



# Associations between Ambient Air Pollution Exposure and Menstrual Cycle Irregularity in Premenopausal Women

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**Purpose:** This study investigates the associations between various air pollutants and menstrual cycle irregularity.

**Materials and Methods:** Data for premenopausal women were obtained from the Korea National Health and Nutrition Examination Survey (n=4478). We evaluated the associations of moving averages of five air pollutants over 90, 120, 150, 180, and 365 days with short-interval (menstruation occurring at least once every 3 months) and long-interval (menstruation skipped for  $\geq 3$  months) menstrual cycle irregularity using multinomial logistic regression models. The joint effects of air pollution mixtures were explored using the quantile g-computation method.

**Results:** Interquartile range increases in moving averages of nitrogen dioxide (NO<sub>2</sub>) and sulfur dioxide (SO<sub>2</sub>) over 90, 120, 150, and 180 days were associated with short-interval menstrual cycle irregularity [e.g., odds ratio (OR)=1.24, 95% confidence interval (CI): 1.03, 1.50 for NO<sub>2</sub> over 120 days; OR=1.07, 95% CI: 1.03, 1.12 for SO<sub>2</sub> over 150 days]. Each quintile increase in air pollution mixture (NO<sub>2</sub> over 120 days and SO<sub>2</sub> over 150 days) was also associated with short-interval menstrual cycle irregularity (OR=1.07, 95% CI: 1.00, 1.14).

**Conclusion:** Our results indicate associations between various exposure indices of NO<sub>2</sub> and SO<sub>2</sub> and short-interval menstrual cycle irregularity in a representative sample of Korean premenopausal women. This research represents one of the first investigations on this issue; therefore, further longitudinal studies are warranted to confirm these findings.

**Key Words:** Air pollution, menstrual cycle irregularity, premenopausal women, representative sample

## INTRODUCTION

The menstrual cycle is tightly regulated by a cyclic production

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of hormones generated by the hypothalamus, pituitary, and ovaries. Menstrual cycle irregularity, which is common among menstruating women with a reported prevalence of 9.1% to 30.3% across regions,<sup>1-5</sup> has been associated with various reproductive and non-reproductive health outcomes, such as infertility,<sup>6</sup> ovarian cancer,<sup>7</sup> breast cancer,<sup>8</sup> type 2 diabetes,<sup>5</sup> nonalcoholic fatty liver disease,<sup>9</sup> cardiovascular disease,<sup>10</sup> and premature mortality.<sup>4</sup>

Air pollution can disrupt the endocrine system, affecting the normal cyclic changes and functions of sex hormones, such as estrogen and progesterone, which are critical for normal menstruation. For example, air pollution exposure was reportedly associated with higher estrogen levels and the estrogen-to-progesterone ratio during the early luteal phase among urban

women.<sup>11</sup> Laboratory studies have demonstrated that air pollution exhibits both estrogenic and anti-estrogenic activities at the estrogen receptor and anti-progesteronic activity at the progesterone receptor.<sup>12,13</sup>

However, despite the growing body of evidence on the adverse effects of air pollution on women's reproductive health, to our knowledge, only one epidemiological study has investigated air pollution as a risk factor for menstrual cycle irregularity.<sup>14</sup> This previous study, conducted in the U.S., focused solely on total suspended particulates (TSPs) among various air pollutants and found that TSP levels during high school were associated with irregular menstrual cycles and a longer time to cycle regularity in high school and early adulthood.<sup>14</sup> For reproductive health outcomes other than menstrual cycle irregularity, one time-series study conducted in China reported an association between short-term exposure to nitrogen dioxide (NO<sub>2</sub>) and an increase in outpatient visits for menstrual disorders.<sup>15</sup> In another time-series study in China, exposure to air pollutants such as NO<sub>2</sub> and sulfur dioxide (SO<sub>2</sub>) was associated with an increased risk of reproductive system diseases.<sup>16</sup>

To address this knowledge gap, we investigated the associations between various air pollutants and menstrual cycle irregularity using a representative sample of Korean premenopausal women.

## MATERIALS AND METHODS

### Data source and study population

This study utilized data from the Korea National Health and Nutrition Examination Survey (KNHANES), a nationally representative cross-sectional survey conducted by the Korea Disease Control and Prevention Agency (KDCA) since 1998. KNHANES evaluates the health and nutritional status of non-institutionalized Korean civilians and is conducted annually using a multi-stage clustered probability design with a rolling survey sampling model. Since menstrual cycle irregularity was only assessed in the fifth cycle (2010–2012) of the KNHANES, data from these 3 years were analyzed in this study.

Of the 25534 individuals who participated in the fifth cycle of the survey, we excluded male (n=11616); participants who had already experienced menopause (n=5188); those who were currently pregnant (n=128) or breastfeeding (n=149); those with missing or incomplete data on menopausal status (n=190); those using oral contraceptives (n=399) or female hormone pills (n=75) for more than 1 month; those who underwent bilateral oophorectomy (n=9); and those with missing or incomplete data on menstrual cycle irregularity (n=2667); or covariates [household income, n=55; educational level, n=8; marital status, n=1; body mass index (BMI), n=14; and perceived stress, n=557], leading to a final sample size of 4478 (Fig. 1).

