomes.

[b] Models adjusted for maternal age, history of smoking, drinking during pregnancy, pre-pregnancy BMI, maternal education, gestational age, birth order, family income, and pet ownership.

Table 3 shows results from modified Poisson regression represented as RRs and 95% CIs in the single-pollutant models. The results from fully adjusted models showed significant positive associations between an IQR increase of $PM_{2.5}$ (RR = 1.15, 95% CI: 1.04, 1.27), PM_{10} (RR = 1.13, 95% CI: 1.04, 1.23), and NO_2 (RR = 1.15, 95% CI: 1.03, 1.29) during the second trimester and maternal depressive symptoms. A significant association of NO_2 was also seen for the first-trimester exposure. For O_3, a significant positive association was observed for exposure during the third trimester (RR = 1.09, 95% CI: 1.01, 1.18); however, the exposure in the first trimester was associated with a decreased risk of depressive symptoms (RR = 0.89, 95% CI: 0.82, 0.96). Similarly, in the adjusted models, an IQR increase in exposure to $PM_{2.5}$ and PM_{10} during the second trimester was significantly associated with anxiety symptoms. Exposure to NO_2 during the first and second trimesters was significantly associated with anxiety symptoms, with a larger magnitude of RR for the second-trimester exposure (RR = 1.07, 95% CI: 1.02, 1.12). A positive association was found between the exposure to O_3 during the third trimester and anxiety symptoms, but the association was only marginally significant ($p < 0.10$). Patterns of associations from adjusted models were generally consistent with those from unadjusted models.

Spline regression analysis showed that the overall associations of $PM_{2.5}$ and PM_{10} during the second trimester with depressive symptoms were significant ($p = 0.049$; $p = 0.014$, respectively) (Fig. 1A and B): NO_2 during the second trimester and O_3 during the third trimester were only marginal level of significance for the overall association ($p = 0.101$; $p = 0.085$, respectively) (Fig. 1C and D). The p value testing for nonlinearity was marginally significant for PM_{10} ($p = 0.051$) and for other pollutants, p values were insignificant ($PM_{2.5}$, $p_{\text{nonlinearity}} = 0.982$; NO_2, $p_{\text{nonlinearity}} = 0.916$; and O_3, $p_{\text{nonlinearity}} = 0.172$), indicating a linear exposure-response function as shown in Fig. 1. The spline curves for exposure to $PM_{2.5}$, PM_{10}, and NO_2 during the first and third trimesters and exposure to O_3 during the first and second trimesters did not have significant positive overall associations and did not significantly deviate from linearity (Fig. S2). As with depression, the overall associations between exposure to $PM_{2.5}$ and PM_{10} during the second trimester and anxiety symptoms were significant (Figs. S3B and F). In addition, exposure to NO_2 during the second trimester had a significant overall association ($p = 0.038$) (Fig. S3J). The tests of nonlinearity in the associations between exposure to $PM_{2.5}$, PM_{10}, NO_2, and O_3 and anxiety symptoms were insignificant at the 0.05 level (Fig. S3), which were consistent with depression.

Effect modifications of the association between maternal depressive and anxiety symptoms and exposures to $PM_{2.5}$, PM_{10}, and NO_2 during the second trimester and O_3 during the third trimester, the exposure windows that show generally significant associations, are presented in Fig. 2 and supplementary material (Tables S3 and S4). We found no significant effect modification by the eight risk factors for the association between PM_{10} and depressive symptoms (Fig. 2). The results for the other three pollutants examined were also consistent with the findings for PM_{10} (Table S3). We observed stronger associations of $PM_{2.5}$ and PM_{10} with anxiety symptoms for individuals with a history of smoking ($PM_{2.5}$, p-interaction = 0.021 and PM_{10}, p-interaction = 0.049) (Table S4). In addition, family income was found to be an effect modifier in the association of NO_2 exposure with anxiety symptoms (p-interaction = 0.025), with stronger association in participants with lower income (Table S4).

