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Association between annual concentration of air pollutants and incidence of metabolic syndrome among Korean adults: Korean Genome and Epidemiology Study (KoGES)

Hanuel Shin[1,2], Minkyo Song[3] and Sanghyuk Bae[4*]

Abstract

Background Air pollution is a global public health concern and incidence rates of metabolic syndrome (MetS) are increasing. To evaluate the effect of long-term air pollution exposure, we examined the association between long-term exposure to ambient air pollution and the incidences of MetS among Korean adults.

Methods We used data from the Korean Genome and Epidemiology Study's Cardiovascular Disease Association Study, a population-based cohort consisting of community-dwelling Korean adults between 2005 and 2011, who were followed up with until 2016 ($n = 7,428$). Air pollution exposure was estimated using the Congestion Mitigation and Air Quality model based on the participants' addresses. The participants had a physical examination at every visit during follow-up, and MetS was defined based on the National Institute of Health's National Cholesterol Education Program-Adult Treatment Panel III. We used Cox proportional hazard model to analyze the association between long-term air pollution exposure and incidences of MetS per interquartile range (IQR) increment of the annual concentration after adjusting for potential confounders using single and two-pollutant analysis.

Results The hazard ratios (HR) of MetS per IQR increment in $PM_{2.5}$, SO_2, NO_2, and CO were 1.19 (95% CI: 1.12-1.27), 1.57 (95% CI: 1.47-1.68), 1.11 (95% CI: 1.03-1.20), and 1.63 (95% CI: 1.48-1.78), respectively. The incidences of MetS components, which are high blood pressure, elevated fasting glucose, abdominal obesity, high fasting triglyceride (TG), and low fasting high-density lipoprotein (HDL-C), were significantly associated with an IQR increment especially in SO_2 and CO. In subgroup analysis, males had higher risk of MetS than females. The HR was the highest in the 60–69 year old age group for all pollutants.
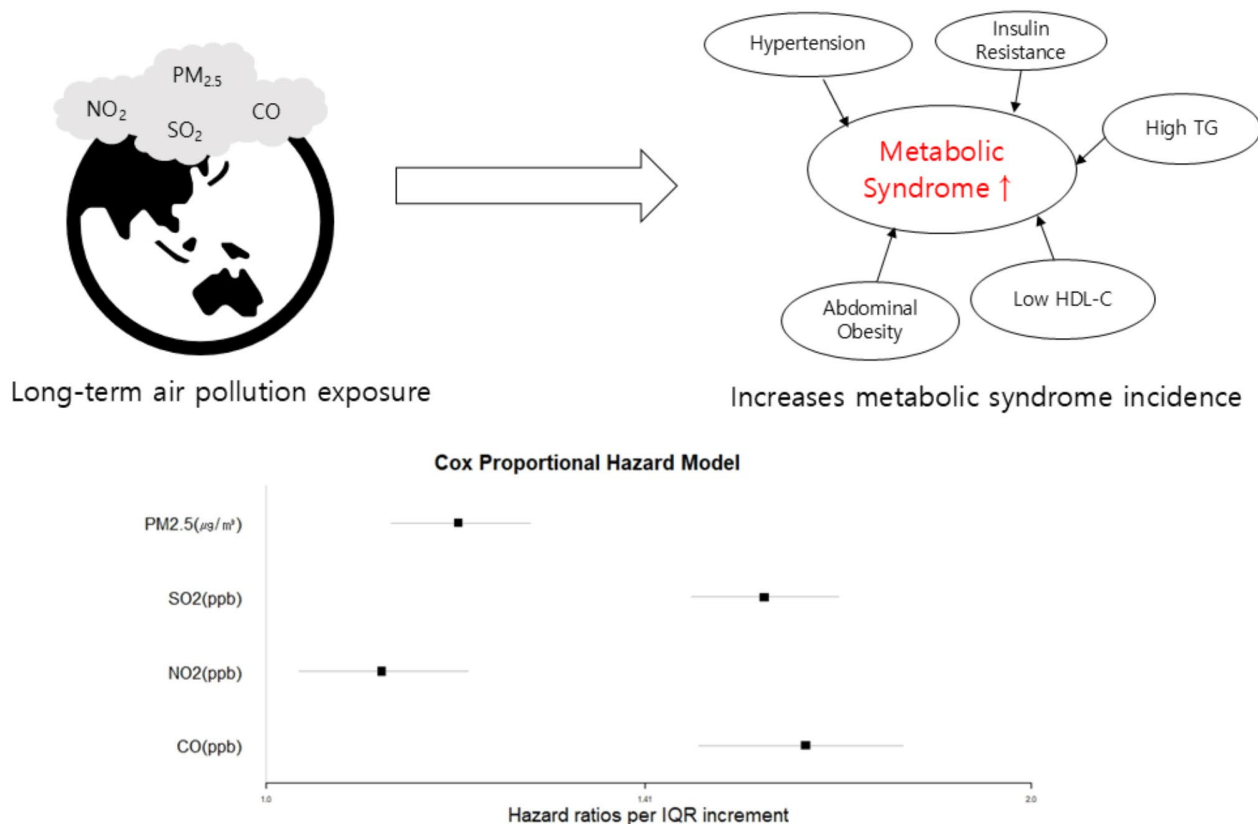
Conclusion In the present study, we found that long-term ambient air pollution exposure increased the incidences of MetS and its components among Korean adults, especially in males and the elderly population.

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Graphical abstract

Background

Metabolic syndrome (MetS) is defined as the presence of three or more of the following symptoms: high blood pressure, elevated fasting glucose, abdominal obesity, high fasting triglyceride (TG) level, and low fasting high-density lipoprotein cholesterol (HDL-C) levels. MetS affects quality of life, leading to chronic diseases, such as cardiovascular disease, cancer, and diabetes [1–3]. The prevalence of MetS globally varied from 12.5% (95% CI: 10.2-15.0) to 31.4% (95% CI: 29.8-33.0) depending on ethnic or cultural background [4]. In year 2011–2012, the prevalence of MetS among American adults was 32.5% and increased to 36.9% in year 2015–2016 [5].