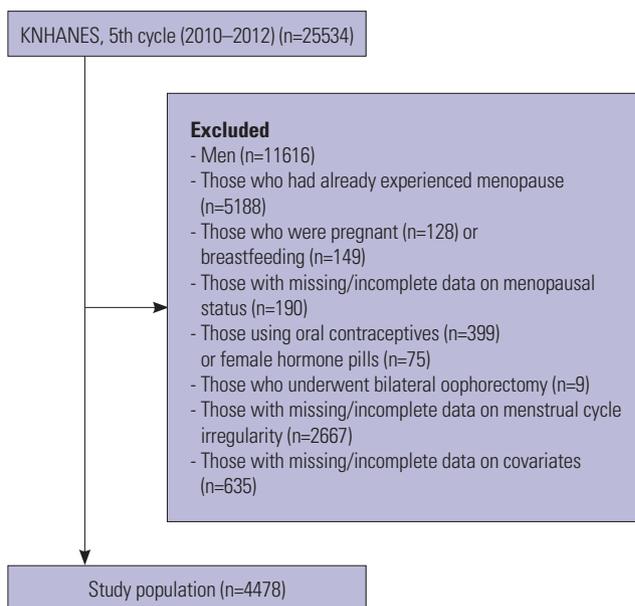
The study protocol was reviewed and approved by the Institutional Review Board of the KDCA (2010-02CON-21-C,

2011-02CON-06-C, and 2012-01EXP-01-2C). All study participants provided written informed consent, and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

### Estimation of air pollution concentrations and individual exposure assignment

The details of air pollution concentration estimation and individual exposure assignment have been described elsewhere.<sup>17,18</sup> Briefly, concentrations of particulate matter with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$  (PM<sub>2.5</sub>), NO<sub>2</sub>, ozone (O<sub>3</sub>), SO<sub>2</sub>, and carbon monoxide (CO) were initially predicted using the U.S. Environmental Protection Agency Models-3 Community Multiscale Air Quality (CMAQ) model (version 4.7.1; the U.S. Environmental Protection Agency, Research Triangle Park, NC, USA). This model integrated information from three-dimensional meteorological datasets and accounted for chemical reactions involving aerosol and gas components to predict air pollution concentrations. The initial prediction results from the CMAQ model were then assimilated using data from air pollution monitoring stations in Korea (n= 323) and China (n=1496) with Pun's interpolation method. Finally, for PM<sub>2.5</sub>, multiple linear regression models were further applied with various input information, including aerosol optical depth data from National Aeronautics and Space Administration (NASA) Terra and Aqua satellites, meteorological factors, and air quality modeling results. The R<sup>2</sup> values of the prediction models in 2015 were as follows: 0.60 for PM<sub>2.5</sub>; 0.71 for NO<sub>2</sub>; 0.72 for O<sub>3</sub>; 0.44 for SO<sub>2</sub>; and 0.68 for CO.

Air pollution exposure for each participant was estimated based on their residential addresses at the time of the survey. Among short-, medium-, and long-term air pollution exposure



**Fig. 1.** Flowchart of the study population selection process and reasons for exclusion. KNHANES, Korea National Health and Nutrition Examination Survey.

indices provided by the KDCA, we selected medium- (moving averages of air pollution levels over 90, 120, 150, and 180 days before survey dates) and long-term indices (moving averages of air pollution levels over 365 days) as exposures of interest.

### Assessment of menstrual cycle irregularity

Menstrual cycle irregularity was classified as regular, short-interval irregularity (average interval between menstrual cycles of <3 months), or long-interval irregularity (average interval between menstrual cycles of  $\geq 3$  months), based on the following questions asked during the survey: “Is your menstrual cycle currently regular? 1) Regular, 2) Irregular” and “If your menstrual cycle is irregular, how irregular is it? 1) Menstruation occurs at least once every 3 months, 2) Menstruation is skipped for 3 months or more.” Although no universally accepted consensus has been established for evaluating menstrual cycle irregularity, this definition of irregularity has been commonly employed in previous studies utilizing KNHANES data.

### Determination and definition of covariates

The covariate set for the analytical models was determined a priori through a directed acyclic graph (Supplementary Fig. 1, only online) constructed based on previous literature.<sup>19,20</sup> We adjusted for age (year) and age-squared terms in our analyses to consider a possible non-linear association. We further adjusted for equalized household income (the entire household's income divided by the square root of the number of household members) categorized into quartiles, educational level ( $\leq$  elementary school, middle school, high school, or  $\geq$  college), and marital status (married vs. unmarried) to account for various aspects of socioeconomic status. Tobacco smoking (current smoker, ever smoker, or never smoker), total number of deliveries, perceived stress (usually feeling a lot of stress or not usually feeling a lot of stress), and BMI ( $\text{kg}/\text{m}^2$ ; <18.5, 18.5–22.9, 23.0–24.9, or  $\geq 25.0$ ), which are reportedly related to menstrual cycle irregularity,<sup>19,20</sup> were also adjusted for in the analyses. BMI, defined as body weight (kg) divided by height (m) squared, was calculated using weight and height measurements taken with light clothing and barefoot by trained staff. Information on covariates other than BMI was obtained via interviews with a structured questionnaire during the survey.

