International Journal of Hygiene and Environmental Health 222 (2019) 533–540

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Fine particulate matter and incidence of metabolic syndrome in non-CVD patients: A nationwide population-based cohort study

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ARTICLE INFO

Keywords:
Air pollution
Fine particulate matter
Metabolic syndrome
Body mass index
Recurrent events
Andersen-Gill model

ABSTRACT

Background: It has been reported that particulate matter (PM) is associated with cardiovascular diseases (CVD) while metabolic syndrome is also an important risk factor for CVD. However, few studies have investigated the epidemiological association between PM and metabolic syndrome.

Objective: To investigate the association between one-year exposure to PM with an aerodynamic diameter < 2.5 μm ($PM_{2.5}$) and the risk of metabolic syndrome in Korean adults without CVD.

Methods: Exposure to $PM_{2.5}$ was assessed using a Community Multiscale Air Quality (CMAQ) model. Metabolic syndrome was defined by National Cholesterol Education Program Adult Treatment Panel III. Andersen and Gill model with time-varying covariates, considering recurrent events, was used to investigate the association between one-year average $PM_{2.5}$ and the risk of incident metabolic syndrome in 119,998 adults from the national health screening cohort provided by Korea National Health Insurance from 2009 to 2013.

Results: Higher risk of metabolic syndrome, waist-based obesity, hypertension, hypertriglyceridemia, low HDL cholesterol, and hyperglycemia were significantly associated with a 10-μg/m^3 increase in $PM_{2.5}$ [adjusted hazard ratio (HR): 1.070, 1.510, 1.499, 1.468, 1.627 and 1.380, respectively]. In addition, the risk of metabolic syndrome associated with $PM_{2.5}$ exposure was significant in the consistently obese group (obese at baseline and endpoint).

Conclusion: Exposure to one-year average $PM_{2.5}$ is associated with an increased risk of metabolic syndrome and its components in adults without CVD. These associations are particularly prominent in the consistently obese group (obese at baseline and endpoint). Our findings indicate that $PM_{2.5}$ affects the onset of MS and its components which may lead to increase the risk of CVD.

1. Introduction

Metabolic syndrome is a constellation of metabolic risk factors that include abdominal obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and hyperglycemia (Alberti et al., 2009). Along with global obesity epidemic, the prevalence of metabolic syndrome is also rapidly increasing worldwide. Metabolic syndrome has emerged as an urgent health problem (Kassi et al., 2011). Age-adjusted prevalence of metabolic syndrome has increased from 23.7% in the late 1990s to 34% recently in the USA (Ervin,

Abbreviations: $PM_{2.5}$, Particulate matters whose diameters are equal to or less than 2.5μm; CVD, Cardiovascular disease; BMI, Body mass index; HDL-C, High-density lipoprotein cholesterol; HR, Hazard ratio; CI, Confidence interval; SD, Standard deviation

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https://doi.org/10.1016/j.ijheh.2019.01.010
Received 30 October 2018; Received in revised form 22 January 2019; Accepted 29 January 2019

2009; Ford et al., 2002) and from 28.8% in the 1990s to 30.5% recently in the Republic of Korea (Lee et al., 2018; Lim et al., 2011). The main risk factors for metabolic syndrome appear to be abdominal obesity (Carr et al., 2004) and environmental factors such as physical inactivity (Gustat et al., 2002; Longo-Mbenza et al., 2011) and aging (Kawada et al., 2010). Recent epidemiological evidence also suggests that particulate matter (PM) might be a factor that can increase the risk of metabolic syndrome (Eze et al., 2015; Park et al., 2010; Wei et al., 2016).

Inhalation of PM can instigate pulmonary oxidative stress, systemic inflammation, vascular dysfunction, and atherosclerosis in the body (Brook et al., 2010). It is well known that exposure to PM increases the risk of cardiovascular disease (CVD) (Brook et al., 2010; Dabass et al., 2016; Martinelli et al., 2013). In addition, recent studies have shown a link between particulate matter and individual components of metabolic syndrome. Long-term exposures to $PM_{2.5}$ (particulate matters with diameter equal to or less than 2.5㎛) might increase the risk for hypertension (Xie et al., 2018) and diabetes (Pearson et al., 2010; Solimini et al., 2015) while long-term exposure to PM10 is associated with hypertriglyceridemia (Shanley et al., 2016).

Investigating the association between PM and metabolic syndrome is important to control disease burden of CVD (Eze et al., 2015). Such investigation might also reveal mediators that could help describe the link of PM exposure to CVD risk (Wallwork et al., 2017). Nonetheless, the possible relationship between PM exposure and incidence of metabolic syndrome has been rarely reported. Moreover, previous studies related to metabolic syndrome related studies have focused on incidence of metabolic syndrome from the general population including CVD patients (Eze et al., 2015; Wallwork et al., 2017). Therefore, the objective of this study was to investigate the association between ambient $PM_{2.5}$ and incidence of metabolic syndrome in Korean adults without CVD from a general population sample. Those who might be susceptible to CVD risk associated with PM exposure were also identified.