In the multi-pollutant models (Table 4), the association of $PM_{2.5}$ during the second trimester with maternal depressive symptoms was slightly attenuated (RR = 1.12, 95% CI: 1.01, 1.25), but remained statistically significant after adjusting for NO_2 and O_3. The multi-pollutant model results were similar to the single-pollutant model for O_3. The multi-pollutant model for NO_2 remained positive but was not significant after adjusting for $PM_{2.5}$ and O_3 concentrations. For anxiety, the associations were consistent across single- and multi-pollutant models

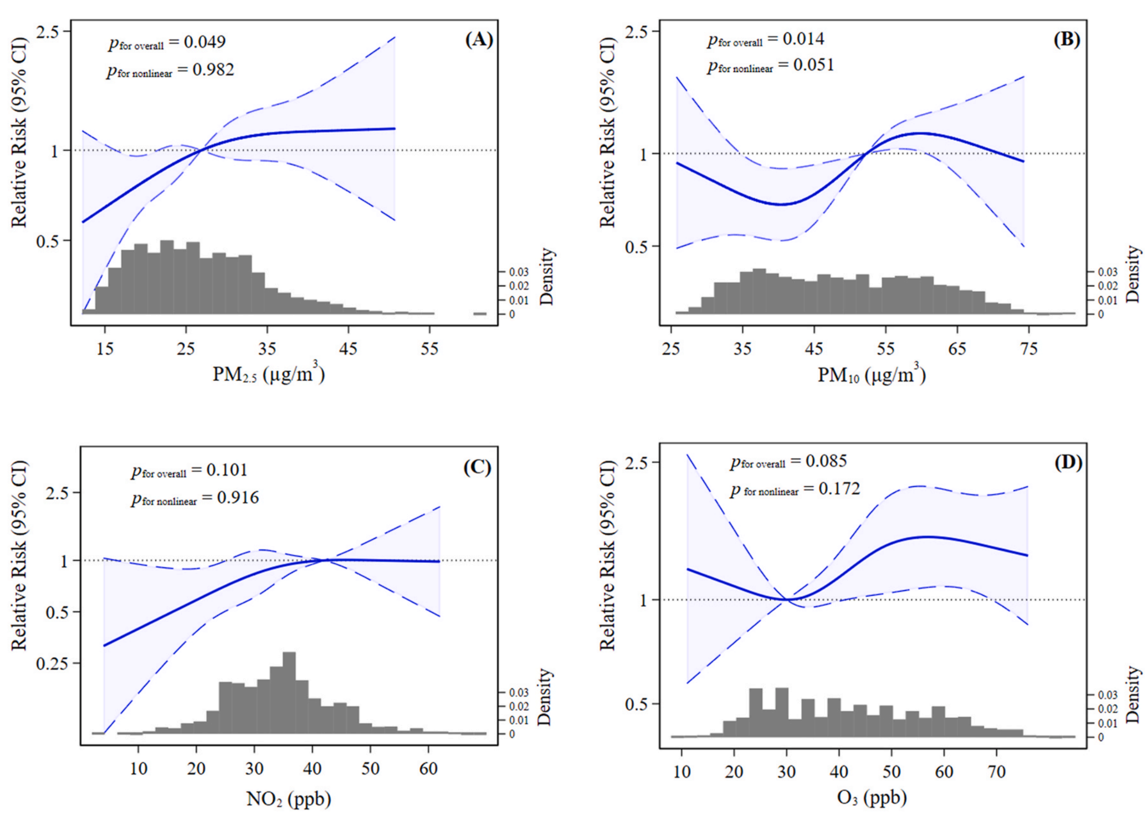

Fig. 1. Nonlinear effects of $PM_{2.5}$ (A), PM_{10} (B), NO_2 (C), and O_3 (D) concentrations on maternal depressive symptoms (CES-D-10 ≥ 12). This dose-response curve was calculated using restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentile of the distribution of $PM_{2.5}$, PM_{10}, and NO_2 concentrations during the second trimester and O_3 concentration during the third trimester. The solid line represents the relative risks, and the dashed lines represent the confidence intervals. The reference $PM_{2.5}$, PM_{10}, NO_2, and O_3 for these plots (with RR fixed as 1.0) was 26.9 μg/m³, 52.3 μg/m³, 42.0 ppb, and 30.0 ppb, respectively. The relative risks were adjusted for maternal age, history of smoking, drinking during pregnancy, pre-pregnancy BMI, maternal education, gestational age, birth order, family income, and pet ownership. The histograms show the distribution of $PM_{2.5}$ (A), PM_{10} (B), NO_2 (C), and O_3 (D) exposures.