### Strategies and methods for statistical analysis

Since no appreciable deviations from linearity were observed for any pairs of exposure indices and menstrual cycle irregularities in analyses comparing logistic regression models with restricted cubic spline terms to those with linear terms (all  $p$ -values for nonlinearity  $> 0.05$  (Supplementary Table 1 and Supplementary Figs. 2 and 3, only online), we used continuous air pollution exposure indices, assuming linear associations, in further analyses.

The associations of moving averages of  $\text{PM}_{2.5}$ ,  $\text{NO}_2$ ,  $\text{O}_3$ ,  $\text{SO}_2$ , and CO levels over 90, 120, 150, 180, and 365 days before sur-

vey dates with short-interval and long-interval menstrual cycle irregularity were explored using multinomial logistic regression models with appropriate stratification, cluster, and weight variables (the SURVEYLOGISTIC procedure of the SAS), following the analysis guideline by the KDCA.

Moving averages of  $\text{NO}_2$  and  $\text{SO}_2$  were found to be associated with irregular menstrual cycles over various periods in the models mentioned above; therefore, we selected a single exposure index with the lowest Akaike information criterion (AIC) value for  $\text{NO}_2$  and  $\text{SO}_2$ , respectively (i.e., moving average of  $\text{NO}_2$  over 120 days,  $\text{AIC}=9201056$ ; moving average of  $\text{SO}_2$  over 150 days,  $\text{AIC}=9200383$ ) (Supplementary Table 2, only online), and used them for further stratified analyses and air pollution mixture analyses. Although we could not find direct biological evidence supporting the selection of 90-day or 150-day exposure windows, we assume that using an exposure index over a time span that generally corresponds to the outcome definition—based on average cycle intervals of <3 months and  $\geq 3$  months—may yield a more direct and stronger association with the outcome.

We performed a series of stratified analyses by age (<30 years, 30–39 years, and  $\geq 40$  years), BMI (<23.0 and  $\geq 23.0$ ), and stress (usually feeling a lot of stress and not usually feeling a lot of stress). Age-stratified analyses were conducted due to the continual changes in sex hormones during women's lifespans and increased susceptibility to air pollution concerning various health outcomes at older ages. Analyses stratified by BMI were performed because adipose tissue can affect sex hormone (estrogen) levels through various mechanisms (e.g., conversion of androgens to estrogen by aromatization), possibly modifying the effects of air pollution. We conducted analyses stratified by stress levels based on previous research indicating that elevated cortisol levels resulting from the activated hypothalamus-pituitary-adrenal axis under stress may alter sex hormone levels and disrupt menstrual cycles.<sup>21</sup>

The joint effects of moving averages of  $\text{NO}_2$  over 120 days and  $\text{SO}_2$  over 150 days were estimated separately for short-interval and long-interval menstrual cycle irregularity as an outcome, using logistic regression models combined with the quantile g-computation method. Since we constructed analytical models with exposures categorized as quintiles, association estimates can be interpreted as increased risks of short-interval or long-interval menstrual cycle irregularity per quintile increase in the levels of all considered air pollutants in the mixture. Confidence intervals (CIs) were calculated using 500 bootstrap iterations for estimation (the Qgcomp package in R).

As sensitivity analyses, we first repeated analyses not adjusted for BMI because BMI may act as a mediator between air pollution exposure and menstrual cycle irregularity.<sup>19,22</sup> Second, to control for the potential impact of seasonality on the results, we performed analyses further adjusted for the moving average of ambient temperatures over the same period as air pollution, using it as a proxy for seasonality due to the unavailability of survey date information. Data regarding daily ambient temper-

atures at each study participant’s residential address were constructed using the same models used for estimating air pollution exposure. Third, we explored the joint effects of exposures to moving averages of NO<sub>2</sub> and SO<sub>2</sub> over 90, 120, 150, and 180 days, respectively, using the same analytical approach to the main analyses. Fourth, instead of using the complete case analysis approach adopted in the main analyses, we performed multiple imputations for missing values of covariates (household income, educational level, BMI, and stress), creating 20 imputed data sets and combining the results according to Rubin’s rules (the MI and MIANALYZE procedures of the SAS). Fifth, we repeated the association analyses after excluding one outlier aged 65 years who was included in the regular menstrual cycle group, given that it is unlikely for a woman of this age to exhibit regular menstrual cycles. Sixth, as adjusting for household income, educational level, and marital status is sufficient to control for potential confounding according to the directed acyclic graph,

we conducted analyses adjusting only for these variables.

We reported association findings based on interquartile range increases for moving averages of air pollutant concentrations over 365 days (4.7 µg/m<sup>3</sup> for PM<sub>2.5</sub>; 16.1 ppb for NO<sub>2</sub>; 4.7 ppb for O<sub>3</sub>; 1.1 ppb for SO<sub>2</sub>; and 133.3 ppb for CO). All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.3.2 (R Project, Institute for Statistics and Mathematics, Vienna, Austria).

## RESULTS

The mean age of the study participants was 35.2 years. A total of 34.7% of participants reported that their household income was in the fourth quartile (Q4, high), whereas 7.0% reported theirs to be in the first quartile (Q1, low). In addition, 44.8% indicated that their highest educational attainment was college or above.

