Cardiovascular Effects of Long-Term Exposure to Air Pollution: A Population-Based Study With 900 845 Person-Years of Follow-up

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Background—Studies have shown that long-term exposure to air pollution such as fine particulate matter (≤ 2.5 μm in aerodynamic diameter [$PM_{2.5}$]) increases the risk of all-cause and cardiovascular mortality. To date, however, there are limited data on the impact of air pollution on specific cardiovascular diseases. This study aimed to evaluate cardiovascular effects of long-term exposure to air pollution among residents of Seoul, Korea.

Methods and Results—Healthy participants with no previous history of cardiovascular disease were evaluated between 2007 and 2013. Exposure to air pollutants was estimated by linking the location of outdoor monitors to the ZIP code of each participant's residence. Crude and adjusted analyses were performed using Cox regression models to evaluate the risk for composite cardiovascular events including cardiovascular mortality, acute myocardial infarction, congestive heart failure, and stroke. A total of 136 094 participants were followed for a median of 7.0 years (900 845 person-years). The risk of major cardiovascular events increased with higher mean concentrations of $PM_{2.5}$ in a linear relationship, with a hazard ratio of 1.36 (95% confidence interval, 1.29–1.43) per 1 μg/m^3 $PM_{2.5}$. Other pollutants including $PM_{2.5-10}$ of CO, SO_2, and NO_2, but not O_3, were significantly associated with increased risk of cardiovascular events. The burden from air pollution was comparable to that from hypertension and diabetes mellitus.

Conclusions—This large-scale population-based study demonstrated that long-term exposure to air pollution including $PM_{2.5}$ increases the risk of major cardiovascular disease and mortality. Air pollution should be considered an important modifiable environmental cardiovascular risk factor. (***J Am Heart Assoc***. 2017;6:e007170. DOI: 10.1161/JAHA.117.007170.)

Key Words: air pollution • cardiovascular disease risk factors • epidemiology • particulate matter

Air pollution affects human health. The World Health Organization estimates that 7 million deaths were attributable to air pollution exposure worldwide in 2012.[1]

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Accompanying Tables S1 through S3 and Figures S1, S2 are available at http://jaha.ahajournals.org/content/6/11/e007170/DC1/embed/inline-supplementary-material-1.pdf

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The Global Burden of Disease Study 2015 ranked ambient exposure to fine particulate matter with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$) as the fifth most important risk factor for mortality worldwide.[2,3]

The cardiovascular health consequences of air pollution exceed all its other health effects such as pulmonary diseases.[4,5] Deaths from cardiovascular causes account for more than two thirds of the premature deaths attributable to ambient $PM_{2.5}$ air pollution.[2] Increasing amounts of data suggest exposure to $PM_{2.5}$ increases the risk of cardiovascular deaths and diseases in the short and long terms.[6–10] It also has been suggested that the long-term effects of $PM_{2.5}$ have a greater impact on cardiovascular mortality than the short-term effects.[4,5]

Nevertheless, there are still limited data on the long-term effects of air pollution on specific cardiovascular diseases.[11,12] In addition, most previous studies were conducted in the United States or Europe. This population-based study was performed to estimate the cardiovascular effects of long-term exposure to air pollution among residents of Seoul, Korea. The risks of all-cause and cardiovascular mortality and the incidence of cardiovascular diseases including acute

myocardial infarction (AMI), congestive heart failure (CHF), and stroke were evaluated while controlling for potential confounders.

Methods

Study Design and Participants

Administrative information on individuals who resided in Seoul was linked with health insurance claims data, which allowed for long-term follow-up without loss. The study participants were extracted from the National Health Insurance Service–National Sample Cohort (NHIS-NSC). The design and profile of the cohort have been described previously.[13] The NHIS is the single insurance provider in Korea that covers all citizens. The NHIS-NSC is a population-based cohort including 1 025 340 individuals who were randomly sampled from the population database—equivalent to ≈2% of the Korean population. Participants' personal information, demographic characteristics, and medical treatment data are included in the data set.