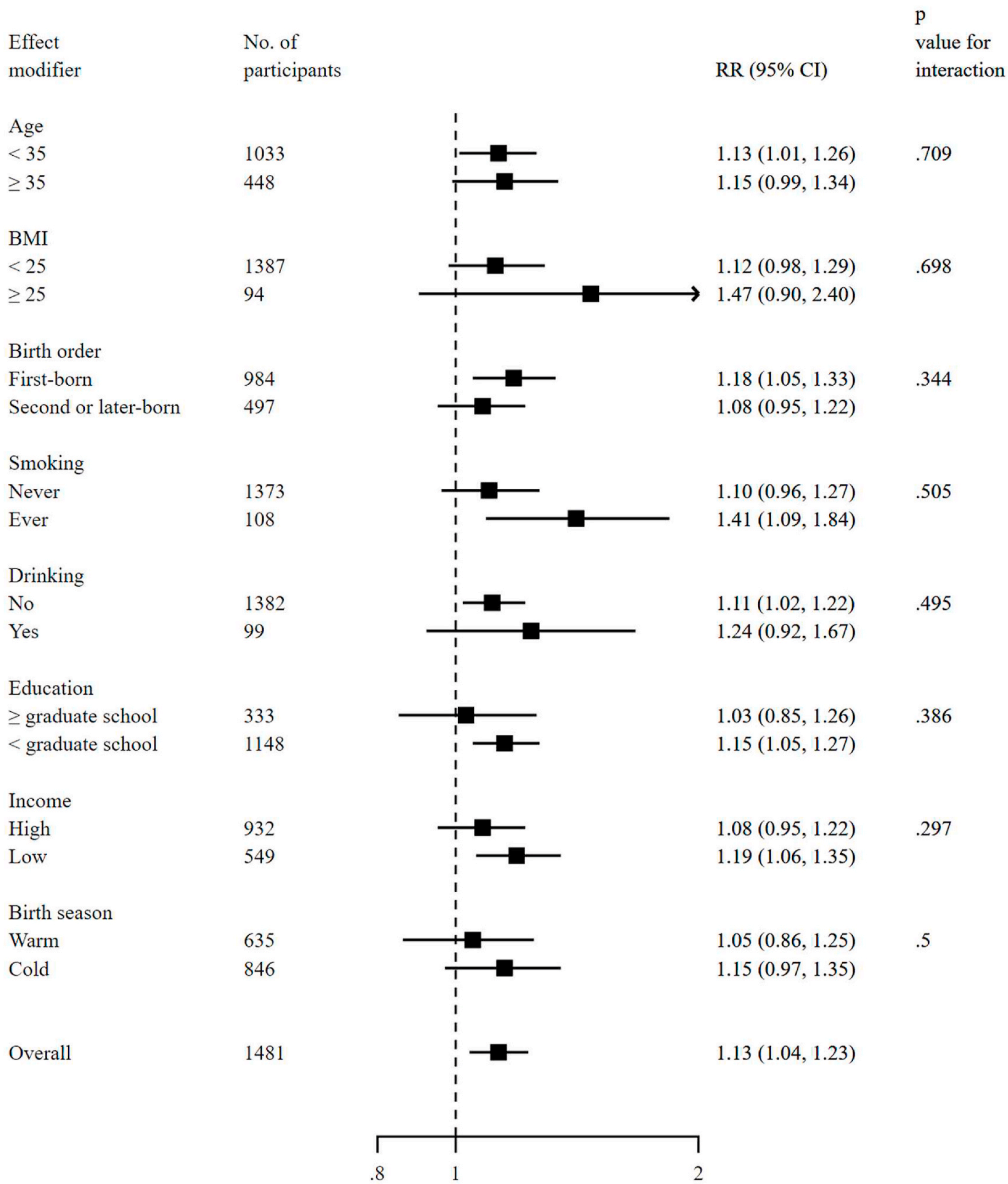

Fig. 2. Relative risks (95% confidence intervals) for maternal depressive symptoms (CES-D-10 ≥ 12) associated with an IQR increase in PM_{10} concentration during the second trimester, stratified by a modifier. Analyses were adjusted for maternal age, history of smoking, drinking during pregnancy, pre-pregnancy BMI, maternal education, gestational age, birth order, family income, and pet ownership. Education was categorized as graduate level or above and less than graduate level, including no education, elementary school, middle school, high school, technical college, and undergraduate school.