**Table 1.** Characteristics of Study Participants according to Menstrual Cycle Regularity Status

Variables	Total (n=4478)	Irregular menstrual cycle		
		No (n=3868)	Short-interval* (n=511)	Long-interval <sup>†</sup> (n=99)
Age (yr)	35.2±9.9	35.2±9.4	34.0±11.6	39.3±13.8
Range (min–max)	12–56 <sup>‡</sup>	12–56	12–56	12–56
Household income <sup>§</sup>				
Q1 (low)	311 (7.0)	266 (6.9)	37 (7.2)	8 (8.1)
Q2	1117 (24.9)	975 (25.2)	118 (23.1)	24 (24.2)
Q3	1496 (33.4)	1305 (33.7)	162 (31.7)	29 (29.3)
Q4 (high)	1554 (34.7)	1322 (34.2)	194 (38.0)	38 (38.4)
Educational level				
≤Elementary school	233 (5.2)	181 (4.7)	37 (7.2)	15 (15.2)
Middle school	294 (6.6)	225 (5.8)	52 (10.2)	17 (17.2)
High school	1946 (43.5)	1663 (43.0)	238 (46.6)	45 (45.5)
≥College	2005 (44.8)	1799 (46.5)	184 (36.0)	22 (22.2)
Marital status				
Yes	3126 (69.8)	2745 (71.0)	312 (61.1)	69 (69.7)
No	1352 (30.2)	1123 (29.0)	199 (38.9)	30 (30.3)
Tobacco smoking				
Current smoker	279 (6.2)	228 (5.9)	49 (9.6)	2 (2.0)
Ever smoker	289 (6.5)	242 (6.3)	42 (8.2)	5 (5.1)
Never smoker	3910 (87.3)	3398 (87.9)	420 (82.2)	92 (92.9)
Total number of deliveries	1.3±1.1	1.3±1.1	1.1±1.1	1.4±1.1
Usually feeling a lot of stress				
Yes	1408 (31.4)	1173 (30.3)	199 (38.9)	36 (36.4)
No	3070 (68.6)	2695 (69.7)	312 (61.1)	63 (63.6)
Body mass index (kg/m <sup>2</sup> )				
<18.5	442 (9.9)	385 (10.0)	47 (9.2)	10 (10.1)
18.5–22.9	2393 (53.4)	2105 (54.4)	249 (48.7)	39 (39.4)
23.0–24.9	751 (16.8)	647 (16.7)	93 (18.2)	11 (11.1)
≥25.0	892 (19.9)	731 (18.9)	122 (23.9)	39 (39.4)

Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

Values are presented as the mean±standard deviation for continuous variables and n (%) for categorical variables.

\*Irregular menstrual cycle with menstruation occurring at least once every 3 months; <sup>†</sup>Irregular menstrual cycle with menstruation skipped for 3 months or more;

<sup>‡</sup>One participant aged 65 years was excluded; <sup>§</sup>Household income was divided by the square root of the number of household members.

Most study participants were married (69.8%) and never smokers (87.3%). Approximately one-third (31.4%) of participants reported feeling stress. The mean BMI was 22.4 kg/m<sup>2</sup>, with the proportion of BMI ≥25.0 kg/m<sup>2</sup> being 19.9% (Table 1 and Supplementary Table 3, only online). Compared to the participants excluded from this study, the included participants were more likely to be older, have a higher household income and educational level, be married, be never smokers, have a higher total number of deliveries, and have a higher BMI (Supplementary Table 4, only online).

The mean ± standard deviation of moving averages of PM<sub>2.5</sub>, NO<sub>2</sub>, O<sub>3</sub>, SO<sub>2</sub>, and CO over 365 days before survey dates was 25.6±3.5 µg/m<sup>3</sup>, 25.9±9.1 ppb, 23.2±3.3 ppb, 5.0±1.7 ppb, and 489.4±86.4 ppb, respectively (Supplementary Table 5, only online). Moving averages of PM<sub>2.5</sub>, NO<sub>2</sub>, O<sub>3</sub>, SO<sub>2</sub>, and CO over 365 days were correlated with each other (all *p*-values for correlation <0.0001), with Pearson correlation coefficient  $\rho$  ranging between -0.87 (correlation between NO<sub>2</sub> and O<sub>3</sub>) and 0.81 (correlation between NO<sub>2</sub> and CO) (Supplementary Table 6, only online).

Interquartile range (16.1 ppb) increases in moving averages of NO<sub>2</sub> over 90, 120, 150, and 180 days were associated with a higher risk of short-interval menstrual cycle irregularity [odds ratio (OR)=1.24, 95% CI: 1.03, 1.49 for 90 days; OR=1.24, 95% CI: 1.03, 1.50 for 120 days; OR=1.24, 95% CI: 1.02, 1.50 for 150 days; and OR=1.23, 95% CI: 1.01, 1.49 for 180 days]. Interquartile range (1.1 ppb) increases in moving averages of SO<sub>2</sub> over 90, 120, 150, and 180 days were also associated with a higher risk of short-interval menstrual cycle irregularity (OR=1.07, 95% CI: 1.02, 1.11 for 90 days; OR=1.07, 95% CI: 1.03, 1.12 for 120 days; OR=1.07, 95% CI: 1.03, 1.12 for 150 days; and OR=1.07, 95% CI: 1.02, 1.12 for 180 days). However, no evidence of associations was found between exposures to PM<sub>2.5</sub>, O<sub>3</sub>, and CO and short-interval menstrual cycle irregularity and between all air pollution exposure indices and long-interval menstrual cycle irregularity (Table 2).