Air pollution is ambient atmospheric contamination due to chemical substances, gases, or particulate matter. The pollutants majorly affecting human health are particulate matter (PM) and gaseous substances, such as carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), and these pollutants form through human activity and natural sources [6]. Most air pollutants originate from human activities, such as transportation, industrial and agricultural activities, power plants, residential heating and cooking, and combustion of fossil fuels [7, 8]. Air pollution exposure affects almost all the world's population. The World Health Organization (WHO) estimated that 99% of the world's population was exposed to air pollutants that exceeded the WHO standards in 2019 [6]. As of 2019, air pollution is the fourth leading cause of death worldwide, and 667 million people die annually from air pollution [9, 10]. Although the concentration of air pollutants in Korea is generally decreasing due to environmental regulations, it is still higher than the environmental standards of Korea or the WHO [6].

Although the main risk factor for MetS is unhealthy lifestyle patterns [11, 12], previous studies have shown that ambient air pollution exposure is also a risk factor for MetS [13, 14]. Thus far, studies have shown a strong association between PM exposure and MetS incidences, especially from long-term exposure in both younger and older populations [15–19]. A meta-analysis study showed that 5 μg/m³ increase in the annual $PM_{2.5}$ or PM_{10} concentration increases MetS risks by 14% and 9%, respectively [20]. Gaseous substances, such as SO_2, NO_2, and

O_3, also showed a significant increase in MetS risks from long-term exposures [21–23]. The prevalence of MetS components, such as hypertension and hyperglycemia, also showed a significant association with air pollution in previous studies conducted in Korea [24, 25] and other countries [26–29].

However, the evidence of the association between long-term air pollution exposure and MetS is still limited in terms of study design and pollutant models. For study design, most of the previous studies were conducted using cross-sectional datasets, and more longitudinal studies are needed. There have not yet been many studies conducted using longitudinal dataset in Korea, assessing air pollutant exposure and MetS incidence. Due to the regional differences in the composition of air pollutants in geographical context, more longitudinal studies are needed in Korea. In terms of pollutant models, previous studies analyzed the association between air pollution and MetS incidence using a single pollutant model, mostly using PM. To the best of our knowledge, there has not yet been a study that analyzed the association between PM, gaseous substances and Mets incidence for a longer duration, using a population-based dataset. Two- or multi-pollutant analysis is used to estimate the independent effect between the outcome disease and each pollutant after adjusting for potential confounders [30]. Thus, it is necessary to assess the association between the long-term effects of air pollution and MetS incidences using two- or multi-pollutant models, in order to isolate the effect of each pollutant and to refine the environmental regulations.

Therefore, we aimed to analyze the association between long-term air pollution exposure and the incidences of MetS among Korean adults using the dataset from the Korean Genome and Epidemiology Study (KoGES) cohort, a large-scale population-based cohort study conducted in the long term, using both single and two-pollutant model, in the present study.

Methods
Study population
We used the dataset of the KoGES cohort with estimated air pollution data. The KoGES is a population-based prospective cohort study conducted by the National Institute of Health, Korea Disease Control and Prevention Agency [31]. Cohort construction and detailed descriptions were provided in a previous study [32]. Among the KoGES sub-studies, we used the KoGES Cardiovascular disease Association Study (CAVAS), which consists of community-dwelling Korean adults between the ages of 40 and 69, in the present study. The purpose of this sub-study was to identify the risk factors related to the development of cardiovascular diseases and establish measures for disease prevention and early diagnosis, by investigating the

impact of lifestyle, diet, and environmental factors on the development of chronic diseases in community-dwelling populations. In addition, CAVAS covers the largest regions, which may be more suitable for generalizing the study results. The six study areas were Yangpyeong (area 877.1 km^2), Namwon (area 752.6 km^2), Goryeong (area 384.0 km^2), Wonju (area 867.3 km^2), Pyeongchang (area 1,464.1 km^2), and Ganghwa (area 411.4km^2). Figure S1 shows the geographical location of six study regions. In baseline and every follow-up visits, same protocol was used by providing identical questionnaires, physical examinations, and clinical investigations. Trained interviewers interviewed the participants regarding the sociodemographic status, lifestyle patterns such as smoking, drinking and physical activity, diet, disease, family history and health conditions. Participants' blood and urine samples were collected by trained technicians according to the standard procedures [32].

The baseline survey was conducted between 2005 and 2011, and follow-ups were conducted from 2007 to 2016 in six regions. The first follow-up survey was completed within 36 months after the baseline survey, the second within 4–6 years after the baseline survey, the third within 7–9 years after the baseline survey, and the fourth within 10–12 years after the baseline survey. A detailed timeline of recruitment and follow-up survey was presented in Figure S2. An event was defined as the concurrent occurrence of three or more components of MetS after cohort enrollment.

The KoGES CAVAS enrolled 28,337 participants at baseline. Among the 28,337 participants, those without follow-up data, those without physical assessment data to diagnose MetS, those without air pollution exposure data, and those with MetS at the baseline were excluded. In total, 7,428 participants were included in the current analysis (Fig. 1). The present study was approved by the Institutional Review Board at College of Medicine, The Catholic University of Korea (No.MC22ZASI0062).