2. Material and methods

2.1. Study population

Participant selection flow diagram is shown in Fig. 1. Detailed data source and study period are summarized in Fig. 2. We enrolled participants who received health screening provided by the Korean Medical Insurance Corporation in a National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) between 2009 and 2010 (Lee et al., 2016). These examinations are referred to as “baseline visit”. A total of 495,061 people received such health examinations. We excluded 217,800 people who did not receive a health screening during the follow up period. Additional 87,098 participants who were diagnosed with metabolic syndrome at the time of enrollment and 55,646 participants who were diagnosed with cardiovascular diseases or were undergoing treatment with warfarin from 2002 to 2013 were excluded. In addition, we excluded 14,519 participants who had incomplete information for covariates. Finally, a total of 119,998 participants, including 21,941 (18.3%) who had metabolic syndrome and 98,057 (81.7%) who were free from metabolic syndrome, were analyzed in this study.

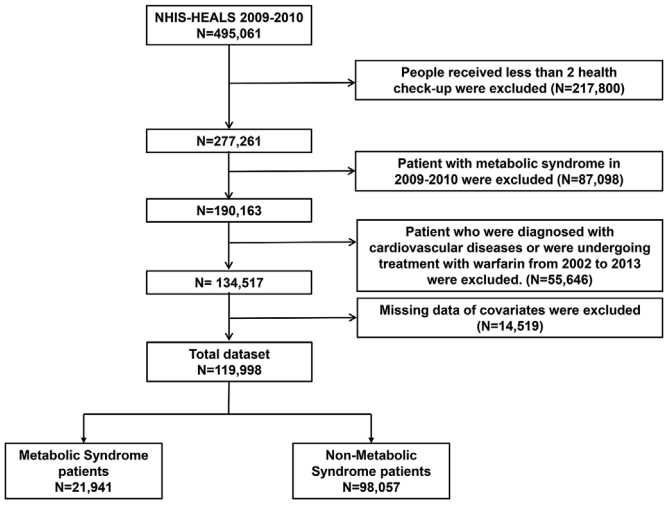

Fig. 1. Participant selection flow diagram.

The study protocol was approved by the Institutional Review Board of Ewha Womans University, College of Medicine, Republic of Korea. Informed consent was waived due to its retrospective nature.

2.2. Data collection

During the health examination, demographic and clinical data were recorded, including age, sex, waist, and body mass index (BMI). Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as the ratio of weight (kg)/height^2 (m^2). Waist circumference was measured at the narrowest point between the lower border of the rib cage and the iliac crest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after the examinee had rested for at least 5 min. When the result was greater than 120 mmHg for SBP or greater than 80 mmHg for DBP, a re-measurement was performed after an interval of 2 min or more. Blood samples were obtained from antecubital veins of participants after 8 h of overnight fasting and used to measure fasting blood glucose, triglyceride, and HDL-cholesterol levels (Kang et al., 2010). The following questionnaire data were collected at the same time when these subjects underwent health examinations: income level, smoking status, drinking habit, and walking exercise status.

2.3. Exposure assessment

To determine the individual exposure level, ambient measurement data continuously observed at air quality monitoring stations can be utilized to prepare the spatiotemporal distribution. Interpolation techniques can also be used if adequate spatial and temporal data coverages were available. Unfortunately, the national official $PM_{2.5}$ measurements were initiated in South Korea since 2015, with few $PM_{2.5}$ monitoring stations maintained prior to 2015. To ensure the efficiency of $PM_{2.5}$ observation data, we generated ambient $PM_{2.5}$ concentrations based on a three-dimensional photochemical air quality model named Community Multiscale Air Quality (CMAQ) model (http://www.cmascenter.org/cmaq/). The CMAQ model was developed by the U.S Environment Protection Agency (EPA). We utilized this model to estimate the formation, concentrations, and distribution of $PM_{2.5}$ over spatial scales (Byun and Ching, 1999). CMAQ with the aerosol module and the Statewide Air Pollution Research Center can be used to simulate time-dependent, 3-dimensional distributions of $PM_{2.5}$ using meteorological inputs based on initial chemical condition, boundary condition, and emission (Stewart et al., 2017). In order to reduce the differences in $PM_{2.5}$ concentration between the observed and the simulated data, data assimilation based on the Kriging interpolation was applied for the spots for which the observations were available. Finally, the post-processed $PM_{2.5}$ data were resampled to obtain hourly $PM_{2.5}$ concentrations for each administration in Korea (Han et al., 2018). To perform the model evaluation, we calculated R^2 and root mean squared error (RMSE) between predicted and observed $PM_{2.5}$ concentrations. The values of R^2 and RMSE of the $PM_{2.5}$ model were 0.64 and 4.17 μg/m^3, respectively, which suggested a good fitted between the predicted values and the measured values (Fig. S1).