In the age-stratified analyses, the associations between moving averages of NO<sub>2</sub> over 120 days and SO<sub>2</sub> over 150 days and short-interval menstrual cycle irregularity were more pronounced in women aged ≥40 years than in those aged <30 years or 30–39 years. We found no heterogeneity in the associations of NO<sub>2</sub> and SO<sub>2</sub> with long-interval menstrual cycle irregularity according to age or in the associations of NO<sub>2</sub> and SO<sub>2</sub> with short-interval and long-interval menstrual cycle irregularity according to BMI and stress levels (Fig. 2 and Supplementary Table 7, only online). However, the results from the age-stratified analyses for long-interval menstrual cycle irregularity should be interpreted with caution due to the small sample size within the exposure–outcome strata (Supplementary Table 7, only online).

A quintile increase in the air pollution mixture (moving averages of NO<sub>2</sub> over 120 days and SO<sub>2</sub> over 150 days) was associated with short-interval menstrual cycle irregularity (OR=1.07,

**Table 2.** Weighted Associations between Air Pollution Exposure Indices and Short-Interval and Long-Interval Menstrual Cycle Irregularity in a Representative Sample of Premenopausal Women in Korea

Moving averages of air pollution levels	Short-interval menstrual cycle irregularity*		Long-interval menstrual cycle irregularity <sup>†</sup>	
	OR	95% CI	OR	95% CI
PM <sub>2.5</sub>				
90 days	1.03	0.93, 1.14	0.85	0.68, 1.06
120 days	1.04	0.93, 1.17	0.83	0.65, 1.06
150 days	1.04	0.92, 1.17	0.83	0.65, 1.07
180 days	1.02	0.90, 1.16	0.82	0.62, 1.07
365 days	0.92	0.78, 1.08	0.72	0.49, 1.06
NO <sub>2</sub>				
90 days	1.24	1.03, 1.49	0.72	0.48, 1.07
120 days	1.24	1.03, 1.50	0.71	0.47, 1.07
150 days	1.24	1.02, 1.50	0.71	0.47, 1.07
180 days	1.23	1.01, 1.49	0.70	0.47, 1.06
365 days	1.13	0.92, 1.40	0.68	0.45, 1.02
O <sub>3</sub>				
90 days	0.97	0.89, 1.05	1.10	0.94, 1.29
120 days	0.94	0.86, 1.03	1.10	0.93, 1.29
150 days	0.92	0.84, 1.01	1.12	0.94, 1.34
180 days	0.90	0.81, 0.99	1.15	0.94, 1.40
365 days	0.90	0.77, 1.05	1.16	0.87, 1.56
SO <sub>2</sub>				
90 days	1.07	1.02, 1.11	0.91	0.79, 1.05
120 days	1.07	1.03, 1.12	0.90	0.78, 1.04
150 days	1.07	1.03, 1.12	0.90	0.78, 1.04
180 days	1.07	1.03, 1.12	0.90	0.78, 1.04
365 days	1.04	0.99, 1.10	0.88	0.74, 1.05
CO				
90 days	1.07	0.96, 1.20	0.85	0.67, 1.07
120 days	1.10	0.98, 1.24	0.83	0.65, 1.06
150 days	1.12	0.99, 1.27	0.83	0.64, 1.07
180 days	1.12	0.98, 1.28	0.82	0.63, 1.07
365 days	0.99	0.82, 1.20	0.74	0.54, 1.02

OR, odds ratio; CI, confidence interval.

Results were estimated using multinomial logistic regression models adjusted for age, age squared, household income, educational level, marital status, tobacco smoking, total number of deliveries, stress, and body mass index, with appropriate stratification, clustering, and weighting. Association estimates are presented per interquartile range increase for moving averages of air pollutants over 365 days (4.7 µg/m<sup>3</sup> for PM<sub>2.5</sub>; 16.1 ppb for NO<sub>2</sub>; 4.7 ppb for O<sub>3</sub>; 1.1 ppb for SO<sub>2</sub>; and 133.3 ppb for CO).