Exposure assessment
The air pollutants measured were PM ≤ 2.5 microns in diameter ($PM_{2.5}$), SO_2, NO_2, CO, and O_3. Air pollution concentrations were calculated using the United States Environmental Protection Agency (US EPA)'s Model-3 Congestion Mitigation and Air Quality (CMAQ) version 4.7.1. The CMAQ model included a meteorological, emission model, and chemical transport model. Using the CMAQ model combined with satellite-derived aerosol optical depth (AOD), the concentrations of PM were estimated in a 1 km by 1 km grid. The concentrations of the gaseous pollutants were estimated in a 9 km by 9 km grid. Multiple linear regression (MLR) was additionally applied for PM and O_3 to further validate the results. According to a meta-analysis study that analyzed the
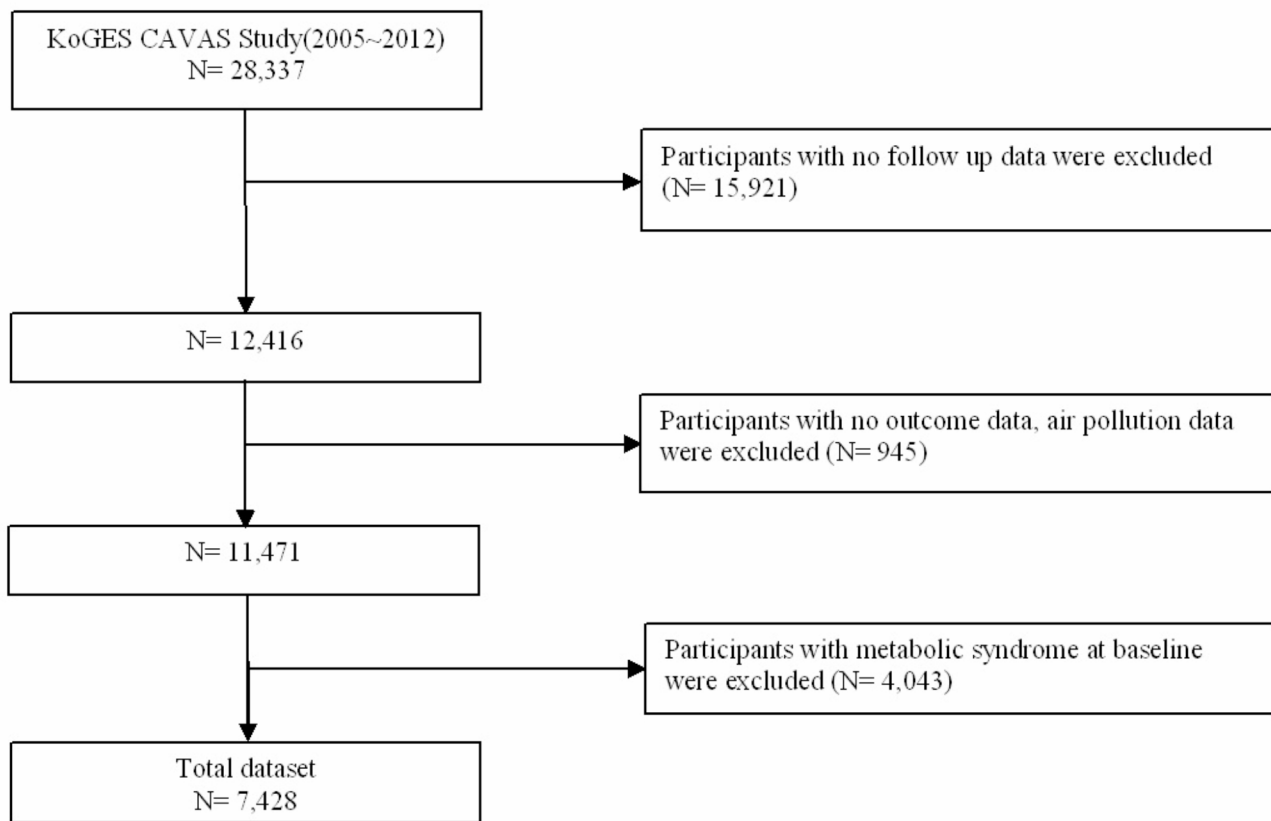
Fig. 1 Flowchart of study population selection

source apportionment (SA) of PM by regions, the SA of PM in Yangpyeong and Ganghwa was highest for secondary aerosol (including secondary nitrate and secondary sulfate) and motor vehicle, while Namwon was highest for motor vehicle and secondary aerosol. In Wonju and Pyeongchang, SA was not accurately known as no studies were conducted [33]. The verification of the modeling data was conducted by comparing it with the monitoring station data. The square of the correlation coefficient (R^2) values on a daily scale were 0.66 for $PM_{2.5}$, 0.74 for NO_2, and 0.69 for CO. The description of the air pollution modeling methods was provided previously [34]. The participants' addresses were geocoded using the geocoding software GeoService-Xr (Geoservice, Seoul, Republic of Korea) into latitude and longitude, and matched to the center of the estimated air pollutant concentration grid. If a participant's address was changed due to relocation between follow-up surveys, the average exposure was calculated assuming that the participant moved at the midpoint between the previous and current follow-up survey.

In this present study, the association between annual air pollution exposure and MetS incidences was analyzed using the average annual concentration data of $PM_{2.5}$, NO_2, CO, SO_2, and O_3. To observe the personal cumulative long-term air pollution exposure concentration,

personal annual average exposure was calculated from 1 year prior to the study enrollment to the occurrence of MetS or to the point when the participant is censored. Personal exposure assessment calculation was presented in Figure S2.

Definition of metabolic syndrome (MetS)

MetS was diagnosed using the participants' physical examination data, specifically height, weight, and blood and urine samples. We defined MetS cases according to the National Institute of Health (NIH)'s National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III). Individuals with three or more of the symptoms noted below were diagnosed as MetS [35]. Components of MetS include high blood pressure (systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg, or taking antihypertension medication), elevated fasting glucose (fasting blood glucose ≥ 100 mg/dL), abdominal obesity (waist circumference ≥ 90 cm in male, ≥ 80 cm in female), fasting TG (≥ 150 mg/dL), or fasting HDL-C (< 40 mg/dL in males, < 50 mg/dL in females).

Covariates

We adjusted the sociodemographic variables, lifestyle characteristics, and meteorological variables.

Sociodemographic characteristics included age, sex, region, occupational status, monthly household income level, education level, and family history of hypertension and hyperglycemia. The education level was grouped into four categories: 'Elementary school', 'Middle school', 'High school', and 'Over college'. The monthly household income level was classified into four groups: '<1,000,000 won/month', '1,000,000–1,990,000 won/month', '2,000,000–3,990,000 won/month', and '≥4,000,000 won/month' in Korean Won (KRW) monthly. Occupational status, and family history of hypertension and hyperglycemia were grouped into three categories, which were 'yes', 'no', and 'unknown'. If the covariate variable was not surveyed (the data was missing, specific year or specific unit), then the answer was classified as 'unknown'.

