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Original article

Long-term fine particulate matter exposure and cardiovascular mortality in the general population: a nationwide cohort study

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ABSTRACT

Background: Although eastern Asian countries are exposed to high levels of air pollution, the impact of long-term exposures to fine particulate matter ($PM_{2.5}$) air pollution on all-cause and cardiovascular mortality is not well identified. We assessed the relationship between long-term $PM_{2.5}$ exposure and all-cause/cardiovascular mortalities.

Methods: We included 436,933 subjects who received national health examinations from the Korean National Health Insurance Service-based National Sample Cohort. We matched subjects' residential-address areas with hourly-measurements of $PM_{2.5}$ concentration data. We estimated the risk of mortality with average $PM_{2.5}$ exposure during the study period using a Cox proportional-hazards model.

Results: During 1,683,271 person·years, all-cause and cardiovascular mortalities were observed in 6432 and 1603 subjects (382 and 95 per 100,000 person·years, respectively). An increase in 10 $\mu g/m^3$ in $PM_{2.5}$ was associated with increases in all-cause and cardiovascular mortalities by 3.4 % [2.7–4.1] and 4.7 % [3.6–5.8], respectively (each $p < 0.001$). $PM_{2.5}$ was linearly and significantly correlated with these all-cause and cardiovascular mortalities above 18 $\mu g/m^3$ of $PM_{2.5}$ ($p < 0.001$), but it was not significant below 18 $\mu g/m^3$ of $PM_{2.5}$. To investigate the specific $PM_{2.5}$ concentration for raising cardiovascular mortality more, we analyzed the sensitivities/specificities for different $PM_{2.5}$ levels, and 18 $\mu g/m^3$ showed the highest Youden's index (sensitivity + specificity-1) with c-index of 0.85 (0.84–0.86). $PM_{2.5}$ effect on all-cause mortality was more profound in subjects with previous myocardial infarction compared to the opposite population.

Conclusions: In the Korean general population exposed to high-air pollution, long-term $PM_{2.5}$ exposure was linearly associated with increased risk for all-cause and cardiovascular mortality, especially above 18 $\mu g/m^3$ of $PM_{2.5}$.

Introduction

Epidemiological studies from Western countries have suggested that elevated ambient particulate matter <2.5 μm ($PM_{2.5}$) in aerodynamic diameter are consistently associated with adverse cardiovascular events or even mortality [1]. The suggested mechanism is that these events are associated with various systemic inflammatory responses after inhalation [2–4]. Current air quality standards in the USA and European societies are based on a 3-year average of the annual arithmetic means of $PM_{2.5}$ concentration [5,6], but clear evidence of a threshold $PM_{2.5}$ concentration associated with increased risks of cardiovascular or all-cause mortality is lacking [1,7,8]. As the average air pollutant concentration is much lower in the USA [5] and European [6] countries (Supplementary Fig. 1) compared to eastern Asian [9] countries (who are affected by Asian dust phenomenon from the

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industrial facilities and the Gobi Desert in Central Asia thought to produce more than 20 % of global dust emissions via westerly wind) [10,11]; the effect sizes could be lower in the USA and European countries. Besides, concentration-responsive harmful effects of long-term exposures of $PM_{2.5}$ on cardiovascular mortality have not been well-identified in these countries exposed to higher levels of air pollution. Accordingly, accurately identifying such exposure effects and allocating necessary attention and resources to the underlying conditions are crucial for successful patient care and prophylaxis.

We conducted a large, comprehensive study using a Korean cohort covering the general population in an attempt to identify the association between long-term exposure to $PM_{2.5}$ and all-cause/cardiovascular mortalities. We also investigated whether there was the specific $PM_{2.5}$ concentration more associated with increased risks of these mortalities. Subgroup analyses were performed to investigate $PM_{2.5}$-related mortality according to cardiovascular comorbidities.

Methods

The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Yonsei University College of Medicine, and informed consent was waived.

Data source

This study was based on the Korean National Health Insurance Service (NHIS)-based National Sample Cohort (NSC) database. This sample cohort (n = 1,025,340) was extracted by probability sampling, not by a randomized sampling method, from all beneficiaries of the National Health Insurance and National Medical Aid in 2002 based on the entirety of the national cohort data. Systematic sampling was acquired from each of the 1476 strata based on age, sex, eligibility status, socioeconomic status, and income level, with the sample size proportionate to the cohort size of the strata. The sample's representativeness was examined previously by comparing the sample and the entire Korean population [12].

The NSC database consisted of the three following datasets: (i) sociodemographic information of the beneficiaries, (ii) medical claims including information on diagnoses based on the 10^{th} revision of the International Classification of Disease (ICD-10) codes, outpatient (including individual physician office) visits, admission, and treatment, (iii) and National Health Examination data of the cohort members. The National Health Examination dataset was created for the entire Korean population from 2002 to 2013 by the National Health Insurance Corporation. The National Health Examination was conducted biennially with regular blood tests including serum creatinine (mL/min), chest X-rays, physical examinations, and detailed questionnaires regarding medical history and lifestyle behaviors (smoking and alcohol intake). The death registration database of the Korea National Statistical Office, which includes the date and cause of death, was linked with the NHIS cohort database. Every subject in the sample cohort was linked using Korean social security numbers, and all social security numbers were deleted after constructing the cohort by assigning serial numbers to each subject to prevent leakage of personal information.