During the follow up period, non-office workers received annual health examination while other participants received health

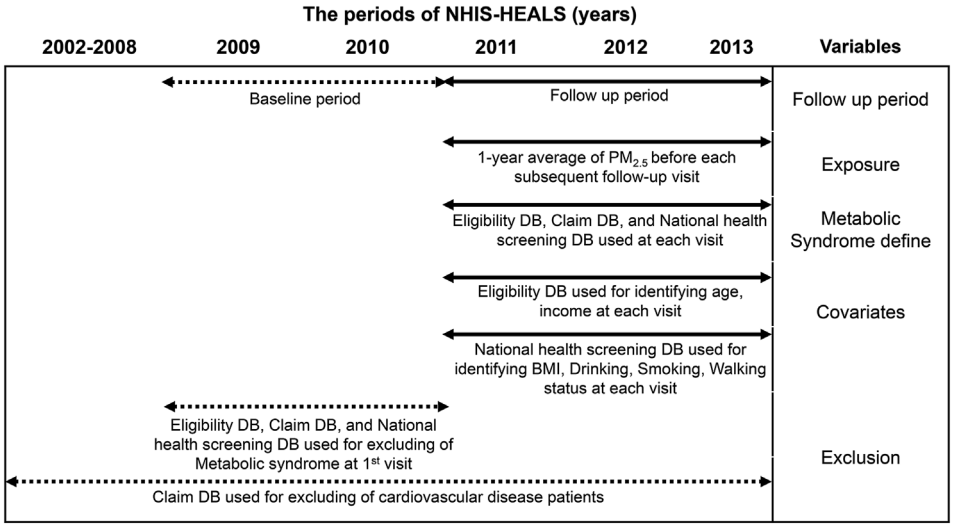

Fig. 2. Schematic diagram showing data source and periods of NHIS-HEALS used. Abbreviations: NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort; Database; DB, database; BMI, Body mass index.

examination every two years. We used $PM_{2.5}$ exposure as the time dependent variable, and assessed exposures to an average $PM_{2.5}$ level during the previous year from the day each participants received health screening during the follow-up (Chen and Schwartz, 2008; Eze et al., 2015; Wallwork et al., 2017). Each individual participant address was divided by 16 administrative divisions across South Korea: nine provinces and seven metropolitan cities (Wallwork et al., 2017). Participant's data derived from NHIS-HEALS were linked to $PM_{2.5}$ modeling data using an administrative division code (Fig. 2).

2.4. Definition of metabolic syndrome

We applied condition-specific cut points for metabolic syndrome using the criteria described by the National Cholesterol Education Program (NCEP) for Detection, Evaluation, and Treatment of High Blood Cholesterol in Adult Treatment Panel III (Expert Panel on Detection, 2001). That criteria had five components: waist-based obesity, hypertension, hypertriglyceridemia, low HDL-C, and diabetes. Waist-based obesity was defined according to ethnically specific cutoff points of waist circumference (WC). We used Korean-specific WC criteria: WC > 90 cm for men and WC > 85 cm for women (Lee et al., 2007). Hypertension was defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, treatment with antihypertensive drugs within 6 months from the date of health examination or a diagnosis of hypertension in the year of health examination. Hypertriglyceridemia was identified based on triglycerides ≥150 mg/dL for hypertriglyceridemia. Low HDL-C was identified based on HDL-C < 40 mg/dL in men or < 50 mg/dL in women. Hyperglycemia was defined as fasting glucose ≥100 mg/dL or a diagnosis of diabetes in the year of health examination.

2.5. Definition of cardiovascular disease

Cardiovascular diseases were defined based on principal and secondary diagnosis using the *International Classification of Diseases, Tenth Revision (ICD-10)*. We considered cardiovascular diseases including ischemic heart disease (I20-I25), heart rhythm disturbances (I44-I49), heart failure (I50), and cerebrovascular disease (I60-69). From 2002 to 2013, patients who had cardiovascular disease or were treated with warfarin were excluded from our study.

2.6. Statistical analysis

Continuous variables are expressed as arithmetic or geometric mean ± standard deviation while categorical variables are presented as number and percentage. To compare between groups, the student's *t*-test was used for continuous variables while Pearson's Chi-square test was used for categorical variables. The Andersen and Gill (AG) model (Castaneda and Gerritse, 2010), the extended Cox models for counting process, has been used to evaluate the association between $PM_{2.5}$ exposure and recurrent events of metabolic syndrome. This approach was formulated with increasing number of events along the time line, as follows:

$$\lambda_{ik}(t; X, \beta) = I_{ik}(t)\lambda_0(t)e^{X_{ik}\beta}$$

$\lambda_{ik}(t)$ represents the hazard function for the k^{th} event of the i^{th} subject at time t; $\lambda_0(t)$ represents the baseline hazard for all events over times; X_{ik} represents the vector of covariates process for the i^{th} individual; β is a fixed vector of coefficients of covariates; and I_{ik} is a predictable process indicating when the i^{th} individual is under observation.