Lifestyle characteristics were alcohol consumption, smoking status, and physical activity. Alcohol consumption and smoking status were categorized into 'current', 'past', and 'never'. As for physical activity, it was classified into '1–2 times a week', '3–6 times a week', 'every day', and 'no'.

BMI was calculated using height and weight from physical examination data by dividing weight (kg) by the square of height (m). We used the criteria for the Asian population by the WHO for which the values were classified into five groups [36]. The categories were underweight (BMI < 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), obese I (25.0–29.9 kg/m^2), and obese II (BMI ≥ 30 kg/m^2).

We adjusted the average annual temperature (℃) and relative humidity (%) to adjust the regional and climate effects. Based on previous studies, we designed a directed acyclic graph (DAG) using the software DaGitty [37]. DAG was presented in Figure S3.

Statistical analysis

We analyzed the distribution of the sociodemographic characteristics using descriptive statistics. The Spearman correlation coefficients were estimated between the air pollutants and meteorological variables. The mean (± standard deviation), median, minimum, maximum, and interquartile range (IQR) of the air pollutants exposure concentrations during the follow-up were presented. We used Cox proportional hazard model to analyze the association between long-term air pollution exposure per IQR increment and the incidences of MetS, and the results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Also, to check for the independent effect of each pollutant, we performed two-pollutant model between $PM_{2.5}$ and NO_2, SO_2, and O_3 respectively. We used age as the timescale when performing Cox regression by using the age at which MetS occurred or when censoring happened. This method is used when the covariate of interest is strongly associated with age,

and since age is a major risk factor for MetS, we assumed this method was suitable. Censoring was defined as those who did not have MetS until the end of the study period, or a follow-up loss due to migration or drop out. An individual's follow-up period was defined as from the time of the baseline study to the point when MetS was diagnosed, or the time between the baseline survey and censoring. Model 1 was an unadjusted model, and Model 2 was adjusted for age and sex. In addition to model 2 covariates, Model 3 was adjusted for sociodemographic and lifestyle characteristics, which were monthly household income, education level, smoking and drinking status, physical activity. Model 4, which was our main model, was additionally adjusted for temperature and humidity. Stratified analyses by sex (male, female), age groups (40–49 years, 50–59 years, 60–69 years, 70 years older), and smoking status (current, past, never, unknown) were performed to find the association between subgroups. Sensitivity analysis was conducted by adding region, and BMI to the main model, respectively. This sensitivity analysis allowed us to observe whether region act as a confounder and BMI as an intermediate. MetS is diagnosed when concurrent occurrence of the component diseases, and the association between air pollution and MetS component diseases may vary. Therefore, we also analyzed the association between MetS components, which were hypertension, hyperglycemia, abdominal obesity, high TG, and low HDL-C, and air pollution exposure. When performing analyses for each component, we excluded participants with abnormal symptoms at baseline. We used R (version 4.2.3) and a two-tailed *P*-value less than 0.05 to determine the statistical significance.

Results

Descriptive statistics

The cohort was comprised of 7,428 participants and a total of 37,780 person-years of follow-up. The mean follow-up duration was 5 years (1-10.8 years) and there were 1,773 new MetS cases during the follow-up period. The average age at the time of enrollment was 58.2 years old (± 9.6), and 51.2% of the participants were male. A majority of the study participants had a job (87.9%), an education level of elementary school (48.3%), never consumed alcohol (46.5%), never smoked (52.0%), and did not exercise regularly (65.8%) (Table 1). We compared the baseline characteristics of those who excluded and included. The excluded were older (58.7 years) and 66.4% was female. The excluded group included those with MetS at baseline, so the physical examination and biochemistry results were either higher or worse than that of study population. The average air pollution exposure value was also compared. The participants who were included in the study had higher exposure value for all six air pollutants. In some cases, air pollution values were missing

Table 1 Baseline descriptive characteristics of study population (2005–2012)

Characteristics	Value (*n* = 7,428)
Age, year, mean ± SD	58.2 ± 9.6
Sex, n (%)	
Male	3804 (51.2)
Female	3624 (48.8)
Residence, n (%)	
Yangpyeong	1411 (17.7)
Namwon	1109 (14.9)
Goryeong	1215 (16.4)
Wonju	1278 (17.2)
Pyeongchang	1029 (13.9)
Ganghwa	1486 (20.0)
Monthly household income, KRW, n (%)	
< 1,000,000 won/month	1260 (17.0)
1,000,000 ~ 1,990,000 won/month	1005 (13.5)
2,000,000 ~ 3,990,000 won/month	1030 (13.9)
≥ 4,000,000 won/month	304 (4.1)
Unknown	3829 (51.6)
Job status, n (%)	
Yes	6528 (87.9)
No	287 (3.9)
Unknown	613 (8.3)
Education, n (%)	
Elementary school	3585 (48.3)
Middle school	1382 (18.6)
High school	1697 (22.9)
Over college	747 (10.1)
Unknown	17 (0.2)
Drinking status, n (%)	
Current	3482 (46.9)
Past	485 (6.5)
Never	3454 (46.5)
Unknown	7 (0.1)
Smoking status, n (%)	
Current	1112 (15.0)
Past	1286 (17.3)
Never	3863 (52.0)
Unknown	1167 (15.7)
Physical activity, n (%)	
1–2 times a week	565 (7.6)
3–6 times a week	1080 (14.5)
Everyday	868 (11.7)
No	4890 (65.8)
Unknown	25 (0.3)
BMI, n (%)	
< 18.5 kg/m^2	184 (2.5)
18.5–22.9 kg/m^2	2915 (39.2)
23.0–24.9 kg/m^2	1991 (26.8)
25.0–29.9 kg/m^2	2338 (31.5)
≥ 30 kg/m^2	0
Family history of Hypertension, n (%)	
Yes	1518 (20.4)
No	5855 (78.8)
Unknown	55 (0.7)