Study cohort

This study used the Korean NHIS-based NSC database from 2002 to 2013 [12]. Among the entire South Korean population (about 47 million people in 2002), 96.6 % were registered in the NHIS. About 70 % of the entire cohort underwent a National Health Examination. Adults over 18 years of age who received a National Health Examination at least once between 2009 and 2013 (n = 506,805) among the total population (n = 1,025,340) were included in the NHIS-NSC (NHIS-2016-2-189) (Fig. 1) [12]. Each was followed from health examination day to 31 December 2013. To apprehend enrolled subjects' past medical history, they were screened from January 2002 to December 2008 (2002-2008: disease-free baseline period). Past medical histories, such as heart failure, hypertension, diabetes mellitus, stroke, myocardial infarction (MI), peripheral vascular disease, or atrial fibrillation diagnosed before undergoing a health examination, were assessed based on the ICD-10 codes (Supplementary Table 1). Each diagnosis was defined as the first occurrence during at least two different days of outpatient hospital visits or on the first hospital admission (Supplementary Table 1) [13,14]. The following exclusion criteria were applied (Fig. 1): (i) under the age of 18 years, (ii) changed residence to another region in 2009–2013, and (iii) missing data regarding residential-address, smoking status, and alcohol intake. A final population of 436,933 subjects was included in the analysis (Fig. 1). For sensitivity analysis, we excluded those with current- or former-smokers because smoking status is a major confounding factor to analyze true air pollution effects. After that, a population of 272,264 subjects with non-smokers was included in the sensitivity analysis to investigate the robustness of our main analysis. The cohort was followed to the time of death; to a condition disqualifying receipt of the NHIS services, such as emigration; or to the end of the study (31 December 2013).

Air pollution measurements and national ambient air quality standards

$PM_{2.5}$, O_3, temperature, and humidity were measured hourly during the study period at the 313 sites of the Korean Nationwide Meteorological Observatory by the Korean Department of Environmental Protection. The entire Korean area was divided into 256 residential-addresses, including 74 address areas within metropolitan areas (average 73 km^2). The nearest monitor to each residence was identified and used to assess the average annual pollutant concentration for each study subject [15]. Long-term average (during the total study period for each subject) air pollutant concentrations were calculated from these hourly measurements for each site.

Geographically-based long-term average of each air pollutant concentration ($PM_{2.5}$ and O_3) was measured hourly by the monitoring facilities during the study period [16], and each residential-address area was matched with the nearest monitoring facilities. If a residential area was halfway between two monitors, average concentration of these monitors was applied at this residential area.

The annual National Ambient Air Quality Standards (NAAQS) of $PM_{2.5}$ for each society differed from country to country: <12, <25, <10, and <15 $\mu g/m^3$ for the USA, European Union, World Health Organization, and Korea, respectively [5,9,17].

Clinical variables and outcomes

The clinical variables and the frequency and proportion of all-cause or cardiovascular mortalities were described depending on the Korean annual NAAQS of $PM_{2.5}$ (15 $\mu g/m^3$) [9]. The primary outcomes were the concentration-response relationships between $PM_{2.5}$ and all-cause or cardiovascular mortality. All-cause mortality was determined by counting the number of deaths of any cause. Cardiovascular mortality was defined as the immediate cause of death provided on the death certificate focusing on MI (I21-23), heart failure (I11.0, I50), peripheral vascular diseases (I71-74), and

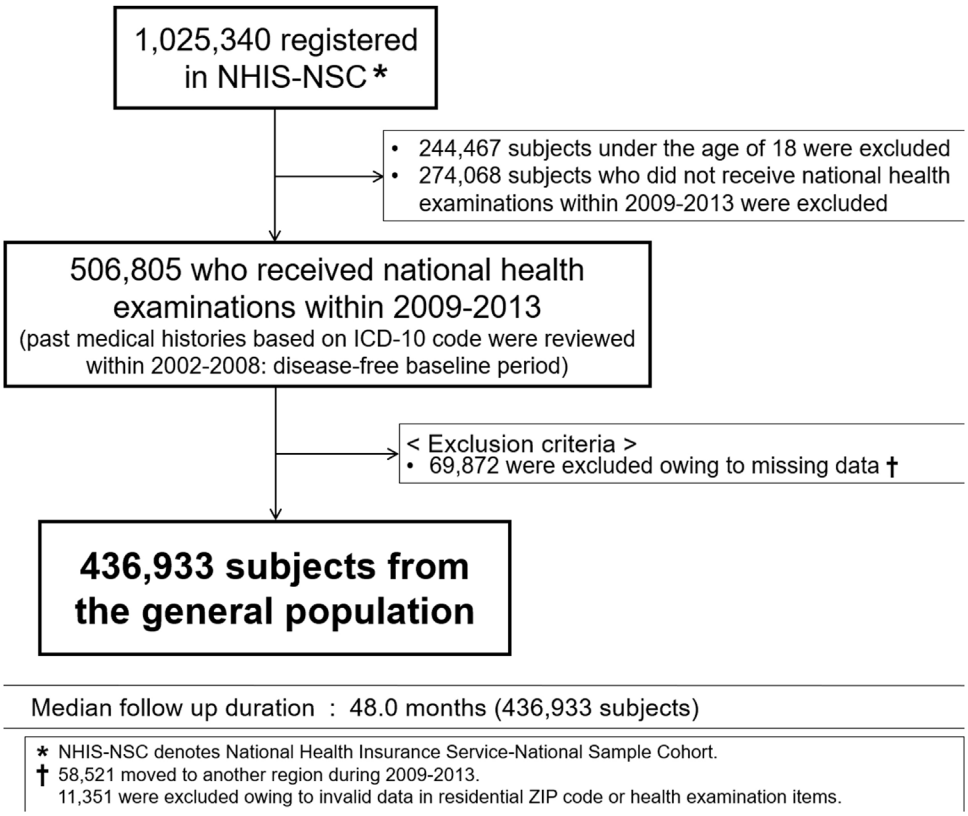

Fig. 1. Study cohort and included subjects in NHIS-NSC (overall general population).

ischemic and hemorrhagic stroke (I60-64) [18]. For stroke history, we investigated cerebral bleeding and infarction (ICD-10 code: I60-64) and excluded transient ischemic attacks (G45) or other kinds of thromboembolisms. The accuracy of the diagnosis of stroke in the NHIS database was also previously validated [12].

Life-style factors

Past medical histories were analyzed using medical claim data with ICD-10 codes (Supplementary Table 1) and using questionnaires regarding disease history and measurements of blood pressure and fasting blood glucose levels collected during health examinations. Subjects were classified as obese [body mass index (BMI) $\geq$27.5 kg/m^2], overweight (23.0–27.4 kg/m^2), normal BMI (18.5–22.9 kg/m^2), and underweight ($<$18.5 kg/m^2) [19]. Smoking status was classified as non-, $<$20 pack·years or $\geq$20 pack·years (former- or current-) smokers. The amounts of alcohol intake were classified as 0–220.5 g/week or $\geq$220.5 g/week.