The AG model assumes that the correlation between event times for a person can be explained by past events, which means that if covariates are provided, the time increments between events are not conditionally correlated (Amorim and Cai, 2015). The AG model has as number of advantages including time-varying covariates and multiple events (Castaneda and Gerritse, 2010). Therefore, we used the one-year average $PM_{2.5}$ level as the time varying exposure, based on the individual address during each visit. Moreover, the participant's age (years; continuous), BMI (kg/m^2; continuous), income level (≤30%, 31–70%, > 70%), smoking status (non, past, current), drinking habit (number of drinks per week: non, < 3 days, ≥3 days), walking status (number of walking exercises over 30 min per week: none, < 3 days, ≥3 days), statins usages (treated or untreated with statins within 6 months), antiplatelet therapy (treated or untreated with antiplatelets within 6 months), one-year average temperature, and one-year average relative humidity were used as time-varying covariates, and sex and occupation (office worker or non-office worker) were used as fixed covariates. In addition, we adjusted for calendar time (year since the first examination date) to capture the population wide period effects when conducting longitudinal model with time-varying exposures (Adar et al., 2018). Metabolic syndrome and five individual components of metabolic syndrome were modeled separately.

We additionally analyzed results from each $PM_{2.5}$ model according to sex and obesity group. The obesity group was divided based on BMI

Table 1
Characteristics of active participants at baseline visit.

Characteristic	Total[a] (N = 119,998)	Metabolic Syndrome		P-value[b]
		Non-Event[a] (N = 98,057)	Event[a] (N = 21,941)	
Age, years	55.1±7.1	54.9±7.0	56.2±7.6	< 0.001
Female sex, n (%)	53,634 (44.7)	44,486 (45.4)	9148 (41.7)	< 0.001
Body mass Index, kg/m^2	23.3±2.6	23.0±2.5	24.5±2.6	< 0.001
Waist, cm	79.4±7.4	78.7±7.2	82.8±7.0	< 0.001
Systolic blood pressure, mmHg	121.5±14.0	120.3±13.7	126.8±14.1	< 0.001
Diastolic blood pressure, mmHg	75.8±9.4	75.1±9.2	78.9±9.3	< 0.001
Triglyceride, mg/dL	104.3±1.6	99.7±1.6	127.4±1.7	< 0.001
High density lipoprotein cholesterol, mg/dL	56.4±13.1	57.2±13.2	53.1±12.2	< 0.001
Fasting blood glucose, mg/dL	95.3±18	94.2±16.4	100±23.3	< 0.001
Income level, n (%)				< 0.001
0–30%	24,750 (20.6)	19,868 (20.3)	4882 (22.3)	
31–70%	38,788 (32.3)	31,309 (31.9)	7479 (34.1)	
71–100%	56,460 (47.1)	46,880 (47.8)	9580 (43.7)	
Occupation				< 0.001
Office worker	63,472 (52.9)	52,261 (53.3)	11,211 (51.1)	
Non-office worker	56,526 (47.1)	45,796 (46.7)	10,730 (48.9)	
Smoking status, n (%)				< 0.001
Non-Smoker	75,008 (62.5)	61,967 (63.2)	13,041 (59.4)	
Past Smoker	21,162 (17.6)	17,076 (17.4)	4086 (18.6)	
Current Smoker	21,642 (18)	17,262 (17.6)	4380 (20.0)	
Missing	2186 (1.8)	1752 (1.8)	434 (2.0)	
Drinking habit, days/week, n (%)				< 0.001
Non-Drinker	66,882 (55.7)	55,182 (56.3)	11,700 (53.3)	
< 3	35,891 (29.9)	29,353 (29.9)	6538 (29.8)	
≥3	15,994 (13.3)	12,532 (12.8)	3462 (15.8)	
Missing	1231 (1.0)	990 (1.0)	241 (1.1)	
Walking ≥0.5 h, days/week, n (%)				< 0.001
None	36,554 (30.5)	29,586 (30.2)	6968 (31.8)	
< 3	27,505 (22.9)	22,633 (23.1)	4872 (22.2)	
≥3	54,689 (45.6)	44,849 (45.7)	9840 (44.8)	
Missing	1250 (1.0)	989 (1.0)	261 (1.2)	
CV drug				
Statin usages	3759 (3.1)	2427 (2.5)	1332 (6.1)	< 0.001
Antiplatelet therapy	2286 (1.9)	1324 (1.4)	962 (4.4)	< 0.001
Visit order	1.9±1.2	1.9±1.1	2.1± 1.2	< 0.001
Calendar time	2.9±1.0	2.9± 1.0	3.2± 1.0	< 0.001
Waist based obesity, n (%)	9044 (7.5)	5904 (6.0)	3140 (14.3)	< 0.001
Hypertension, n (%)	25,838 (21.5)	17,335 (17.7)	8503 (38.8)	< 0.001
Hypertriglyceridemia, n (%)	34,501 (28.8)	25,251 (25.8)	9250 (42.2)	< 0.001
Low HDL cholesterol, n (%)	16,197 (13.5)	12,433 (12.7)	3764 (17.2)	< 0.001
Hyperglycemia, n (%)	32,353 (27.0)	24,615 (25.1)	7738 (35.3)	< 0.001

[a] Geometric mean and standard deviation are presented for triglyceride while arithmetic means and standard deviations are presented for other continuous variables. Frequencies and percentages are presented for categorical variables.
[b] T-test was used for continuous variables while Chi-square test was used for categorical variables.

values (at baseline and endpoint). Obesity was defined by BMI of 25 or higher. These groups were: Normal-Normal, Normal-Obesity, Obesity-Normal, and Obesity-Obesity.