Table 1 (continued)

Characteristics	Value (*n* = 7,428)
Family history of Hyperglycemia, n (%)	
Yes	934 (12.6)
No	6443 (86.8)
Unknown	51 (0.7)
Waist circumference, cm, mean ± SD	82.7 ± 8.8
Systolic blood pressure, mmHg, mean ± SD	121.5 ± 16.5
Diastolic blood pressure, mmHg, mean ± SD	77.3 ± 10.5
Fasting blood glucose, mg/dL, mean ± SD	94.7 ± 18.9
Total cholesterol, mg/dL, mean ± SD	195.4 ± 34.9
Triglyceride, mg/dL, mean ± SD	123.1 ± 74.3
High density lipoprotein cholesterol, mg/dL, mean ± SD	46.6 ± 11.4

Note: Data were shown as mean ± SD for continuous variables and number (%) for categorical variables

Abbreviations: SD, Standard deviation; KRW, Korean won; BMI, Body mass index

Table 2 Average annual concentration of air pollutants and meteorological exposure during follow-up

Exposure	Mean ± SD	Median	Minimum	Maximum	IQR
$PM_{2.5}$ (μ/m³)	26.86 ± 2.74	26.59	17.91	35.67	3.48
SO_2 (ppb)	4.37 ± 0.94	4.30	2.34	8.75	1.17
NO_2 (ppb)	15.30 ± 5.31	15.05	4.98	36.77	8.87
CO (ppb)	487.86 ± 98.22	468.00	288.35	725.73	172.71
O_3 (ppb)	25.39 ± 2.167	25.09	18.04	37.36	2.65
Temperature (℃)	10.65 ± 1.48	10.75	6.50	13.64	2.28
Humidity (%)	71.97 ± 1.34	71.99	61.70	76.72	1.62

Abbreviations: SD, Standard deviation; IQR, Interquartile range; $PM_{2.5}$, particulate matter with aerodynamic diameters ≤ 2.5 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; ppb, parts per billion

Table 3 Hazard ratios of metabolic syndrome per interquartile range width increment in air pollution exposure during follow-up (*n* = 7,428)

Exposure	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
$PM_{2.5}$ (μg/m³)	1.19 (1.11–1.26)	1.17 (1.10–1.24)	1.17 (1.10–1.25)	1.19 (1.12–1.27)
SO_2 (ppb)	1.48 (1.40–1.58)	1.55 (1.45–1.64)	1.71 (1.60–1.83)	1.57 (1.47–1.68)
NO_2 (ppb)	1.16 (0.73–1.83)	1.22 (1.13–1.32)	1.20 (1.11–1.30)	1.11 (1.03–1.20)
CO (ppb)	1.53 (1.41–1.67)	1.59 (1.46–1.73)	1.68 (1.54–1.84)	1.63 (1.48–1.78)
O_3 (ppb)	0.71 (0.67–0.76)	0.47 (0.44–0.51)	0.42 (0.39–0.45)	0.48 (0.45–0.52)

Note: IQR for $PM_{2.5}$: 3.48 μg/m³, SO_2: 1.17 ppb, NO_2: 8.87 ppb, CO: 172.71 ppb, O_3: 2.65 ppb

Abbreviations: HR, Hazard ratio; 95% CI, 95% confidence interval; $PM_{2.5}$, particulate matter with aerodynamic diameters ≤ 2.5 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; ppb, parts per billion

[a]Model 1 Unadjusted model

[b]Model 2 adjusted for age, sex

[c]Model 3 adjusted for age, sex, monthly household income, education, smoking, drinking, physical activity

[d]Model 4 adjusted for age, sex, monthly household income, education, smoking, drinking, physical activity, temperature, humidity

for the excluded, which may explain the greater exposure values for those included in the study (Table S1). The population with new cases of MetS were older (58.6 years), had more female (57.2%) and evenly distributed in study regions (Table S2). Table S3 shows the distribution of MetS and non-MetS cases by each air pollutant variable by quartiles. In this analysis, the MetS incidence among participants living in regions with higher air pollution was higher. Year 2008 had the greatest number of MetS incidences in all regions, followed by year 2011 in Yangpyeong, Pyeongchang, and Ganghwa (Table S4).

The annual averages of air pollutants and meteorological variables during follow-up are shown in Table 2. The annual mean concentrations of $PM_{2.5}$ was 26.86 μg/m³, which was higher than the WHO standards [38]. The IQR values of air pollutant exposure during follow-up were 3.48 μg/m³ for $PM_{2.5}$, SO_2 for 1.17 ppb, NO_2 for 8.87 ppb, CO for 172.71 ppb, and O_3 for 2.65 ppb. The average temperature during follow-up was 10.65℃, and the average relative humidity was 71.97%. The correlation coefficients were highest between SO_2 and CO which was 0.88. There

was a negative correlation between O_3 and other air pollutants, and temperature was negatively correlated with air pollutants. Relative humidity was positively correlated with NO_2 and O_3, and negatively correlated with other air pollutants (Figure S4).

Long-term exposure to ambient air pollution and incidence of metabolic syndrome and its component

Table 3 shows the HRs (95% CIs) for the incidences of MetS per IQR increment of air pollution exposure. Exposure to ambient air pollution was significantly associated with a higher risk of incidences of MetS except for O_3. From Model 4, which was our main model, the HR of MetS per IQR increment for $PM_{2.5}$, SO_2, NO_2, and CO were 1.19 (95% CI: 1.12-1.27), 1.57 (95% CI: 1.47-1.68),

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1.11 (95% CI: 1.03-1.20), and 1.63 (95% CI: 1.48-1.78), respectively.