Statistical analyses

Cox proportional-hazards model regression analyses were used to analyze the association between average $PM_{2.5}$ concentration during the study period and all-cause or cardiovascular mortalities with adjustments for confounding variables. Models adjusting for the clinical variables [including age, sex, body mass index (BMI), socioeconomic status, heart failure, hypertension, dyslipidemia, diabetes, previous stroke/transient ischemic attack (TIA) history, previous MI or peripheral vascular disease, serum estimated glomerular filtrate rate, and lifestyle factors such as smoking status and alcohol intake] were used to assess these associations [20]. To adjust for potential confounders, we fit a two-pollutant Cox-regression analysis [1,21] to assess correlations between each pollutant and mortality (all-cause and cardiovascular). These mortalities associated with $PM_{2.5}$ exposure was adjusted for O_3 exposure each. Mortality events were analyzed with geographically-based long-term average of each air pollutant concentration during the study period for each subject. Included subjects were followed from their national health examination until development of death, disqualification (immigration), or the end of study in Cox-regression analysis.

We assumed that the study subjects were exposed to ambient air pollution within their residential-address areas during the study period [1]. Individual subjects were matched with average air pollution concentrations during the study period from their nearest monitoring facilities according to their residential address. The relationships between $PM_{2.5}$ and all-cause or cardiovascular mortality were analyzed by a Cox proportional-hazard model regression analysis using a generalized estimating equation approach with a random effects analysis [22,23].

To minimize the effects of the potential sources of confounders and to investigate the robustness of our study results, a sensitivity analysis was performed: an analysis for subjects with non-smokers (see Methods – Study Cohort) to investigate the pure air pollution effect on mortality in these population. Linear estimates of hazard ratio about concentration-response relationship between air pollution and mortality were tested by log-linear model with a thin-plate spline for $PM_{2.5}$ with adjusting age and sex. Also, we estimated the predictive accuracy of $PM_{2.5}$ for all-cause and cardiovascular mortality by calculating the c-index on the basis of the receiver operating characteristic (ROC) curve from logistic regression models. To investigate the specific $PM_{2.5}$ concentration for raising these mortalities more, we analyzed the sensitivities and specificities for different $PM_{2.5}$ levels and determined the point having the highest Youden's index (sensitivity + specificity - 1) [24].

Table 1
Cohort characteristics according to average $PM_{2.5}$ level (≥15 or <15 μg/m^3 based on the annual NAAQS of Korea) (n = 436,933).

Variables	Entire cohort	$PM_{2.5}$ concentration ≥15 μg/m^3	<15 μg/m^3
Person, n	436,933	353,209	83,724
All-cause deaths, n (per 100,000 person·year)	6432 (382)	5302 (390)	1130 (350)
Cardiovascular deaths, n[a] (per 100,000 person·year)	1603 (95)	1496 (98)	107 (82)
Median follow-up year	4.0	4.0	4.0
Average $PM_{2.5}$ concentration (/m^3)	18.8	20.3	12.2
Male sex (%)	(50.1)	(50.1)	(50.2)
Age, years (mean)	47.8	47.3	49.6
≥75 (%)	(3.5)	(3.4)	(4.1)
BMI, kg/m^2 (mean)	23.7	23.6	23.9
Obesity (BMI ≥ 27.5 kg/m^2) (%)	(11.9)	(11.6)	(12.9)
Smoking, pyrs (mean)	6.1	6.0	6.3
Non- (%)	(61.4)	(61.2)	(62.1)
<20pyrs (%)	(24.3)	(24.5)	(23.6)
≥20pyrs (%)	(12.9)	(12.8)	(13.3)
Alcohol intake, g/week (mean)	62.8	62.6	63.5
≥220.5 g/week	(8.0)	(8.0)	(8.2)
Socioeconomic status, higher[b] (%)	(60.5)	(60.1)	(62.3)
Hypertension (%)	(22.1)	(20.5)	(29.2)
Diabetes (%)	(6.4)	(6.0)	(8.1)
Dyslipidemia (%)	(19.6)	(18.8)	(23.2)
CKD (%)	(6.0)	(5.9)	(6.5)
Previous MI (%)	(1.0)	(1.0)	(1.3)
Peripheral vascular disease (%)	(2.5)	(2.4)	(2.8)
HF (%)	(2.5)	(2.4)	(2.9)
Previous stroke/TIA (%)	(3.9)	(3.7)	(4.7)
Previous history of AF (%)	(1.6)	(1.7)	(1.2)
Medications at enrollment			
Antiplatelet agent (%)	(10.0)	(9.5)	(12.2)
Beta-blocker (%)	(7.8)	(7.4)	(9.6)
Statin (%)	(8.5)	(8.1)	(10.2)

AF, atrial fibrillation; BMI, body mass index (kg/m^2); CKD, chronic kidney disease; HF, heart failure; MI, myocardial infarction; NAAQS, National Ambient Air Quality Standards; $PM_{2.5}$, particulate matter <2.5 μm in diameter; pyrs, pack·years; TIA, transient ischemic attack.
[a] Cardiovascular death was defined as the immediate cause of death provided on the death certificate focusing on MI (I21-23), HF (I11.0, I50), peripheral vascular diseases (I71-74), and ischemic and hemorrhagic stroke (I60-64) (See Methods).
[b] In our cohort, socioeconomic status was divided into 11 categories (0∼10) and was applied in main analysis. In this Table, socioeconomic status was divided into two groups: higher (6∼10 categories of income level) and lower (0∼5 categories of income level).