All statistical analyses were performed using R software version 3.3.3 (R Development Core Team, 2013) and SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). A *P*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of active participants at baseline visit

Table 1 shows demographic characteristics and clinical data of active participants at baseline visit. Among a total of 119,998 participants, 9044 (7.5%) had waist-based obesity, 25,838 (21.5%) had hypertension, 34,501 (28.8%) had hypertriglyceridemia, 16,197 (13.5%) had low HDL cholesterol, 32,353 (27.0%) had hyperglycemia, and 21,941 (18.3%) were diagnosed with metabolic syndrome. For those who had metabolic syndrome (female: 41.7%), their mean age was 56.2 ± 7.6 years and their mean BMI was 24.5 ± 2.6 kg/m^2. Their mean waist, SBP, DBP, triglyceride, HDL cholesterol, and hyperglycemia were 82.8 ± 7.0 cm, 126.8 ± 14.1 mmHg, 78.9 ± 9.3 mmHg, 127.4 ± 1.7 mg/dL, 53.1 ± 12.2 mg/dL, and 100.0 ± 23.3 mg/dL, respectively. Regarding income level of participants who had metabolic syndrome, 9580 (43.7%) participants had upper 30% income level and 7479 (34.1%) had middle income level (31%–70%) while the remaining 4882 (22.3%) had low income level (lower 30%).

Based on questionnaire data, among patients with metabolic syndrome, 4380 (20.0%) were current smokers at baseline visit of health examination while 17,127 (78.0%) were non-smokers (including past smokers). A total of 3462 (15.8%) participants drink alcohol more than 3 times a week while 9840 (44.8%) walk more than 30 min a day for more than 3 times a week.

According to the drug prescriptions of the subjects, among those with metabolic syndrome, 6.1% were undergoing treatment with statins and 4.4% were on antiplatelet agents. The rates of use of both drugs in patients with metabolic syndrome were higher than those without metabolic syndrome.

Fig. 3 shows the daily incidence of metabolic syndrome cases during the follow-up period (2011–2013) and daily average levels of $PM_{2.5}$ data used in the analysis (2010–2013). The median number of

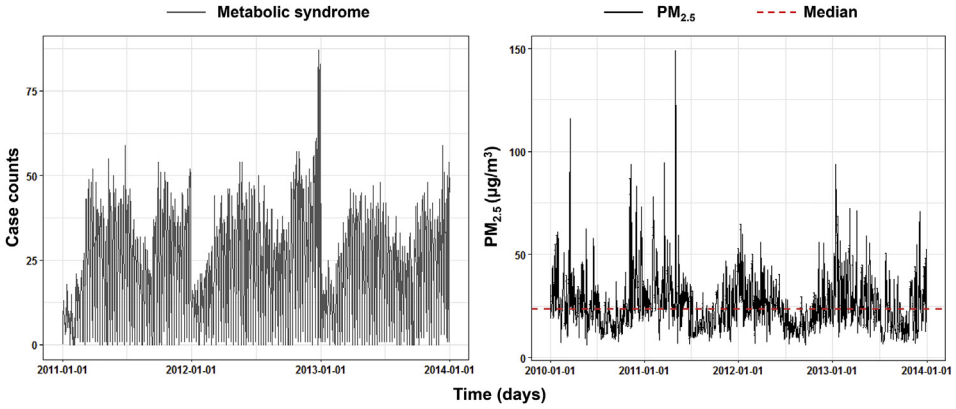

Fig. 3. Daily number of metabolic syndrome patients during follow up period (2011–2013) and daily average levels of $PM_{2.5}$ data (2010–2013) used in the analysis.

incidence of metabolic syndrome cases per day was 26 (IQR: 12 to 36) and median level of $PM_{2.5}$ over this period (2010–2013) was 23.6 μg/m^3 (IQR: 17.2–31.2 μg/m^3).

3.2. Association of PM exposure with metabolic syndrome risk and components of metabolic syndrome

The one-year average $PM_{2.5}$ level in all regions ranged from 9.1 μg/m^3 to 35.7 μg/m^3 (mean ± SD: 26.6 ± 4.0 μg/m^3). The one-year average daily temperature ranged from 5.6 °C to 11.6 °C (mean ± SD: 9.3 ± 1.3 °C) while one-year average relative daily humidity ranged from 53.3% to 76.4% (mean ± SD: 64.3 ± 4.9%) (Table 2).