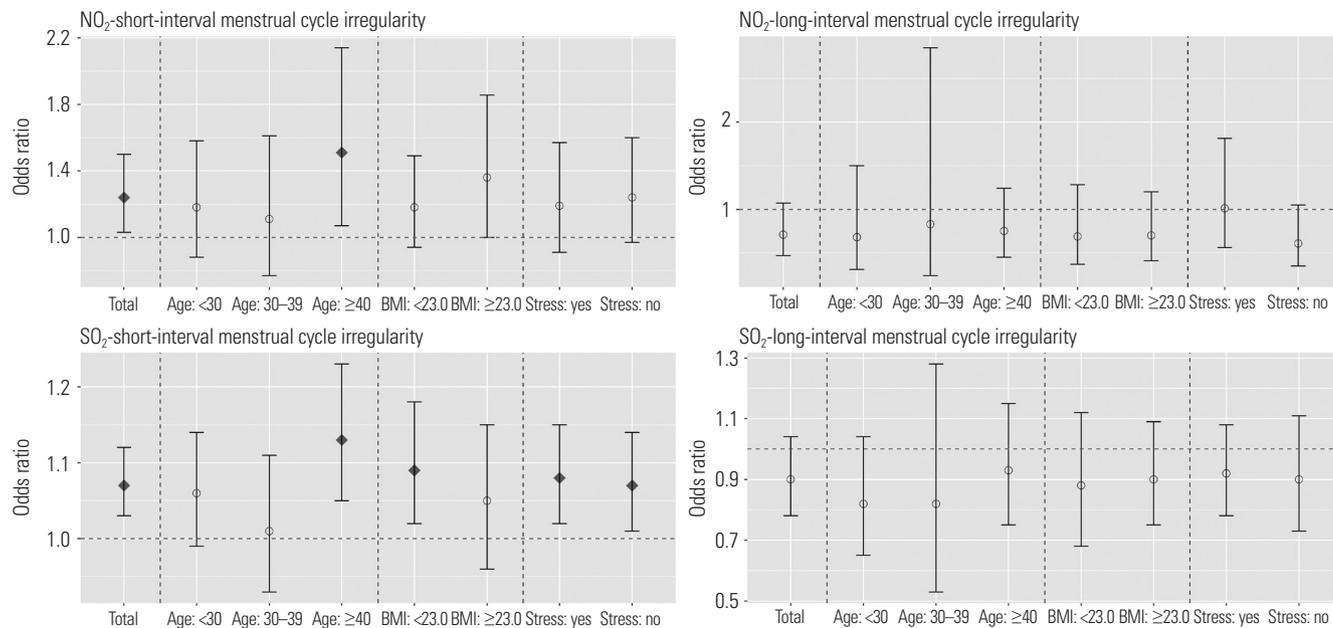
\*Irregular menstrual cycle with menstruation occurring at least once every 3 months; <sup>†</sup>Irregular menstrual cycle with menstruation skipped for 3 months or more.

95% CI: 1.00, 1.14) but not with long-interval menstrual cycle irregularity (OR=0.90, 95% CI: 0.76, 1.07) (Fig. 3 and Supplementary Table 8, only online).

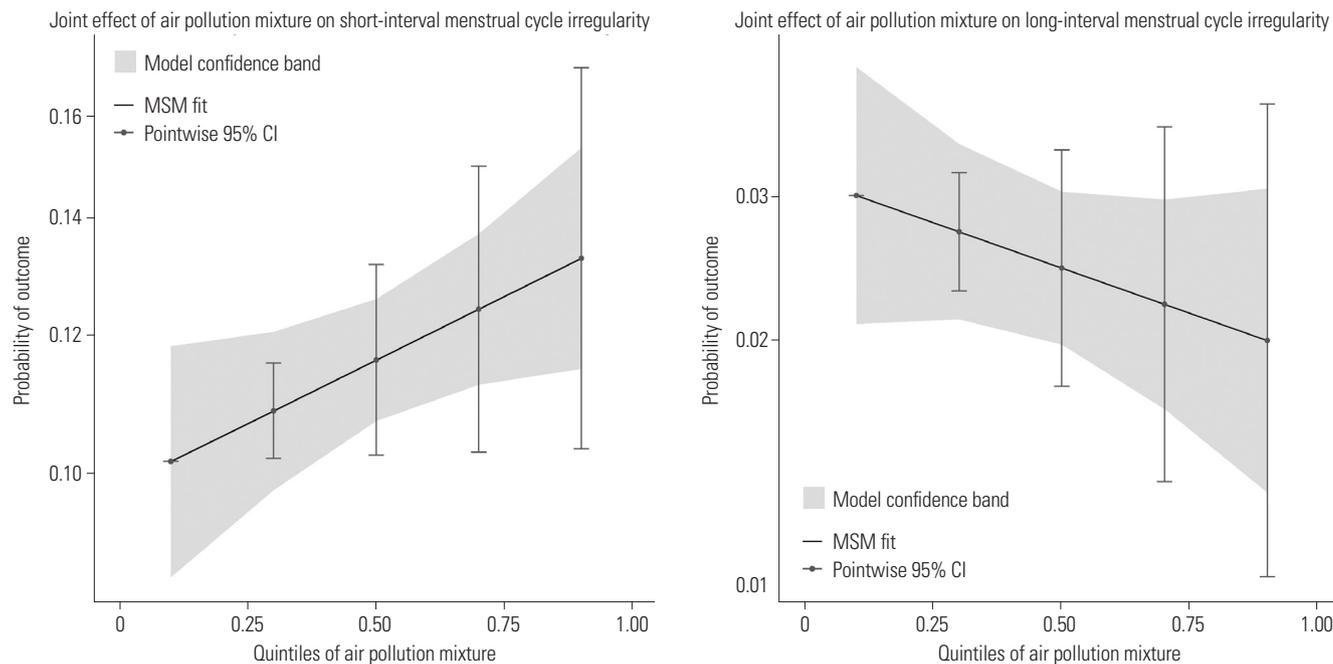
The sensitivity analyses yielded consistent results. First, the analysis without adjustment for BMI exhibited almost the same results (Supplementary Table 9, only online). Second, in the analyses further adjusted for ambient temperature, the associa-

tions between NO<sub>2</sub> and short-interval menstrual cycle irregularity were slightly attenuated with wider CIs. However, the associations between SO<sub>2</sub> and short-interval irregularity remained similar (Supplementary Table 10, only online). Third, air pollu-

tion mixtures, consisting of moving averages of NO<sub>2</sub> and SO<sub>2</sub> over 90, 120, and 150 days, were associated with an increased risk of short-interval menstrual cycle irregularity, although the CIs were slightly wider for moving averages of NO<sub>2</sub> and SO<sub>2</sub> over