A p-value of <0.05 was considered statistically significant. The proportionality of the hazards assumption was checked with a log minus log graph and a test on the Schoenfeld residuals, and as a consequence, the test results were found to be valid for each life-style factor. All-cause and cardiovascular mortality events in Figs. 2, 4, and 5 are represented as 'age-, sex-adjusted mortality event rates per 100,000 person·year' to provide more accurate comparisons among groups because the follow-up time periods differed among groups. Age- and sex-adjustment was calculated by age and sex stratification with dividing 5-year of age groups. All statistical analyses were performed with R software (version 3.5.2; R Project for Statistical Computing) and SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Overall, the entire cohort included 436,933 subjects who received national health examinations within 2009–2013 with 1,683,271 person·years of follow-up. Total all-cause and cardiovascular deaths occurred in about 382 and 95 (per 100,000 person·year) of the study population, respectively. Daily $PM_{2.5}$ levels were within 10–45 μg/m^3 during 77.0 % of measurement days of the study period (Supplementary Fig. 2). To understand cohort characteristics according to average $PM_{2.5}$ level, we divided subjects into average $PM_{2.5}$ concentration exposure ≥15 μg/m^3 or <15 μg/m^3 groups based on NAAQS of Korea. The average $PM_{2.5}$ concentrations during the study period for these groups were measured as 20.3 and 12.2 μg/m^3, respectively (Table 1). Although younger with lower proportions of hypertension and diabetes histories, there were more all-cause (390 versus 350 subjects per 100,000 person·years, $p < 0.001$) and cardiovascular deaths (98 versus 82 subjects per 100,000 person·years, $p < 0.001$) when average $PM_{2.5}$ concentration was above 15 μg/m^3 compared to the remainder of the population during median 4.0 years of follow-up (Table 1). The risks of all-cause and cardiovascular mortalities are described in Table 2.

Ambient $PM_{2.5}$ air pollution is associated with increased all-cause and cardiovascular mortality

(***Air pollution and meteorological measurements*** are described in detail in the Supplementary Results.)

Fig. 2A and B show age- and sex-adjusted mortality events (per 100,000 person·years) for all-cause and cardiovascular causes, and each increase of $PM_{2.5}$ concentration was associated with increased risk (each $p < 0.01$). In Cox proportional-hazards models using covariates of clinical variables, an increase in $PM_{2.5}$ concentration of 10 μg/m^3 was associated with increased risks of all-cause [HR 1.034 (1.027–1.041), $p < 0.001$] and cardiovascular [HR 1.047 (1.036–1.058), $p < 0.001$) mortality (Table 3; and Supplementary Table 3 for sensitivity analysis).

Above 18 μg/m^3 of $PM_{2.5}$ concentration associated with more increased risks of mortality

We fit age- and sex-adjusted Cox proportional-hazards log-linear models with thin-plate spline curves to $PM_{2.5}$, and an

Table 2
Comorbidities and the risk of mortality based on Cox regression analysis (overall general population, n = 436,933).

	All-cause death Adjusted HR (95 % CI)[b]	*p*-value	Cardiovascular death[c] Adjusted HR (95 % CI)[b]	*p*-value
$PM_{2.5}$ (by 10 μg/m^3 increase)[a]	1.034 (1.027–1.041)	<0.001	1.047 (1.036–1.058)	<0.001
Age	1.099 (1.097–1.102)	<0.001	1.112 (1.107–1.118)	<0.001
Male sex	2.003 (1.889–2.124)	<0.001	1.519 (1.342–1.720)	<0.001
BMI	1.122 (1.112–1.131)	<0.001	1.134 (1.050–1.153)	<0.001
Hypertension	1.252 (1.177–1.331)	<0.001	1.531 (1.343–1.747)	<0.001
Diabetes	1.558 (1.458–1.664)	<0.001	2.191 (1.950–2.461)	<0.001
Dyslipidemia	1.152 (1.086–1.222)	<0.001	1.176 (1.050–1.319)	0.005
Heart failure	1.539 (1.421–1.667)	<0.001	1.694 (1.480–1.938)	<0.001
CKD	1.345 (1.264–1.432)	<0.001	1.550 (1.384–1.736)	<0.001
Previous MI	1.405 (1.210–1.632)	<0.001	1.473 (1.216–1.785)	<0.001
Peripheral vascular disease	1.085 (1.008–1.169)	<0.001	1.126 (1.025–1.249)	<0.001
Previous stroke/TIA	1.325 (1.237–1.426)	<0.001	1.763 (1.564–1.987)	<0.001
Previous history of AF	1.314 (1.148–1.496)	<0.001	1.536 (1.167–1.968)	<0.001
Smoking (non-smoker vs. smoker)	1.162 (1.076–1.256)	<0.001	1.099 (0.932–1.295)	0.262
Alcohol intake habit (<220.5 vs. ≥ 220.5 g/week)	1.331 (1.242–1.426)	<0.001	1.227 (1.062–1.418)	0.005

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease with estimated glomerular filtration rate less than 60 mL/min; HR, hazard ratio; MI, myocardial infarction; $PM_{2.5}$, particulate matter <2.5 μm in diameter; TIA, transient ischemic attack.
[a] To adjust for potential confounders, we fit a two-pollutant Cox regression analysis to assess the correlations between $PM_{2.5}$ and mortality by each cause. Risks of all-cause and cardiovascular mortality associated with $PM_{2.5}$ exposure were adjusted for O_3 exposure.
[b] Clinical variables-adjusted hazard ratios are shown. Clinical variables were age, sex, BMI, socioeconomic status, heart failure, hypertension, dyslipidemia, diabetes, previous stroke/TIA history, previous MI or peripheral vascular disease, serum estimated glomerular filtrate rate, smoking status and alcohol intake habit.
[c] Cardiovascular death was defined as the immediate cause of death provided on the death certificate focusing on MI (I21-23), heart failure (I11.0, I50), peripheral vascular diseases (I71-74), and ischemic and hemorrhagic stroke (I60-64) (See Methods).