In this study, participants aged ≥18 years who resided in Seoul between 2007 and 2013 were selected from the NHIS-NSC. Those with a previous history of cardiovascular disease such as AMI, CHF, and stroke were excluded. Variables such as anthropometric measurements, physical examination, laboratory tests, and self-reporting questionnaires were available from the general health examination database. The insurance eligibility database was linked to extract information on each participant's identity and socioeconomic variables such as age, sex, residential area, and income level. The survival time was censored when a participant moved out of

Table 1. Baseline Profiles of Study Population

Characteristics	Values
Total number of participants	136 094
Age, y	42.05±14.83 (136 094)*
<45 y	58.2 (79 245/136 094)
45–54 y	21.3 (29 006/136 094)
55–64 y	11.8 (16 174/136 094)
≥65 y	8.6 (11 669/136 094)
Male sex	49.1 (66 851/136 094)
Income quintiles	
Upper	32.4 (44 127/136 094)
Upper middle	21.1 (28 712/136 094)
Middle	17.7 (24 100/136 094)
Lower middle	15.4 (20 957/136 094)
Lower	11.3 (15 407/136 094)
Covered by medical aid	2.1 (2791/136 094)
Hypertension	9.8 (13 303/136 094)
Diabetes mellitus	3.1 (4154/136 094)
Dyslipidemia	7.5 (10 189/136 094)
Chronic renal failure	0.3 (361/136 094)
End-stage renal disease	0.1 (88/136 094)
Ischemic heart disease	1.4 (1881/136 094)
Peripheral arterial disease	1.3 (1803/136 094)
Chronic obstructive pulmonary disease	0.4 (554/136 094)
Malignancy	1.0 (1367/136 094)
Body mass index, kg/m^2	23.49±3.31 (95 591)
Underweight (<18.5)	4.8 (4628/95 591)
Normal (18.5–24.9)	65.2 (62 290/95 591)
Overweight (25–29.9)	26.6 (25 395/95 591)
Obese (≥30)	3.4 (3278/95 591)
Smoking status	
Never smoker	67.3 (60 081/89 322)
Ex-smoker	8.6 (7641/89 322)
Current smoker	24.2 (21 600/89 322)
Systolic blood pressure, mm Hg	121.60±15.96 (95 583)
Diastolic blood pressure, mm Hg	75.91±10.79 (95 581)
Fasting blood glucose, mg/dL	95.51±23.31 (95 578)
Hemoglobin, g/dL	13.91±1.61 (95 561)
Total cholesterol, mg/dL	193.90±36.61 (95 564)

Data are presented as mean±SD (n) or % (n/N).

the study city (Seoul). Otherwise, all participants were observed until December 31, 2013, or their death. This study was exempt from review by the Seoul National University Bundang Hospital institutional review board (I-2016-4043).

Air Pollution Exposure Estimates

We obtained information on daily air pollution levels provided by the Korean Ministry of Environment website (http://www.airkorea.or.kr). Air pollutants including $PM_{2.5}$, particles with a diameter <10 μm (PM_{10}), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3) were collected from 27 monitoring stations in Seoul. We measured $PM_{2.5}$ by mass concentration, PM_{10} by the β-ray absorption method, CO by the nondispersive infrared method, SO_2 by pulse ultraviolet fluorescence, NO_2 by chemiluminescence, and O_3 by ultraviolet photometry.

Each individual's exposure to air pollutants was determined by linking the location of the monitoring stations to the ZIP code of his or her residence. The long-term average concentrations of the air pollutants were estimated by daily averages from the date of study enrollment to the occurrence of study end points. Data points that were highly discrepant with other observations were excluded from the analysis.