Results of two-pollutant model are presented in Table S5. We performed two-pollutant analysis for $PM_{2.5}$ with SO_2, NO_2, and O_3. After adjusting for $PM_{2.5}$, effect for NO_2 was not statistically significant (HR: 0.90, 95% CI: 0.80-1.01). However, the HR of $PM_{2.5}$ was 1.27 (95% CI: 1.16-1.39), remaining significant after adjusting for NO_2. In two-pollutant analysis, SO_2 was more strongly associated with the outcome in comparison to each individual compound. When combined with $PM_{2.5}$, SO_2 remained significant, showing the HR of 1.75 (95% CI: 1.60-1.91) per IQR increment.

Similar results were found for incidences of MetS components. The HRs (95% CIs) for the incidences of MetS components per IQR increment of air pollution exposure are shown in Table 4. When adjusted for potential confounders, the risk increased the highest for SO_2 and CO.

Subgroup analysis

The results of the stratified analyses are presented in Fig. 2. When adjusted for potential confounders, males had higher risks of developing MetS than females for all air pollutants. In the case of age, 60–69 year old age group showing the highest incidence rate for all air pollutants. As for smoking status, the highest HR was found

Table 4 Hazard ratios of metabolic syndrome components per interquartile range width increment in air pollution exposure during follow-up

Exposure	Hypertension	Hyperglycemia	Abdominal obesity	High TG	Low HDL-C
	($n = 5,208$)	($n = 7,745$)	($n = 6,948$)	($n = 7,358$)	($n = 6,616$)
$PM_{2.5}$ (μ/m³)	1.19 (1.11–1.27)	1.16 (1.09–1.23)	1.30 (1.23–1.39)	1.10 (1.04–1.17)	1.47 (1.34–1.61)
SO_2 (ppb)	1.44 (1.34–1.55)	1.32 (1.24–1.41)	1.67 (1.57–1.79)	1.35 (1.27–1.43)	1.86 (1.67–2.07)
NO_2 (ppb)	1.05 (0.96–1.14)	0.96 (0.89–1.04)	1.40 (1.30–1.52)	1.07 (1.00-1.15)	1.46 (1.29–1.65)
CO (ppb)	1.44 (1.30–1.59)	1.44 (1.32–1.57)	1.79 (1.64–1.96)	1.38 (1.27–1.50)	1.85 (1.61–2.13)
O_3 (ppb)	0.51 (0.48–0.56)	0.48 (0.44–0.51)	0.50 (0.46–0.54)	0.54 (0.51–0.58)	0.44 (0.39–0.49)

Note: IQR for $PM_{2.5}$: 3.48μ/m³, SO_2: 1.17ppb, NO_2: 8.87ppb, CO: 172.71ppb, O_3: 2.65ppb

Abbreviations: HR, Hazard ratio; 95% CI, 95% confidence interval; $PM_{2.5}$, particulate matter with aerodynamic diameters ≤ 2.5 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; ppb, parts per billion

All models adjusted for age, sex, monthly household income, education, smoking, drinking, physical activity, temperature, humidity
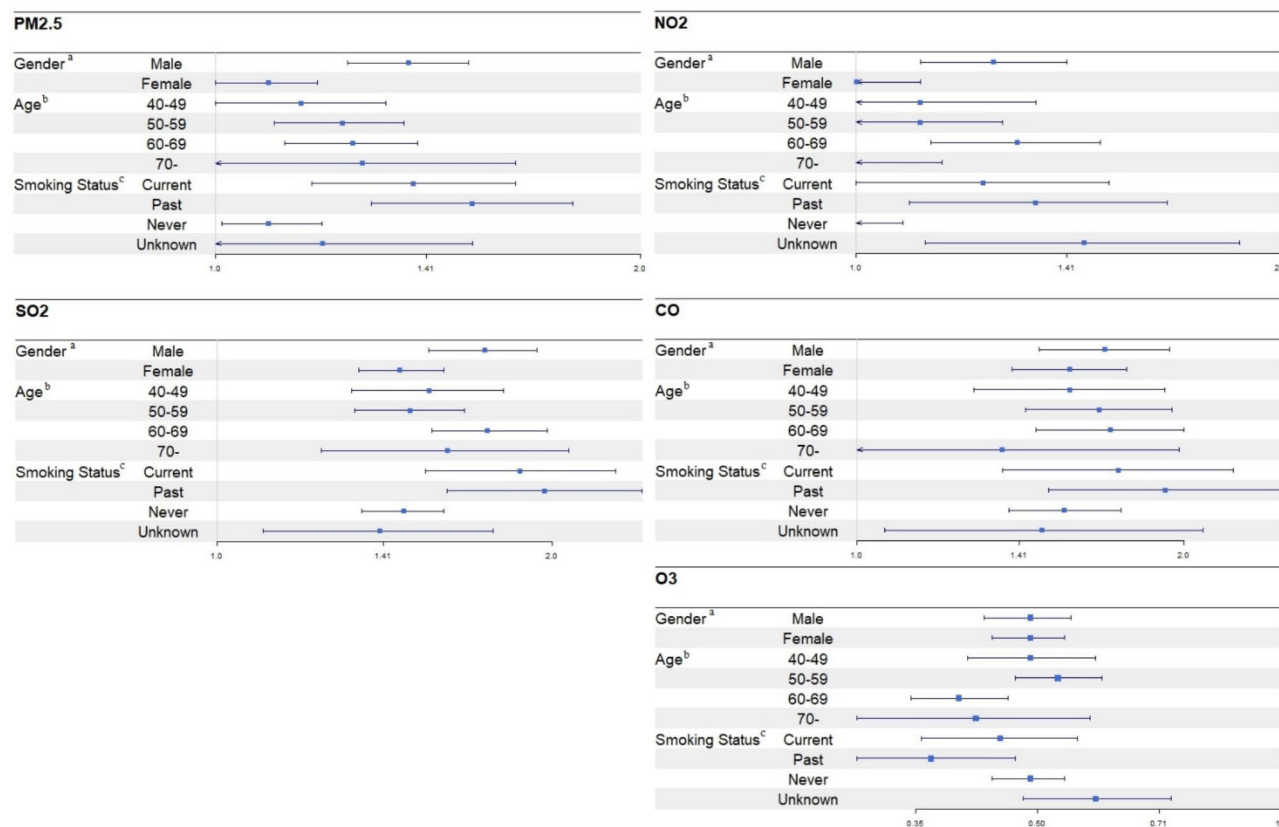
in the past smoking group for all air pollutants followed by current smoking group.