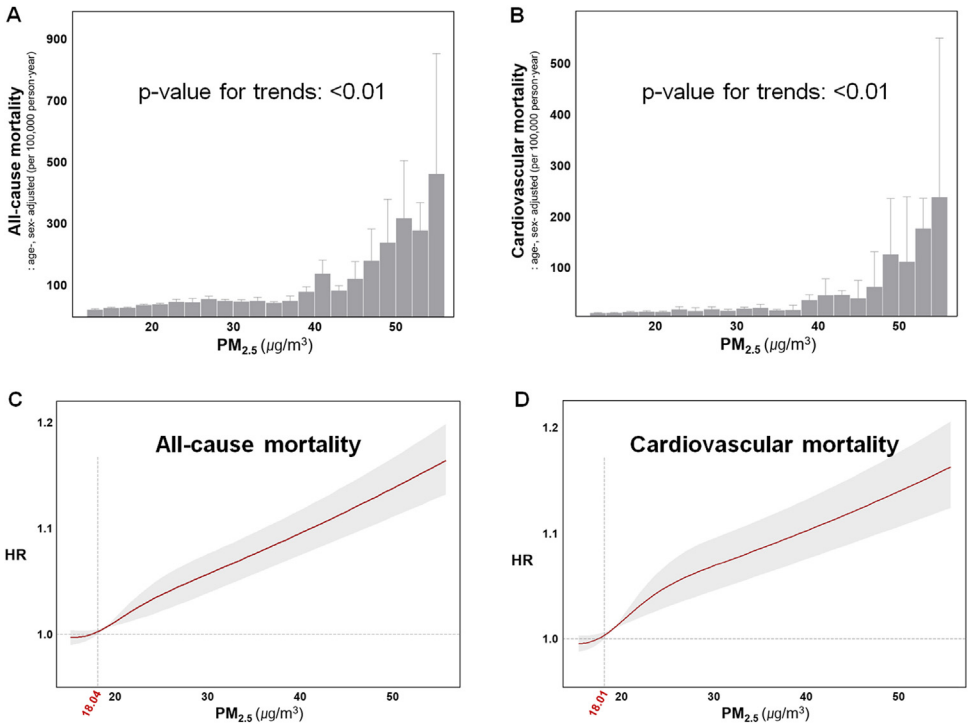

Fig. 2. (A and B) All-cause (A) and cardiovascular (B) mortality events according to $PM_{2.5}$ concentration. Association trends were analyzed by linear regression for each concentration with age- and sex-adjusted mortality event rates.
(C and D) Concentration-response relationships between long-term exposures of $PM_{2.5}$ and all-cause (C) and cardiovascular (D) mortalities tested by log-linear model with thin-plate splines (age- and sex-adjusted HRs). C and D panel also showed the specific $PM_{2.5}$ concentration (which showed lower 95 % CI more than 1.0 of HR) being associated with more increased mortalities.
CI, confidence interval; HR, hazard ratio; $PM_{2.5}$, particulate matter <2.5 μm in diameter.

increment of $PM_{2.5}$ concentration was significantly associated with increased risks for all-cause and cardiovascular mortalities (Fig. 2C and D). Relationships between $PM_{2.5}$ and these mortalities were almost linear above 18.0 μg/m^3. No significant correlations for these mortalities below 18.0 μg/m^3 of $PM_{2.5}$ (HR with its 95 % CI were more than 1.0 above 18.0 μg/m^3 of $PM_{2.5}$, Fig. 2C and D) were demonstrated (Supplementary Fig. 3 for sensitivity analysis).

Fig. 3A and B show the ROC curves based on $PM_{2.5}$ concentration for these associations with all-cause and cardiovascular mortality. The c-indices of $PM_{2.5}$ for the prediction models concerning these associations were 0.82 (0.81–0.83) and 0.85 (0.84–0.86), respectively. The specific levels of $PM_{2.5}$ for being associated with greater increased risk of these mortalities were both analyzed as 18 μg/m^3 based on the highest Youden's index (Fig. 3A, B, and Supplementary

Table 3
$PM_{2.5}$ and the risk of mortality (overall general population, n = 436,933).

Mortality risks[a] (by 10 μg/m³ increase of $PM_{2.5}$)	HR (95 % CI)	*p*-value
All-cause deaths		
Crude (95 % CI)	1.075 (1.067–1.082)	<0.001
Adjusted (95 % CI)[b]	1.034 (1.027–1.041)	<0.001
Cardiovascular deaths[c]		
Crude (95 % CI)	1.097 (1.086–1.108)	<0.001
Adjusted (95 % CI)[b]	1.047 (1.036–1.058)	<0.001

CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; $PM_{2.5}$, particulate matter <2.5 μm in diameter.
[a] To adjust for potential confounders, we fit a two-pollutant Cox regression analysis to assess the correlations between $PM_{2.5}$ and mortality by each cause. Risks of all-cause and cardiovascular mortality associated with $PM_{2.5}$ exposure were adjusted for O_3 exposure.
[b] Clinical variables-adjusted hazard ratios are shown. Clinical variables were age, sex, body mass index, socioeconomic status, heart failure, hypertension, dyslipidemia, diabetes, previous stroke/transient ischemic attack history, previous myocardial infarction or peripheral vascular disease, serum estimated glomerular filtrate rate, smoking status, and alcohol intake habit.
[c] Cardiovascular death was defined as the immediate cause of death provided on the death certificate focusing on MI (I21-23), HF (I11.0, I50), peripheral vascular diseases (I71-74), and ischemic and hemorrhagic stroke (I60-64) (See Methods).

Tables 4,5; and Supplementary Fig. 4 and Supplementary Tables 6,7 for sensitivity analysis).

For comprehensive analysis, we divided subjects according to ≥18 μg/m³ or <18 μg/m³ of average $PM_{2.5}$ exposure level. There were more all-cause (388 versus 376 subjects per 100,000 person·year, $p < 0.001$) and cardiovascular deaths (102 versus 88 subjects per 100,000 person·year, $p < 0.001$) when average $PM_{2.5}$ concentration was above 18 μg/m³ compared to the remainder of the population during the study period (Supplementary Table 8; and Supplementary Table 9 for sensitivity analysis). Kaplan-Meier graphs also showed that there were higher all-cause or cardiovascular deaths when average $PM_{2.5}$ concentration was above 18 μg/m³ compared to the remainder of the population (each log-rank $p < 0.001$, Fig. 3C and D).