Cardiovascular Outcomes

Vital status, date of death, and cause of death were identified using the death certificate records from the National Death Index. Cardiovascular mortality was defined according to the *International Classification of Diseases, 10th Revision* (*ICD-10*) codes (I00–I99). AMI was defined as a hospitalization with *ICD-10* codes I21 to 23 as the primary or secondary diagnosis. CHF was defined based on discharge diagnosis (*ICD-10* codes I11.0, I13.0, I13.2, I25.5, I42, I50, O90.3) after a hospitalization. Stroke was defined by discharge diagnosis (*ICD-10* codes: I60–64) among patients who had been hospitalized and undergone brain imaging studies such as computed tomography and magnetic resonance imaging.[14] Ischemic and hemorrhagic strokes were defined by *ICD-10*

codes I63 to 64 and I60 to 62, respectively. Composite cardiovascular events were defined as a composite of cardiovascular death, AMI, CHF, and stroke.

Statistical Analyses

Baseline characteristics were shown as mean±SD or proportions. Cox proportional hazards models were used to assess the association between air pollution exposure and study outcomes. Hazard ratios (HRs) and 95% confidence intervals were calculated for the risk of time-dependent variables. Multiple statistical models were constructed to adjust for potential confounding factors. We evaluated unadjusted models, age and sex-adjusted models, and multivariable models. Multivariable-adjusted model 1 was controlled for age, sex, socioeconomic status, hypertension, diabetes mellitus, dyslipidemia, chronic renal failure, end-stage renal diseases, ischemic heart disease, peripheral arterial disease, chronic obstructive pulmonary disease, and malignancy. Multivariable-adjusted model 2 was controlled for the variables listed above as well as body mass index (in kg/m^2; <18.5, 18.5–24.9, 25–29.9, and ≥30), fasting blood glucose (<100, 100–125, 126–199, and ≥200 mg/dL), total cholesterol (<200, 200–239, and ≥240 mg/dL), and hemoglobin (<13 and ≥13 g/dL in men, <12 and ≥12 g/dL in women).

Penalized splines were constructed to evaluate the nonlinear relationship between air pollution and cardiovascular outcomes. Population-attributable risks and their 95% confidence intervals were calculated by a method using logistic regression models.[15] Exposure to $PM_{2.5}$ was coded binomially (≥25 or <25 μg/m^3). All statistical analyses used R version 3.3.3 (R Foundation for Statistical Computing; http://www.R-project.org). Two-sided *P* values <0.05 were considered statistically significant.
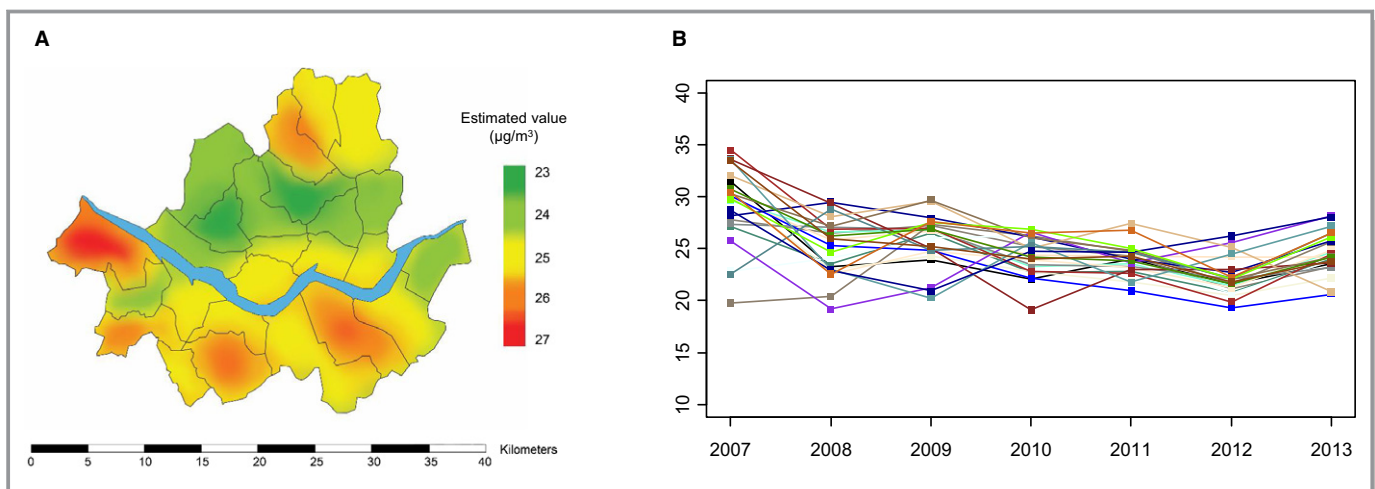