**Fig. 2.** Weighted associations of moving averages of NO<sub>2</sub> over 120 days and SO<sub>2</sub> over 150 days with short-interval and long-interval menstrual cycle irregularity, stratified by age, BMI, and perceived stress. Red diamonds and hollow black circles represent point estimates of significant and insignificant associations, respectively. Error bars represent 95% confidence intervals. Results were estimated using multinomial logistic regression models adjusted for age, age-squared, household income, educational level, marital status, tobacco smoking, total number of deliveries, stress, and BMI, with appropriate stratification, cluster, and weight variables. Association estimates are presented per interquartile range increase for moving averages of air pollutants over 365 days (16.1 ppb for NO<sub>2</sub> and 1.1 ppb for SO<sub>2</sub>). BMI, body mass index.



**Fig. 3.** Joint effects of moving averages of NO<sub>2</sub> over 120 days and SO<sub>2</sub> over 150 days on short-interval and long-interval menstrual cycle irregularity, estimated using quantile g-computation models. Results were estimated using quantile g-computation models adjusted for age, age-squared, household income, educational level, marital status, tobacco smoking, total number of deliveries, stress, and body mass index, with exposures categorized into quintiles. MSM, Marginal Structural Model; CI, confidence interval.

180 days (Supplementary Table 8, only online). The results were robust after employing multiple imputations to handle missing values of covariates (Supplementary Table 11, only online). The results remained robust with all association estimates unchanged after excluding one outlier aged 65 years (data not shown). Finally, consistent results were observed in the analyses adjusted only for household income, educational level, and marital status (Supplementary Table 12, only online).

## DISCUSSION

Moving averages of NO<sub>2</sub> and SO<sub>2</sub> over 90, 120, 150, and 180 days were associated with an increased risk of short-interval menstrual cycle irregularity (irregular menstrual cycles with an average interval of < 3 months) in a representative sample of Korean premenopausal women. Co-exposures to NO<sub>2</sub> and SO<sub>2</sub> were also associated with a higher risk of short-interval menstrual cycle irregularity.

In a study using the Nurses' Health Study II data—which, to our knowledge, is the only previous study exploring the association between air pollution and menstrual cycle irregularity—a 45 µg/m<sup>3</sup> increase in average high school TSP levels was associated with moderate (OR=1.08, 95% CI: 1.03, 1.14) and persistent menstrual cycle irregularity (OR=1.08, 95% CI: 1.02, 1.15) in high school and early adulthood.<sup>14</sup> Although slight differences exist in the study populations (U.S. adolescent and young adult girls vs. Korean premenopausal women) and exposures (TSP vs. various criteria air pollutants), the results of the prior study generally align with those of our study.

In the present study, gaseous air pollutants, such as NO<sub>2</sub> and SO<sub>2</sub>, were associated with menstrual cycle irregularity, whereas PM<sub>2.5</sub> was not. The reason for this distinctive association across different pollutants remains unclear. However, it is notable that nationwide monitoring of PM<sub>2.5</sub> only began in 2015, and the estimated PM<sub>2.5</sub> concentrations for the period prior to 2015 may have involved greater exposure misclassification. Therefore, the lack of association between PM<sub>2.5</sub> and menstrual cycle irregularity in the present study, which used data from 2010 to 2012, may be attributed—at least in part—to this exposure misclassification and should be interpreted with caution.

In contrast to the scarcity of evidence on the association between ambient air pollution and irregular menstrual cycles, several studies have reported that environmental tobacco smoke, one of the major sources of indoor air pollution, may disturb the endocrine system, affect hormonal changes related to menstrual cycles, and cause menstrual dysfunction and cycle irregularity,<sup>23-26</sup> which we consider to provide additional support for the findings of the present study.

Only one epidemiological study, to our knowledge, has assessed the association between air pollution and menstrual cycle irregularity.<sup>14</sup> However, air pollution has been associated

with various women's reproductive health outcomes other than menstrual cycle irregularity, including the deterioration of ovarian function,<sup>27</sup> alterations in menstrual cycle duration,<sup>28,29</sup> diminished ovarian reserve,<sup>30</sup> and low fecundability.<sup>31</sup> Specifically, a recent multinational study using a mobile health app reported that long-term exposure to PM<sub>2.5</sub> was associated with abnormally long (>38 days) or short (<24 days) menstrual cycle lengths.<sup>32</sup> Similarly, exposure to NO<sub>2</sub> has been linked to a more prolonged follicular phase of menstrual cycles, decreased fecundability, and increased miscarriage rates in the general female population, as well as a lower live birth rate after in vitro fertilization procedures.<sup>27,28</sup> Likewise, exposure to SO<sub>2</sub> has been associated with decreased ovarian reserve, reduced conception rates, and elevated miscarriage rates in the general female population.<sup>27,30</sup>