Subgroup analyses

In all subgroups, the increase of $PM_{2.5}$ increased the risk of all-cause (Fig. 4) and cardiovascular deaths (Fig. 5). $PM_{2.5}$ exposure effect on all-cause mortality was more profound in subjects with previous MI compared to the opposite population (interaction $p = 0.018$, Fig. 4). There were nonsignificant higher trends of increased risk of all-cause or cardiovascular mortality among men, older subjects (≥60 years); subjects with a history of heart failure, atrial fibrillation, and stroke; and those who were obese (BMI ≥ 27.5 kg/m²) or underweight (BMI < 18.5 kg/m²) than in those who were not (Fig. 3A and 3B). Interestingly, these correlations were diminished among subjects who were heavy smokers (≥20 pack·years) compared to non-smokers [each HR was 1.026 (1.010–1.042) and 1.044 (1.035–1.053) with interaction $p = 0.029$] (Fig. 4).

Discussion

Main findings

In this nationwide study using a large cohort covering the Korean general population, which showed much higher level of

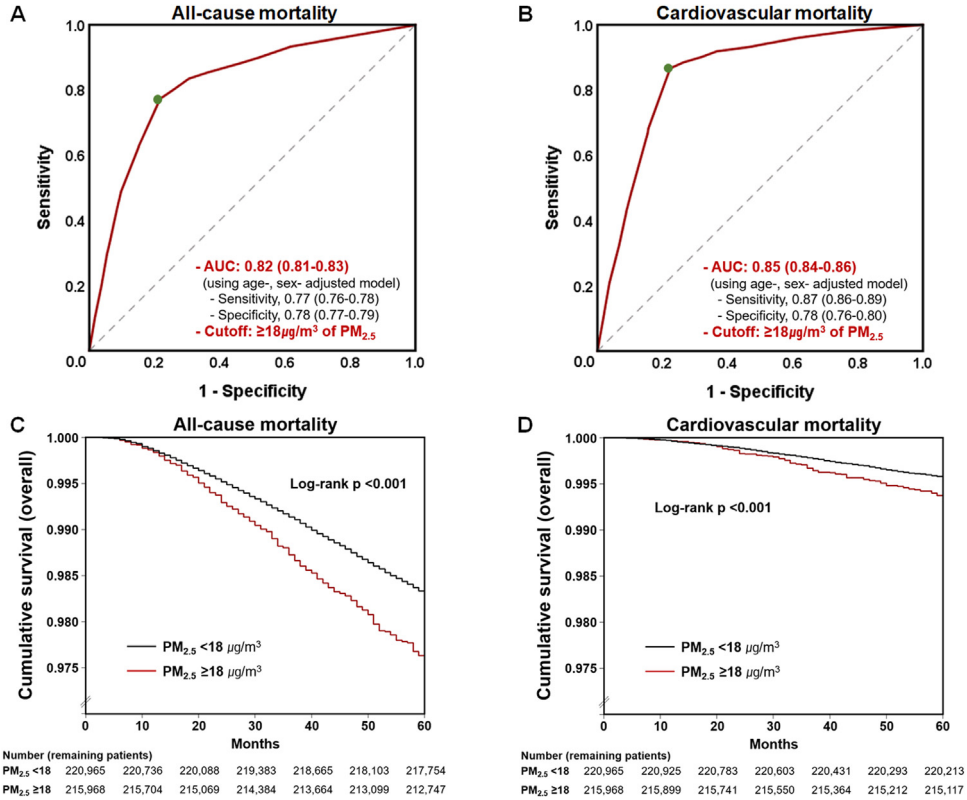

Fig. 3. (A and B) ROC curves of $PM_{2.5}$ in predicting all-cause (A) and cardiovascular (B) mortality. The c-indices on the basis of the AUC for $PM_{2.5}$ in predicting all-cause and cardiovascular mortality were 0.82 and 0.85, respectively. The ≥ 18 μg/m³ of $PM_{2.5}$ concentration showed the highest Youden's index (sensitivity + specificity - 1).
(C and D) Kaplan-Meier curves of all-cause (C) and cardiovascular (D) mortality according to $PM_{2.5}$ level (overall general population with 436,933 subjects): $PM_{2.5}$ <18 μg/m³ and ≥18 μg/m³.
AUC, area under the curve; $PM_{2.5}$, particulate matter <2.5 μm in diameter; ROC, receiver operating characteristics.