Results of AG model with time-dependent covariates on the association between metabolic syndrome and one-year exposure to $PM_{2.5}$ are shown in Table 3. Participants with higher exposure to $PM_{2.5}$ had higher risk of having metabolic syndrome and its components. A 10-μg/m^3 increase in 1-year average $PM_{2.5}$ level was significantly associated with a 7% higher risk for developing metabolic syndrome after full adjustment (hazard ratio (HR) = 1.070, 95% confidence interval (CI): 1.032, 1.110). In the analysis for each component of metabolic syndrome, a 10-μg/m^3 increase in 1-year average PM2.5 level was also significantly associated with a 51% increased risk of waist based obesity (HR = 1.510, 95% CI: 1.422,1.601), a 49% increased risk of hypertension obesity (HR = 1.499, 95% CI: 1.441,1.559), a 46% increased risk of hypertriglyceridemia (HR = 1.468, 95% CI: 1.424,1.513), a 62% increased risk of low HDL-C (HR = 1.627, 95% CI: 1.564,1.693), and a 38% increased risk of hyperglycemia (HR = 1.380, 95% CI: 1.338,1.423) after full adjustment.

3.3. Association of $PM_{2.5}$ exposure with risk of metabolic syndrome according to sex and obesity group

The association between $PM_{2.5}$ and risk of metabolic syndrome was found in both men and women, although the association was stronger in men than that in women (see Table S1). Based on sex and obesity (four obesity groups according to BMI at baseline visit and at endpoint), we investigated the effects of obesity and sex on the risk of metabolic syndrome according to stratified groups (n = 8, see Table S2). We also divided 1-year average $PM_{2.5}$ levels into quartile groups (1st quartile group, 2nd quartile group, 3rd quartile group, and 4th quartile group). In the obesity-obesity group, the risk of metabolic syndrome in the 4th quartile group was significantly increased compared to the 1st quartile group in both men and women (Table 4 and Fig. 4).

Table 2
Distribution of estimated one-year average $PM_{2.5}$ level and weather conditions at participant's home address at each visit for all study participants.

Variable	Mean	SD	Min	1st Q.	Median	3rd Q.	Max
Air pollutant concentration							
$PM_{2.5}$, μg/m^3	26.6	4.0	9.1	24.3	26.7	29.3	35.7
Weather conditions							
Daily temperature range, °C	9.3	1.3	5.6	8.1	9.5	10.5	11.6
Relative humidity, %	64.3	4.9	53.3	60.4	64.5	68.7	76.4

Abbreviations: $PM_{2.5}$ indicates particulate matter < 2.5 μm in aerodynamic diameter; SD, standardized deviation; Min, minimum; 1st Q., the 25th percentile; 3rd Q., the 75th percentile; Max, maximum.

4. Discussion

The current study showed an association between higher long-term $PM_{2.5}$ exposure level and increased risk of metabolic syndrome and its individual components in Korean adults without CVD. We also found that men had stronger association of $PM_{2.5}$ with risk of metabolic syndrome than women. In addition, there was a significant association between $PM_{2.5}$ and risk of metabolic syndrome only in the consistently obesity group (obese at baseline and endpoint). Our findings indicate that exposure to PM2.5 can affect the risk of developing metabolic syndrome based on sex and obesity.

Recent studies have reported that high levels of $PM_{2.5}$ or PM_{10} can significantly increase the risk of metabolic syndrome, hypertriglyceridemia, and high fasting blood glucose (Eze et al., 2015; Wallwork et al., 2017), consistent with our results. However, our results also showed that $PM_{2.5}$ was significantly associated with abdominal obesity, low HDL cholesterol, and hypertension as well as hypertriglyceridemia and high fasting blood glucose. This finding may indicate that $PM_{2.5}$ is also significantly associated with components of metabolic syndrome when effects of CVD are removed by excluding CVD patients at baseline and considering incidence of CVD during the follow-up period. In addition, our results are consistent with results of a previous study showing that the association between PM and risk of metabolic syndrome is stronger in men than that in women (Eze et al., 2015). Our results also support a recent study showing that obesity may increase susceptibility to adverse effects of PM exposure (Cantone et al., 2017).

Exposure to $PM_{2.5}$ might affect incidence of metabolic syndrome. However, the exact biological mechanism remains unclear. Several studies support our hypothesis. For example, numerous studies have reported that exposure to PM causes oxidative stress and inflammation in organ tissues and circulation (Brook et al., 2010; Münzel et al., 2017; Wei et al., 2016). Especially, low-grade inflammation can lead to arteriosclerosis by increasing insulin resistance and reactive oxygen species that are important for the incidence of metabolic syndrome (Rebecca Negrulj, 2013). Previous studies have shown that $PM_{2.5}$ exposure generates reactive oxygen species and oxygen-centered free radicals that interfere with insulin signaling and impair vasorelaxation which may predispose individuals to metabolic dysfunction by

Table 3
Association of $PM_{2.5}$ exposure with risk of metabolic syndrome and its components.