The effects of air pollution were only observed for short-interval menstrual cycle irregularity (average interval between menstrual cycles of <3 months), not for long-interval irregularity (average interval between menstrual cycles of ≥3 months). The reason for this finding remains to be determined. However, long-interval menstrual cycle irregularity or secondary amenorrhea (the absence of regular menstrual cycles for 3 months or the absence of irregular menstrual cycles for 6 months) may be predominantly induced by various underlying conditions affecting the hypothalamic-pituitary-ovarian axis, including polycystic ovary syndrome (PCOS), primary ovarian insufficiency, hyperprolactinemia, and hypothyroidism,<sup>33</sup> rather than by air pollution exposure at current levels (which is similar to or slightly higher than those in the U.S. but substantially lower than those in China).

Women undergoing a late reproductive or perimenopausal transition period may experience diminished ovarian function and reduced damage repair capacity. The decreased functional reserves of the ovaries and insufficient damage repair capacity might be responsible for the stronger associations of NO<sub>2</sub> and SO<sub>2</sub> with short-interval menstrual cycle irregularity among participants aged ≥40 years than those aged <40 years in this study. Although the impact of differences in the overall characteristics between individuals included in the analysis and those excluded is not entirely clear, the fact that the included participants were generally older (35.2 years vs. 23.1 years) suggests that this age distribution may have led to an overestimation of the association in the present study compared to what might be observed in the full population comprising both included and excluded individuals. Meanwhile, in a previous cohort study conducted in the U.S., increased particulate matter exposure and living near a major road at age 40 years were associated with earlier menopause.<sup>34</sup> Although irregular menstrual cycles can serve as an early indicator of natural menopause, particularly among women aged ≥40 years, we believe that our findings support the association between air pollution and menstrual cycle irregularity. This is because we excluded women who had reached menopause from the study popula-

tion and explicitly defined the outcome using a clearly worded question that directly assessed menstrual cycle irregularity.

Given the observed correlations among air pollutants in this study, we postulate that the results from air pollution mixture analyses may more accurately reflect the adverse effects of air pollution than those from conventional analyses that considered only a single air pollutant. Furthermore, since most policies and interventions aimed at mitigating air pollution exposure affect the levels of multiple air pollutants rather than individual ones, the results from these air pollution mixture analyses can be used to predict the impact of air pollution regulation policies on women's reproductive health.

Inhaled toxicants and their metabolites can cross the lung-blood barrier, reach the female reproductive organs (e.g., the ovaries) through systemic circulation, and disturb the normal functioning of these organs.<sup>35-38</sup> Air pollution can disrupt sex hormone profiles by damaging ovarian tissue through oxidative stress and inflammation and/or by exposing ovarian tissue to various chemicals with endocrine-disrupting properties in the air pollution mixture.<sup>39-41</sup> Disturbance in the cyclic rhythm of sex hormones induced by air pollution may result in irregular menstrual cycles.<sup>42</sup>

Several limitations should be noted in the present study. First, due to its cross-sectional design, the associations observed in this study should not be interpreted as indicating causal relationships. Second, air pollution levels were calculated only based on residential addresses, and daily commutes to the workplace or school were not considered in the air pollution estimation process, resulting in potential exposure misclassification. Third, since no established diagnostic criteria and accepted tools for menstrual cycle irregularity exist, the health outcomes were ascertained only based on participants' self-reports. However, a previous study comparing the results of a single-item question on menstrual regularity and those of ultrasound ovulation monitoring found that the results were relatively consistent.<sup>43</sup> Because outcome misclassification in this study is likely nondifferential with respect to air pollution levels, it may lead to associations being biased towards the null hypothesis. Fourth, information on PCOS, a common medical condition closely related to menstrual cycle irregularity, was not available. However, although irregular menstrual cycles are sometimes used as a proxy for PCOS, several studies have linked aberrant menstruation itself with adverse health outcomes, such as type 2 diabetes and nonalcoholic fatty liver disease, independent of PCOS.<sup>9,44</sup>

However, the current study also possesses several strengths. First, it provides one of the first evidence regarding the association between air pollution exposure and menstrual cycle irregularity, which has important public health implications. Second, this study used high-quality national data representing Korean premenopausal women, which enhances the validity of the results and minimizes selection bias. Third, unlike the prior study that examined only average TSP levels during high school,<sup>14</sup> the

present study considered various air pollutants estimated across multiple time periods.

In conclusion, exposures to NO<sub>2</sub> and SO<sub>2</sub> were associated with a higher risk of short-interval menstrual cycle irregularity. Given that the menstrual cycle is a sensitive indicator of a woman's health and that its irregularity is associated with various reproductive and non-reproductive disorders, these findings have significant implications for reducing air pollution exposure to promote women's health. This study represents one of the earliest investigations on this issue; therefore, additional studies, especially those with a longitudinal design and more refined outcome ascertainment methods, should be conducted across diverse populations experiencing varying levels of air pollution.

## DATA AVAILABILITY STATEMENT

Data will be made available upon request.

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## AUTHOR CONTRIBUTIONS

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