Sensitivity analysis

We conducted a sensitivity analysis by adding region, and BMI to the main model, respectively. This sensitivity analysis allowed us to observe whether region act as a confounder and BMI as an intermediate ($n = 7,428$). Table S6 shows the results of sensitivity analysis. Model 3 shows the results of HR after adding region to the main model. The incidence rate increased with a HR of 1.29 (95% CI: 1.13-1.46) for $PM_{2.5}$, 2.78 (95% CI: 2.48-3.12) for SO_2, and 7.08 (95% CI: 5.54-9.03) for CO. Model 4, which shows the results of HR after adding BMI to the main model, the HR for SO_2, NO_2, and CO were 1.58 (95% CI: 1.47-1.69), 1.10 (95% CI: 1.02-1.19), and 1.61 (95% CI: 1.47-1.77) respectively. Model 4 showed similar results to those of the main analysis.

Discussion

Using a large-scale population-based cohort, we observed a significant association between the annual concentration of ambient air pollution and the incidences of MetS after adjusting for potential confounders. Exposure to $PM_{2.5}$, SO_2, NO_2, and CO were positively associated with higher risk of MetS. In a two-pollutant model performed between $PM_{2.5}$ and NO_2, SO_2, O_3, we observed statistical significance in $PM_{2.5}$, and SO_2. In the subgroup analysis, males had a higher risk of developing MetS than females for all air pollutants. In the case of age, the 60–69 year old age group had the highest HR for all air pollutants. We also found a significant association between air pollution exposure and the incidences of MetS components, with the highest HR shown in SO_2 and CO for all of the components.

Depending on the pollutant, there are similarities and differences between the present and previous studies conducted. Positive associations were reported between long-term PM exposure and MetS incidence, however evidence for ozone exposure is highly mixed. Long-term PM exposure increased the MetS incidences, which was consistent with our results [13, 15, 22, 23]. A previous retrospective cohort study among health examinees in Korea showed 10 μg/m³ annual increase of $PM_{2.5}$ significantly increases the MetS incidence by 7% [15]. A study conducted in the UK showed increase in the mean annual $PM_{2.5}$ concentration by 1 μg/m³ was associated with a higher risk of MetS (HR: 1.27, 95% CI: 1.06-1.52) [16], and a study from China also showed similar results (HR: 1.027, 95% CI: 1.006-1.048) for every 10 μg/m³ increase in PM_{10} [13]. We also observed significant increases in MetS components, which were consistent with the results of previous studies conducted worldwide [39–42].

Fig. 2 Hazard ratios of metabolic syndrome per interquartile range width increment in air pollution exposure during follow-up stratified by sex, age, and smoking status (*n*=7,428). Note: IQR for PM$_{2.5}$: 3.48 μg/m^3, SO$_2$: 1.17 ppb, NO$_2$: 8.87 ppb, CO: 172.71 ppb, O$_3$: 2.65 ppb. Abbreviations: PM$_{2.5}$, particulate matter with aerodynamic diameters ≤ 2.5 μm; SO$_2$, sulfur dioxide; NO$_2$, nitrogen dioxide; CO, Carbon monoxide; O$_3$, ozone; ppb, parts per billion. [a]Adjusted for age, monthly household income, education, drinking, smoking, physical activity, temperature, humidity. [b]Adjusted for age, sex, monthly household income, education, drinking, smoking, physical activity, temperature, humidity. [c]Adjusted for age, sex, monthly household income, education, drinking, physical activity, temperature, humidity

However, for ozone exposure, a negative association between O$_3$ exposure and the incidences of MetS and its components was observed in the present study. This is inconsistent with some previous results. A study conducted among Taiwanese population has shown 3.30 ppb increase of ozone exposure increase the incidence of hyperglycemia by 5.8% [43]. 10 μg/m^3 annual increase of ozone increased the incidence of diabetes with HR of 1.015 (95% CI: 1.992-1.027) in a study conducted among the Rome population [44]. The reason for this inconsistency may have been due to first, the association between O$_3$ and other pollutants. O$_3$ is a secondary substance produced by photochemical decomposition of nitrogen oxide (NO$_x$) and volatile organic compounds (VOCs) [45, 46]. Due to this characteristic, O$_3$ and other air pollutants are negatively correlated [47], and generally has a positive correlation with temperature. Second, the inconsistency among studies may have been due to ethnicity, cultural and environmental factors, differences in air pollutant composition and severity, and study design [43]. Third, because MetS is defined by the presence of three or

more symptoms, this might have affected the sample size which can led to inconsistent results [48]. O$_3$ is known to have a positive correlation with temperature, however we observed no correlation in this study. The reason for this inconsistency may be first, because we used the annual average concentration of air pollution and meteorological variables, fluctuation within a year may be largely irrelevant. Second, O$_3$ concentration formed through not only by temperature, but also by other meteorological variables such as relative humidity, wind direction, stability, and Long-Range Transport (LRT) is also known to affect the O$_3$ concentration [49]. LRT was proven to be a major factor affecting ozone concentrations in non-urban areas in Korea by previous studies [49–51]. The lack of a high correlation between O$_3$ and temperature may be explained by the fact that the study regions in this study were mostly non-urban areas.

We adjusted for temperature and relative humidity to adjust the regional and climate effects of air pollutant exposure. We observed a negative correlation between temperature and air pollutants, which was the highest

in CO in this study. For the relative humidity, a negative correlation between air pollutants except for NO_2 and O_3 was observed. This is a similar result to that of previous studies showing a negative correlation between air pollutants, temperature, and relative humidity except for O_3 [50, 52–54]. The reason why the results contrasted with those of this study and previous studies was interpreted as the particles that make up air pollutants may vary by country, region, and period. The correlation coefficient between temperature and CO was the highest in the negative direction in the present study. This correlation between meteorological variables and air pollutants explains the reason that incidence rate of MetS increased the most in CO.