(Table S5). When we evaluated the associations of air pollutants with depressive and anxiety symptoms by changing the depression and anxiety cutoff scores, the associations were robust for depression (Table S6). For anxiety, significant associations for $PM_{2.5}$, PM_{10}, and NO_2 during the second trimester were observed at a cutoff ≥39, and a higher cutoff score (≥44) was found to be significant only for $PM_{2.5}$ and O_3 (Table S7). The associations of air pollution with depressive and anxiety symptoms were consistent with regard to direction of association and critical windows of susceptibility to air pollution across binary and continuous outcomes (Table S8). Our findings were also similar when examining the association using the multiple imputation technique (Table S9). We found that positive associations of exposure to $PM_{2.5}$, PM_{10}, and NO_2 during the second trimester and O_3 during the third trimester with depressive and anxiety symptoms were consistently significant in the trimester model (Table S10). This finding suggested that the second and third trimesters are the sensitive windows for maternal exposure to $PM_{2.5}$, PM_{10}, NO_2, and O_3 and development of prenatal depressive and anxiety symptoms. Further, sensitivity analyses to unmeasured confounding showed that our results were robust to unmeasured confounding bias (Table S11). For example, the E-value for the observed association estimates of exposure to PM_{10} during the second trimester and depressive symptoms was 1.51 (1.24 for the lower confidence interval) (Table S11). This indicates that if the observed RR of 1.13 for PM_{10} in the second trimester would be completely due to unmeasured confounder, a 1.51-fold association between unmeasured confounder and depressive symptoms would be required.

Table 4
Multi-pollutant models of associations between exposure to air pollutants during pregnancy and depressive symptoms (CES-D-10 $\geq$ 12) among pregnant women.[a]

Trimester	+ $PM_{2.5}$	+ NO_2	+ O_3	+ $PM_{2.5}$ + NO_2 + O_3
	RR (95% CI)[b]	RR (95% CI)[b]	RR (95% CI)[b]	RR (95% CI)[b]
First				
$PM_{2.5}$	–	1.000.87, 1.15)	1.01 (0.90, 1.15)	1.00 (0.88, 1.14)
NO_2	1.13 (0.99, 1.28) $^{+}$	–	1.05 (0.92, 1.20)	1.05 (0.91, 1.21)
O_3	0.89 (0.82, 0.97) **	0.90 (0.82, 0.99) *	–	0.90 (0.82, 0.99) *
Second				
$PM_{2.5}$	–	1.12 (1.01, 1.25) *	1.15 (1.03, 1.27) **	1.12 (1.01, 1.25) *
NO_2	1.08 (0.96, 1.22)	–	1.14 (1.00, 1.30) *	1.09 (0.95, 1.25)
O_3	0.98 (0.89, 1.09)	1.01 (0.90, 1.13)	–	1.01 (0.90, 1.13)
Third				
$PM_{2.5}$	–	1.02 (0.89, 1.16)	1.01 (0.89, 1.15)	1.01 (0.89, 1.15)
NO_2	0.94 (0.83, 1.06)	–	1.01 (0.88, 1.15)	1.00 (0.87, 1.15)
O_3	1.09 (1.01, 1.18) *	1.09 (1.00, 1.19) *	–	1.09 (1.00, 1.19) *
Pregnancy				
$PM_{2.5}$	–	1.10 (0.95, 1.28)	1.11 (0.96, 1.28)	1.10 (0.95, 1.27)
NO_2	1.07 (0.94, 1.22)	–	1.07 (0.92, 1.25)	1.05 (0.90, 1.23)
O_3	0.93 (0.79, 1.10)	0.95 (0.78, 1.15)	–	0.96 (0.79, 1.16)

$^{+}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$.
[a] Relative risk (RR) estimated from modified Poisson regression models with robust error variance, representing RRs for depressive symptoms as a dichotomous outcome. RR (95% CIs) were estimated for per IQR increase in $PM_{2.5}$, NO_2, and O_3.
[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 in Table 3.

4. Discussion

This prospective cohort study showed significant positive associations between higher concentrations of air pollutants and maternal depressive (CES-D-10 $\geq$ 12) and anxiety (K-STAI $\geq$ 40) symptoms during pregnancy. An IQR increase in exposure to $PM_{2.5}$, PM_{10}, and NO_2 during the second trimester and O_3 during the third trimester were associated with increased risks of depressive symptoms during the third trimester, 15% for $PM_{2.5}$, 13% for PM_{10}, 15% for NO_2, and 9% for O_3. We also found increased risks of anxiety symptoms associated with an IQR increase in exposure to $PM_{2.5}$, PM_{10}, and NO_2 during the second trimester. Exposure to O_3 during the third trimester was significantly associated with a higher cutoff score of anxiety ($\geq$44). Estimates were mostly closer to the null for other trimesters. The findings were robust across different sensitivity analyses. Our findings suggest that exposure to particulate matter, NO_2, and O_3 during mid to late pregnancy may be associated with mental disorders during pregnancy. No evidence of effect modification was found for the associations between four pollutants examined in this study and depressive symptoms. However, we observed enhanced associations for some pollutants with anxiety symptoms among women who were of low income or had history of smoking.