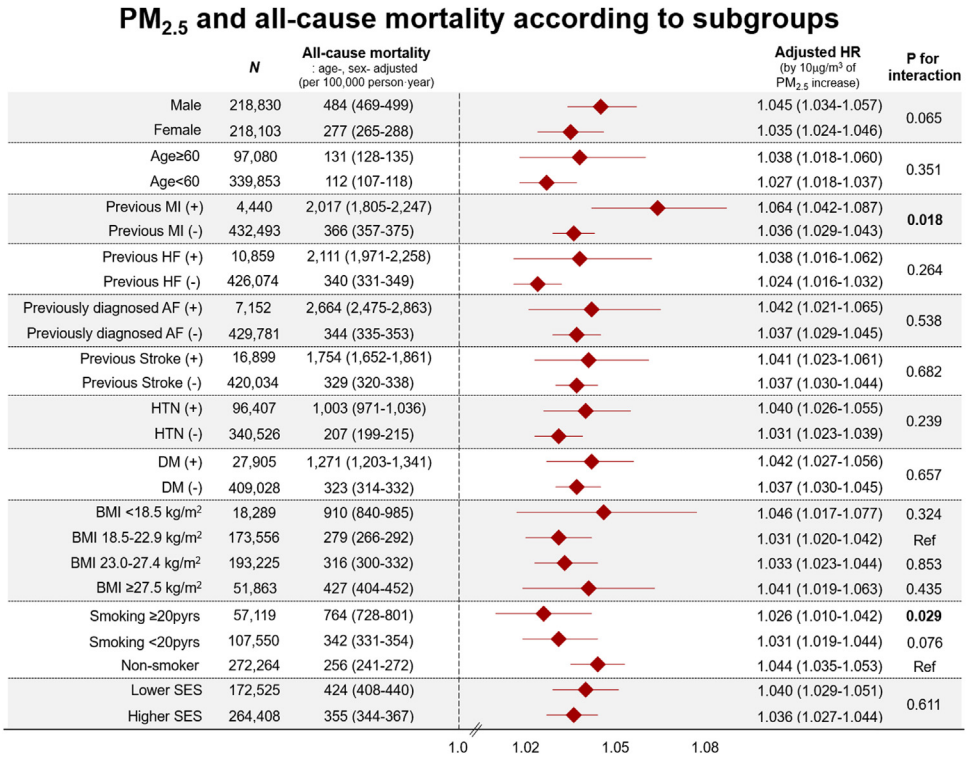

Fig. 4. Effect of $PM_{2.5}$ exposure on all-cause mortality in different subgroups (overall general population with 436,933 subjects). The HRs were adjusted by age, sex, BMI, SES, HF, HTN, dyslipidemia, DM, previous stroke/transient ischemic attack history, previous MI or peripheral vascular disease, serum estimated glomerular filtrate rate, smoking status, and alcohol intake habit.
AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction; $PM_{2.5}$, particulate matter <2.5 μm in diameter; SES, socioeconomic status.

$PM_{2.5}$ concentration compared to Western countries, long-term exposure of $PM_{2.5}$ was associated with increased risks of all-cause and cardiovascular mortality. An increase in $PM_{2.5}$ concentration by 10 $\mu g/m^3$ was also associated with a further increased risk of all-cause and cardiovascular mortality by 3.7 % and 5.2 %, respectively, even after adjusting for clinical variables. We also demonstrated that a specific level of $PM_{2.5}$ concentration as 18 $\mu g/m^3$ was associated with more increased risks of all-cause and cardiovascular mortality.

Clinical importance of the effects of air pollution on mortality

Many studies, including meta-analyses, have investigated associations between air pollution and mortality [1,7,25]. Long-term exposure to ambient air pollution contributes to various adverse cardiovascular effects, including MI, stroke, heart failure [3], or death [2,21]. However, current air quality standards in the US and European societies are based on a 3-year average of the annual arithmetic means of $PM_{2.5}$ concentration [5,6], because previous epidemiological studies reported that it was not obvious whether there was threshold $PM_{2.5}$ concentration associated with increased risk of mortality [1,8,26]. Air pollution levels of US and European societies were much lower compared to Asian countries (Supplementary Fig. 1; 2017 annual average $PM_{2.5}$ concentration was 25.1 $\mu g/m^3$ in Korea, whereas 7.4 $\mu g/m^3$ in USA, and 10.4–12.1 $\mu g/m^3$ in European countries). However, the impact of air pollution in eastern Asian countries with high $PM_{2.5}$ concentration has not been well-identified. This large nationwide cohort study showed continuous and linearly increasing associations between long-term $PM_{2.5}$ exposure and mortality in subjects from the Korean general population. These correlations were shown consistently across all subgroups. And due to a large proportion of the population living in urban areas who are exposed to levels of $PM_{2.5}$ exceeding national air quality standards, attention to higher levels of $PM_{2.5}$ air pollution becomes particularly important [27].

The level of $PM_{2.5}$ associated with more increased risks of mortality

Although there have been many studies on the association between mortality and certain air pollutants [28,29], less is known about the effect of ambient $PM_{2.5}$ air pollution on mortality in Asian general populations. Previous studies also demonstrated significant correlations between $PM_{2.5}$ air pollution and mortality, however, it had not been clear whether there was a threshold $PM_{2.5}$ concentration associated with increased risks of mortality [1,7]. A previous meta-analysis of 22 European cohorts that included 367 000 people and reported 29 000 mortalities included subjects with clinical cardiovascular conditions or comorbidities with residual confounding factors that affect mortality more than air pollution [28,29]. In contrast, our study was (i) a large-scale adult cohort (≥18years) of over 400,000 subjects who underwent National Health Examinations. This allowed for adjustment for major confounding factors such as smoking history, alcohol intake habit, residential information, and socioeconomic status data. Also, the (ii) long-term follow-up duration was extensive, 1,683,271 person·years. (iii) This allowed us to reveal a small but significant concentration-response relationship between $PM_{2.5}$ concentration and all-cause or cardiovascular mortality in our Korean general population cohort. Further, (iv) we demonstrated the specific $PM_{2.5}$ concentration associated with more increased risks of these mortalities, which was not previously well-studied. These (v) associations between $PM_{2.5}$ and all-cause mortality were more profound in subjects with previous MI and non-smokers compared to the opposite population. Since inhaled particulate pollutants