In the sensitivity analysis, we performed analyses by adding region in Model 3, and BMI in Model 4, to the main model respectively. After adding region in the statistical model, we observed a significant increase in HR in the results. The spatiotemporal characteristics of air pollutants are associated with local industries and environments. Also, geographically adjacent cities tend to have similar air pollutant concentrations and meteorological patterns [55]. We adjusted for temperature and relative humidity to adjust the regional and climate effects. Therefore, we did not further adjust for region in the main model, because doing so could lead to an overestimation. In addition, BMI may be a mediator but we did not observe a significant difference in HR with or without adjustment in this study, therefore, we concluded that BMI does not act as a mediator at least in our dataset, therefore we did not adjust for BMI in the present study.

In previous studies where two-pollutant model was performed analyzing the association between air pollution and MetS, $PM_{2.5}$ and PM_{10} was found to be positively associated with MetS incidence [56, 57]. In the present study, we found $PM_{2.5}$, and SO_2 were positively associated with MetS incidence in two-pollutant analysis, showing similar robust results as the main analysis. In particular, SO_2 was more strongly associated with the outcome in comparison to each individual compound. However, when adding O_3 to the model with $PM_{2.5}$ as the main pollutant, the results were not statistically significant nor robust to the main result. This is partly inconsistent with previous studies, and the reason for the inconsistency may be due to differences in environmental factors, air pollutant composition, study design, and sample size. Also, high correlation between air pollutants may under estimated the result of two-pollutant analysis.

Although there were not any interventions provided at follow-up surveys, such as recommendations on changing lifestyle patterns, we observed the highest HR in the past smoking group for all air pollutants in subgroup analysis. To the best of our knowledge, there were not any previous studies that observed the highest HR in the past smoking group. However, the reason for this may be because the effect of air pollution may be lower in current smokers due to the effects of smoking [58].

There is no clear basis for how the air pollutants cause MetS, but it has been shown in previous studies that they have a systematic effect on the body. When air pollutants are inhaled through the respiratory tract, they induce DNA methylation, oxidative stress, and pro-inflammatory cytokine secretion. This causes systematic inflammation and impairment in the autonomic nervous system, circulates throughout the body within the blood, and affects the entire human body. Due to this systematic effect, previous studies have shown that DNA methylation can induce epigenetic changes and increase the susceptibility of MetS [59]. For oxidative stress and inflammatory markers, studies have shown that they play an important role in the pathogenesis of metabolic syndrome. Reactive oxygen species (ROS) was proven to cause mitochondrial dysfunction, promote protein damage, trigger lipid peroxidation, and antioxidant defenses in metabolic syndrome in previous studies. Disrupted cell signaling pathways elevate inflammatory markers, lipid peroxides, and free radicals, leading to cellular damage and the clinical symptoms of metabolic syndrome [60]. According to previous studies, DNA methylation can be observed in as short as 5 to 30 moving-average days [61, 62], systematic inflammation and pro-inflammatory cytokine secretion in less than 1 year [63, 64], and oxidative stress in 7 moving-average days [65]. These mechanisms explain the incidence of hypertension, insulin resistance, abdominal obesity, and MetS [66–70].

Although we found a significant association between air pollution and MetS incidences, there were some potential limitations that should be noted when interpreting the results. First, individual exposure was estimated based on the participants' residential addresses without considering actual exposure during daytime activities. Also, due to lack of information, participants' addresses one year prior to enrollment were not considered. There might be misclassification of exposure due to these reasons, however, this misclassification is likely to be random and causes bias towards the null [71, 72]. Thus, the association between air pollutants and MetS may have been greater if we collected the actual exposure data. Second, two-pollutant analysis was only applied between $PM_{2.5}$, and NO_2, SO_2, and O_3. The air pollutants were highly correlated, and other pollutants need to be analyzed in two- or multi pollutant models to find out how independent pollutants affected the incidences of MetS. Due to the heterogeneity of the study areas, the composition of air pollutants and interaction between air pollutants may have varied [73, 74]. Third, although several important confounders were controlled, there may have been some other unmeasured covariates not

considered. Fourth, the result of present study cannot be generalized to other race or ethnicity since the study participants only consisted of Korean. Fifth, we only considered average annual concentrations of air pollutants as exposure variable. Considering that exposure to the air pollutants in a long period would gradually induce the MetS, there probably exists a certain period which is critical to the MetS occurrence. However, the exact time point of occurrence of MetS cannot be determined and we think average concentration as exposure is appropriate approach. Sixth, the present study did not examine the non-linear association between air pollutants and MetS. Most of the previous studies did not assume non-linearity between air pollutants exposure and MetS incidence [42, 75]. However, there is possibility of the true association being non-linear with threshold, and the present result may be under- or overestimate the true association in the concentration range higher and lower than the threshold, respectively.

Conclusion

We found that long-term exposure to $PM_{2.5}$, SO_2, NO_2, and CO significantly increased the incidences of MetS among Korean adults. Similar results were found for the components of MetS. In two-pollutant analysis, $PM_{2.5}$, and SO_2 showed positive association with MetS. In particular, the incidence rate tended to increase in the males and elderly population, so appropriate environmental regulations and healthcare for susceptible population is needed.

Abbreviations

HR	Hazard ratio
95% CI	95% confidence interval
IQR	Interquartile range
BMI	Body mass index
$PM_{2.5}$	Particulate matter with aerodynamic diameters ≤ 2.5 μm
SO_2	Sulfur dioxide
NO_2	Nitrogen dioxide
CO	Carbon monoxide
O_3	Ozone
ppb	Parts per billion
KoGES	Korean Genome and Epidemiology Study

Supplementary Information

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Supplementary Material 1

Author contributions
H.S. conceptualized, performed the analyses, visualized the results, wrote the original draft, and edited. M.S. supervised and revised the manuscript. S.B. supervised and revised the manuscript. All authors read and approved the final manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The present study was approved by the Institutional Review Board at College of Medicine, The Catholic University of Korea (No.MC22ZASI0062).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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