To our knowledge, this is the first study to investigate the effect of air pollution exposure during a particular period of gestation on depressive and anxiety symptoms among pregnant women. To date, only three epidemiologic studies have examined the association of air pollution with mental health risk among pregnant women (Ahlers and Weiss, 2021; Kanner et al., 2021; Lin et al., 2017). In line with our findings for depression, a recent study in the United States evaluated the relationship between maternal depression and air pollution exposure during 3-month preconception, first trimester, and whole pregnancy, and found that an IQR increase in PM_{10}, $PM_{2.5}$, and NO_2 exposure during the whole pregnancy was associated with 11%–21% increased risk of maternal depression, as defined by International Classification of Diseases (ICD) codes (Kanner et al., 2021). However, this study identified maternal depression based on delivery admission medical records and was unable to provide the timing of diagnosis. Furthermore, they were unable to provide symptoms of depression and may have missed a high proportion of subjects who did not realize that they had depressive symptoms (Bell et al., 2011). Based on data from 50 pregnant women, Ahlers and Weiss (2021) found significant positive associations between prenatal exposure to $PM_{2.5}$ and depressive symptoms in the third trimester, which was assessed by the 9-item Patient Health Questionnaire. A study in China examined the association between air pollution and maternal stress during pregnancy, reporting that exposure to $PM_{2.5}$ and NO_2 was associated with higher scores on Global-Severity-Indices, indicating higher levels of emotional stress (Lin et al., 2017). However, they did not find significant associations specifically with depressive symptoms. We found mid-to-late pregnancy as a vulnerable window for the detrimental impact of air pollution on maternal depressive symptoms, which is consistent with a study in the United States that showed association of $PM_{2.5}$ exposure in mid-pregnancy with postpartum depression based on the Edinburgh Postnatal Depression Scale (EPDS) (Sheffield et al., 2018). Likewise, a recent study in Mexico reported that higher $PM_{2.5}$ in pregnancy was associated with increased maternal postpartum depression, as measured by EPDS score (Niedzwiecki et al., 2020).

To the best of our knowledge, no study has examined the association between ambient air pollution, particularly O_3, and anxiety symptoms during pregnancy. Nevertheless, two studies (Lin et al. (2017; Niedzwiecki et al., 2020) partially investigated the association of our interest. Lin et al. (2017) explored the lag effect of PM_{10} and NO_2 on anxiety subscale of the Symptom Checklist-90-Revised Scale during pregnancy and found no significant associations. Similarly, Niedzwiecki et al. (2020) found no significant association of $PM_{2.5}$ exposure during pregnancy with anxiety subscale of EPDS at 6 months postpartum.

Previous studies in non-pregnant populations reported significant positive associations of short or long-term air pollutant concentrations with depression and anxiety (Kioumourtzoglou et al., 2017; Lim et al., 2012; Pun et al., 2017; Zhang et al., 2019; Zhao et al., 2020). A recent prospective study in Korea (n = 123045) found that long-term exposure to PM_{10} is associated with an increased risk of developing depression, assessed using the CES-D scale, during follow-up (mean follow-up 2.5 years) in middle-aged women (Zhang et al., 2019). A panel study including 560 elderly population in Korea reported that increase in short-term PM_{10}, NO_2, and O_3 was significantly associated with depressive symptoms based on the Geriatric Depression scale (Lim et al., 2012). A cohort study among middle-aged and older women in the United States (n = 41844) found an association between higher $PM_{2.5}$ and O_3 exposure in the past year and an increased risk of depression diagnosis and antidepressant use (Kioumourtzoglou et al., 2017). A study in the general population, conducted in Germany, found that increased levels of PM_{10} and O_3 were associated with increased risks of diagnoses of depression and anxiety, the diagnoses were done according to ICD codes (Zhao et al., 2020). A cohort study among elderly subjects in the United States (n = 4008) identified significant positive associations of $PM_{2.5}$ exposure with depressive and anxiety symptoms based on the CES-D scale (11-items) and Hospital Anxiety and Depression Scale, respectively, particularly among individuals with lower socioeconomic status (Pun et al., 2017). Our findings of significant associations between exposure to particulate matter, NO_2, and O_3 during pregnancy and prenatal depressive or anxiety symptoms are supported by these studies conducted in non-pregnant populations. Nevertheless, some studies found no significant association of air pollution with depression and anxiety (Lin et al., 2017; Wang et al., 2014; Zijlema et al., 2016). The inconsistencies in studies may have arisen from the differences in study areas and populations, exposure levels, exposure assessment methods, measured pollutants, study design, use of depression and anxiety scales, sample size, and covariates included in models (Pun et al., 2017).