Metabolic Syndrome Components	No. of Participants	No. of Observations	No. of Events	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Waist based obesity	132,933	138,570	16,462	1.466 (1.373,1.565)	1.510 (1.422,1.601)
Hypertension	101,970	111,268	25,263	1.359 (1.296,1.426)	1.499 (1.441,1.559)
Hypertriglyceridemia	87,417	100,117	36,676	1.493 (1.441,1.547)	1.468 (1.424,1.513)
Low HDL cholesterol	124,144	132,052	23,578	1.437 (1.368,1.508)	1.627 (1.564,1.693)
Hyperglycemia	92,806	105,733	36,558	1.313 (1.268,1.360)	1.380 (1.338,1.423)
Metabolic Syndrome	119,998	230,838	26,194	1.112 (1.071,1.154)	1.070 (1.032,1.110)

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Unadjusted model.
[b] Model 1 + age, sex, body mass index, income level, occupation, smoking status, drinking habit, walking status, statin usages, antiplatelet therapy, daily temperature range, humidity, visit order and calendar time.

contributing to insulin resistance and vascular disease (Araujo and Nel, 2009; Brook et al., 2010; Houstis et al., 2006; Hutcheson and Rocic, 2012; Münzel et al., 2017; Perticone et al., 2001). Additionally, an increase in C-reactive protein (CRP) level, an inflammatory marker, is associated with high long-term exposure to $PM_{2.5}$ level in a Taiwanese study (Zhang et al., 2017), a Women's Health Across the Nation (SWAN) study (Green et al., 2016), and Heinz Nixdorf Recall (HNR) study (Viehmann et al., 2015). A significant positive association between CRP and $PM_{2.5}$ was reported in a controlled human exposure study of subjects with metabolic syndrome, but not in healthy adults (Graff et al., 2009; Samet et al., 2009). Furthermore, Chen and Schwartz (2008) have found that the observed inflammatory response reflected by white blood cell is increased in populations having more components of metabolic syndrome.

In particular, obesity has been recognized as a major trigger in the pathogenesis of metabolic syndrome (Wärnberg and Marcos, 2008). In previous studies, obesity represents an inflammatory state that might be associated with the release of pro-inflammatory cytokines from fat cells (Zafar et al., 2018). Obese patients also have high circulating CRP levels (Dubowsky et al., 2006; Zeka et al., 2006). In addition, Cantone et al. (2017) have found a negative association between PM exposure and DNA methylation of inflammatory genes in healthy overweight/obese participants. This result suggests that exposure to PM in the obesity group may regulate the transcription of inflammatory gene pathways. These studies strongly support our findings that exposure to $PM_{2.5}$ in the consistent obese group is associated with a higher risk of metabolic syndrome because obesity and $PM_{2.5}$ exposure may have a combined effect, suggesting a possible mechanism for this association.

This study has several limitations. First, the NHIS-HEALS database included 10% of all participants who received health examination between 2002 and 2003 using simple random sampling. They were followed up until 2013 (Lee et al., 2016; Seong et al., 2017). Thus, these data could not represent the whole Korean population. Second, in Korea, health examination is conducted every other year for individuals aged above 40 year. We analyzed subjects who were regularly screened, who may be relatively health-conscious and potentially avoided typical health problems through a health-conscious lifestyle. Third, we only accessed our participants' home addresses to the level of administrative division due to ethical consideration for privacy. Thus, we could not link more sophisticated exposure to individuals. Finally, since modeling $PM_{2.5}$ data used in our study had limitation in that values were estimated to be smaller than measured monitoring values (Fig. S1), the hazard ratios of our study might have been underestimated compared to the actual hazard ratios.

Nevertheless, the major strength of this study was that we used a relatively large cohort database and the large number of cases derived from a population-based cohort were used, thus our data could minimize the uncertainty of random error when collecting detailed information on covariates (Ritz and Wilhelm, 2008). We were also able to reflect changes in covariates during the follow-up period using repeated data measurements of each individual. Indeed, many CVD patients might already have metabolic syndrome or its components. This study emphasized that PM was a risk factor for metabolic syndrome in study participants without CVD. To the best of our knowledge, this is a baseline study that reports association between $PM_{2.5}$ and the risk of metabolic syndrome and its individual components in Korean adults without CVD.

5. Conclusions

In conclusion, we showed that long-term exposure to higher $PM_{2.5}$ increased the risk of metabolic syndrome and its components in general population without CVD. Our results were particularly prominent in the consistently obesity group. However, long-term $PM_{2.5}$ exposure was

Table 4
Association of $PM_{2.5}$ exposure with risk of metabolic syndrome according to sex and obesity.

Quartile group of 1-year average $PM_{2.5}$ exposure	Normal[a]-Normal HR[c] (95% CI)	Normal-Obesity[b] HR[c] (95% CI)	Obesity-Normal HR[c] (95% CI)	Obesity-Obesity HR[c] (95% CI)
Man (ref: 1st quartile)[d]				
2nd quartile[d]	1.020 (0.952,1.092)	0.986 (0.848,1.146)	1.034 (0.842,1.270)	1.016 (0.942,1.097)
3rd quartile[d]	1.014 (0.946,1.087)	0.971 (0.832,1.134)	0.968 (0.787,1.191)	1.006 (0.929,1.088)
4th quartile[d]	0.985 (0.912,1.065)	0.992 (0.834,1.180)	1.104 (0.890,1.368)	1.112 (1.020,1.212)
Woman (ref: 1st quartile)[d]				
2nd quartile[d]	0.953 (0.881,1.030)	1.113 (0.914,1.354)	0.886 (0.701,1.120)	1.070 (0.972,1.177)
3rd quartile[d]	0.941 (0.868,1.020)	1.062 (0.865,1.303)	0.834 (0.657,1.059)	1.022 (0.926,1.128)
4th quartile[d]	0.969 (0.890,1.054)	0.999 (0.807,1.237)	0.928 (0.717,1.200)	1.114 (1.004,1.235)