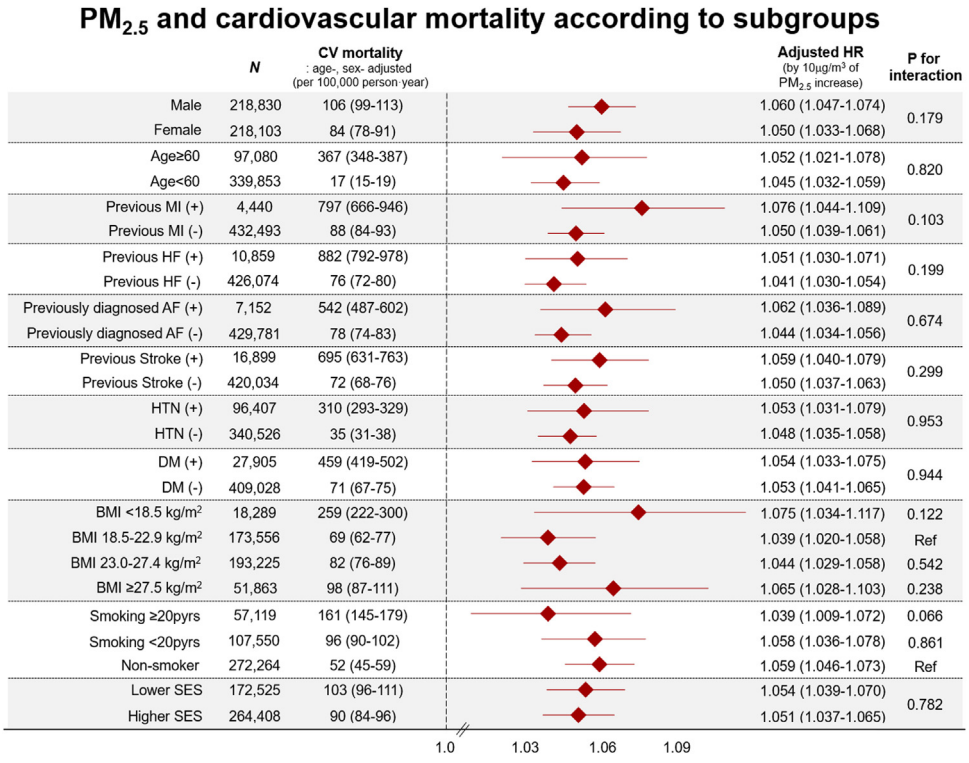

Fig. 5. Effect of $PM_{2.5}$ exposure on cardiovascular mortality in different subgroups (overall general population with 436,933 subjects). The HRs were adjusted by age, sex, BMI, SES, HF, HTN, dyslipidemia, DM, previous stroke/transient ischemic attack history, previous MI or peripheral vascular disease, serum estimated glomerular filtrate rate, smoking status, and alcohol intake habit.
AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction; $PM_{2.5}$, particulate matter <2.5 μm in diameter; SES, socioeconomic status.

may lead to production of some cytokines with systemic inflammatory reactions [30], these adverse inhalation effects can be diminished in patients with chronic lung parenchymal diseases [31]. In this study, there were more subjects with chronic obstructive pulmonary disease (COPD) among heavy smokers (≥20pack·years) compared to those among non-smokers (3.9 % vs 2.5 %, $p < 0.001$). And $PM_{2.5}$ effects on all-cause mortality were more profound in subjects without COPD compared to subjects with COPD [adjusted HR 1.037 (1.029–1.045) vs adjusted HR 1.022 (1.008–1.037), p-value for interaction <0.001). We also (vi) excluded subjects who moved to another region during the study period in an attempt to identify the consistent effect of air pollution on mortality, and (vii) sensitivity analyses with including only non-smokers demonstrated the robustness of our main results. We were also able to investigate the relationship between air pollution and cardiovascular causes of death by linking national health insurance administrative data and death certificate information from the national statistical office.

Clinical implications

Our study supports a small but significant association between $PM_{2.5}$ and both all-cause or cardiovascular mortality, which may be a modifiable risk factor in our study population.

Additionally, our study demonstrated the specific $PM_{2.5}$ concentration for further raising these mortalities which had not been well-studied previously. And we also investigated susceptible subgroups associated with increased risks of these mortalities, which may offer the important cosmopolitical information to general population or even to national administrations dealing with public health for redefining the $PM_{2.5}$ standards.

Limitations

Our study, nonetheless, had its limitations. We excluded subjects who moved to another region within the study period, this may not have fully reflected the subjects' specific locations (such as subjects who worked outside away, or at home) [32]. An epidemiological study investigated that living close to intense traffic roads was associated with increased cardiovascular inflammatory markers [33], however, our study did not investigate these aspects. In addition, we could not identify the exact hour of subjects' death or specific events because this study was from the claims data. For these reasons, the analysis of acute exposure effects was thought as it may draw somewhat biased results from our cohort data, and further investigations are needed [34]. Compared to the previous epidemiological study [32] which was performed with the Medicare population primarily consisting of subjects older than 65 years and cause-specific mortality were not reported, our study included young healthy subjects and investigated the associations between $PM_{2.5}$ exposure and cardiovascular mortality also.

Although we analyzed the effect of air pollution on mortality with adjustment for age and sex, some confounders (e.g. noise [35]) were not considered in this study. Even so, our overall results were consistent after adjusting for additional clinical variables (BMI, socioeconomic status, heart failure, hypertension, dyslipidemia, diabetes, previous stroke/TIA history, previous MI or peripheral vascular disease, serum estimated glomerular filtrate rate, smoking, and alcohol intake status). Because smoking history and alcohol intake behavior were obtained from questionnaires given during the national health examinations, careful interpretation of these results is needed. Also, smoking is a major confounding factor ($PM_{2.5}$ concentration inside smoky rooms are more than 600 μg/m³) for analyzing air pollution effects [36],

however, smokers were more than one third in this population and they included many subjects with cardiovascular risk factors including hypertension, diabetes, dyslipidemia, and previous MI, which were important risk factors of cardiovascular mortality. Therefore, we thought that excluding these many smokers could even draw somewhat biased results for analyzing all-cause and cardiovascular mortalities, then, we analyzed with including smokers as in a recent epidemiological study about $PM_{2.5}$ and mortality [1]. Sensitivity analyses with non-smokers to analyze the true air pollution effects showed consistency (Supplementary Tables 3, 6, 7, 9, and Supplementary Figs. 3 and 4). However, the air pollution data from different sources (such as diesel, benzene, or metal compounds) were not available, therefore, we could analyze with only measured air pollutants. Because smoking history and alcohol intake behavior were obtained from the questionnaires during the national health examinations, careful interpretation of these results is needed. So, we used multivariable adjusted Cox-regression analysis and sensitivity analyses excluding subjects who were current- or former-smokers, and overall results were also consistent. Although the acute effect of $PM_{2.5}$ for endothelial dysfunction was studied recently [37,38], we did not investigate associations between air pollution and vascular/tissue inflammation or myocardial repolarization, and thus the mechanism behind the relationship between exposure to air pollution and clinical cardiovascular diseases remains unclear.

Conclusions

Even in the Korean general population exposed to high-air pollution, long-term exposure of $PM_{2.5}$ was almost linearly associated with increased risks for all-cause and cardiovascular mortality, especially above 18 $\mu g/m^3$ of $PM_{2.5}$. There might be some susceptible patients who should beware of higher levels of $PM_{2.5}$.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2019.11.004.

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