In our study, we observed similar patterns of risk among pollutants averaged over the second trimester for particulate matter and NO_2, reporting increased risks of depression and anxiety for these pollutants. Average O_3 exposure during the third trimester showed a significant positive association with depressive symptoms. On the other hand, the findings for O_3 averaged over the first trimester are in contrast to the findings for the third trimester. We reported that O_3 exposure during the first trimester was associated with a modest decrease in the risk of depression (11%), which is consistent with the finding that O_3 during pregnancy is associated with a decreased odd of any depression (Kanner et al., 2021). Ozone is a secondary pollutant and is produced by photochemical reactions involving primary pollutants (Cho et al., 2014). This may explain the reason why it is associated with lower risk in some time frames. Ozone was negatively correlated with all other pollutants investigated in our study, most strongly with PM_{10} ($r = -0.71$), which corroborated the finding that O_3 levels are often inversely related to particulate matter (Jia et al., 2017).

Different pathways may explain the biological mechanisms linking air pollution to mental disorders. The pathways include oxidative stress or inflammation (Black et al., 2015; Han et al., 2016), the dysregulation of the endocrine system or metabolic processes (Miller et al., 2016; Thomson et al., 2018), and the disturbance of neurotransmitters (Gonzalez-Pina and Paz, 1997). Air pollutants, such as particulate matter, nitrogen oxides, and O_3 are potent oxidants and they may reach the brain and affect the brain by oxidative stress and neuroinflammation (Fonken et al., 2011; Genc et al., 2012). Mice models demonstrated that exposure to dim light at night and $PM_{2.5}$ may result in neuroinflammation, alter the hippocampal structure, and induce a depressive-like response (Hogan et al., 2015). Chronic inflammation in the brain leads to the formation of reactive oxygen species and oxidative stress, which may disrupt the blood-brain barrier and alter the immune response, and thereby affect normal brain function (Calderon-Garciduenas et al., 2015). Furthermore, oxidative stress may also lead to anxiety-depression-like behaviors in rats (Patki et al., 2013)

The present study has several limitations that warrant consideration. First, exposure to air pollution was estimated using the LUR model based on maternal residential address, and this model did not account for exposure when women were away from their homes (e.g., at places of employment or during transportation), which may have resulted in some degree of exposure misclassification. Researchers have reported that maternal mobility during pregnancy is usually limited and generally restricted to residential areas (Bell and Belanger, 2012). Thus, we believe this shortcoming had little effect on our exposure estimates and was unlikely to have changed our findings. Second, depression and anxiety were measured using self-reports and were assessed only once during pregnancy. Third, although we adjusted for a number of important variables considered to potentially confound the association between air pollution and mental disorders, we cannot dismiss the possibility that other potential confounders such as noise pollution, meteorologic conditions, sleep deficit, history of previous delivery, and maternal occupational exposure may have confounded the identified associations. Furthermore, stressful life events, such as serious parental illness, accidents, or marital dissatisfaction, may have played important roles in the onset of mental disorders among pregnant women (Lancaster et al., 2010; Park et al., 2014). However, we evaluated E-values to see the strength of the relationship a hypothetical unmeasured confounder would have with the air pollution and mental disorders to fully account for our results, suggesting that unmeasured confounders might not have a major influence on the association. 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.

5. Conclusions

In the present study, average concentrations of $PM_{2.5}$, PM_{10}, and NO_2 assigned to the residential address of each pregnant woman were positively associated with maternal depressive and anxiety symptoms. The results for O_3 and depression varied depending on the time of exposure; a significant positive association during third-trimester exposure, while it was negative during first-trimester exposure. Our findings add further evidence to recent data suggesting that air pollution is responsible for neuropsychological dysfunction in pregnant women and further reduction of air pollution might provide an effective avenue for reducing the burden of mental disorders. Future research on the influence of air pollution on maternal depression and anxiety may further the understanding of how individual psychological characteristics affect depressive and anxiety symptoms during pregnancy.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113823.

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