Abbreviations: HR, hazard ratio; CI, confidence interval; ref, reference.
[a] Body mass index < 25.
[b] Body mass index ≥ 25.
[c] Adjusted hazard ratio for age, income level, occupation, smoking status, drinking habit, walking status, statin usages, antiplatelet therapy, daily temperature range, humidity, visit order and calendar time.
[d] Quartile groups of 1-year average $PM_{2.5}$.

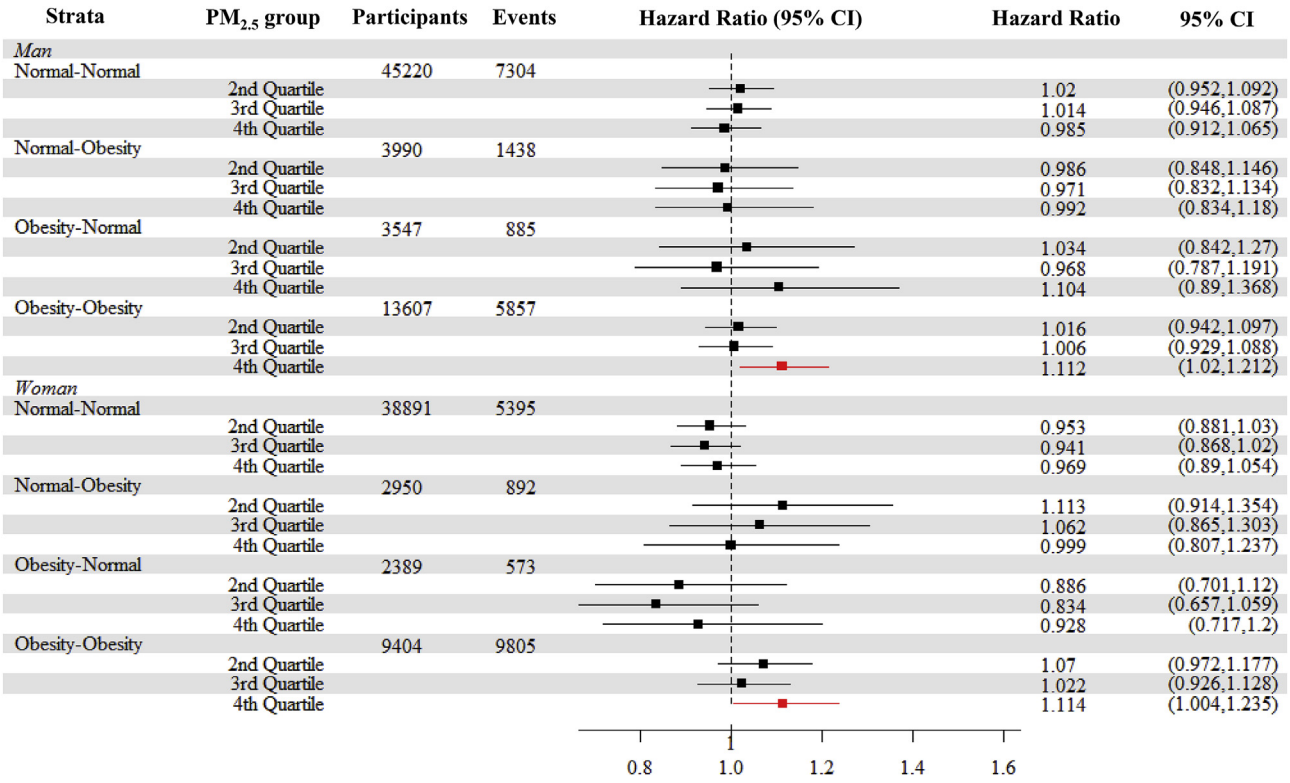

Fig. 4. Association of $PM_{2.5}$ exposure with risk of metabolic syndrome according to sex and obesity group. Andersen-Gill's approach was used in the each of eight groups according to sex and obesity. One-year average $PM_{2.5}$ levels were divided by quartile groups (1st quartile group, 2nd quartile group, 3rd quartile group, and 4th quartile group). The 1st quartile group was the reference group used in the model. Models were adjusted for age, income level, occupation, smoking status, drinking habit, walking status, statin usages, antiplatelet therapy, daily temperature range, humidity, visit order, and calendar time. Association was presented as hazard ratio with 95% confidence interval (CI).

significantly correlated with the risk of metabolic syndrome in the overall population. Therefore, individuals exposed to $PM_{2.5}$ should be aware of the high risk of metabolic syndrome that might lead to the progression of CVD.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.01.010.

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