Figure 1. The concentrations of $PM_{2.5}$ in Seoul, 2007–2013. (A) Maps of average $PM_{2.5}$ concentrations, and (B) yearly concentrations of $PM_{2.5}$ at each monitor. $PM_{2.5}$ indicates fine particulate matter ≤2.5 μm in aerodynamic diameter.

Results

Study Participants and Exposure to Air Pollution

A total of 136 094 residents of Seoul were included in this study. As shown in Table 1, the study participants were representative of the general population. The mean age was 42 years, and 49.1% were men. The proportions of hypertension, diabetes mellitus, dyslipidemia, and active smoking were 9.8%, 3.1%, 7.5%, and 24.2%, respectively. The mean body mass index was 23.5 kg/m^2, and blood pressure was 122/76 mm Hg.

Figure 1 shows the average concentrations of PM$_{2.5}$ within Seoul, which significantly decreased during the study period. The yearly trends for the average concentrations of air pollutants are shown in Figure S1. All measured pollutants except O$_3$ demonstrated consistent decreases. Daily concentrations of air pollutants during the study period and their correlation matrix are summarized in Tables S1 and S2. The daily mean concentration of PM$_{2.5}$ was 25.0 μg/m^3. The individual exposure to air pollutants varied: The mean PM$_{2.5}$ was 25.6 μg/m^3 (minimum, 23.8 μg/m^3; maximum, 27.8 μg/m^3).

Risks of Cardiovascular Events

During a median follow-up of 7.0 years (900 845 person-years), 1658 all-cause deaths (0.21 per 100 person-years) and 1856 composite cardiovascular events (0.18 per 100 person-years) occurred (Table S3). Ischemic stroke was the most

frequently observed cardiovascular event, followed by CHF, AMI, hemorrhagic stroke, and cardiovascular mortality.

A concentration-response curve with the penalized spline Cox regression model suggested that long-term exposure to PM$_{2.5}$, PM$_{2.5-10}$, CO, SO$_2$, and NO$_2$ was associated with an increased occurrence of composite cardiovascular events (cardiovascular mortality, AMI, CHF, and stroke; Figure 2). The risk of composite cardiovascular events was elevated by 36% for a 1-μg/m^3 increase of PM$_{2.5}$ (Table 2, Figure 3). All study outcomes including mortality, CHF, AMI, and stroke were significantly associated with long-term exposure to PM$_{2.5}$. In numerical terms, the increase in risk was highest for CHF and lowest for hemorrhagic stroke for each increment in PM$_{2.5}$ exposure. A variety of adjustment models controlling for potential confounding factors such as age, sex, and other baseline cardiovascular risk factors showed consistent results.

The risks of cardiovascular mortality and stroke were sensitive to increasing ambient NO$_2$ exposure, whereas those of cardiovascular mortality and AMI were sensitive to CO. In contrast, O$_3$ was inversely correlated with the risks of cardiovascular events.

Multipollutant Models, Subgroup Analyses, and Population-Attributable Risks

Two-pollutant and multipollutant models were constructed to estimate the independent roles of various air pollutants (Figure S2). The effects of PM$_{2.5}$ on cardiovascular composite outcomes were largely unchanged after adjustment for PM$_{2.5-}$
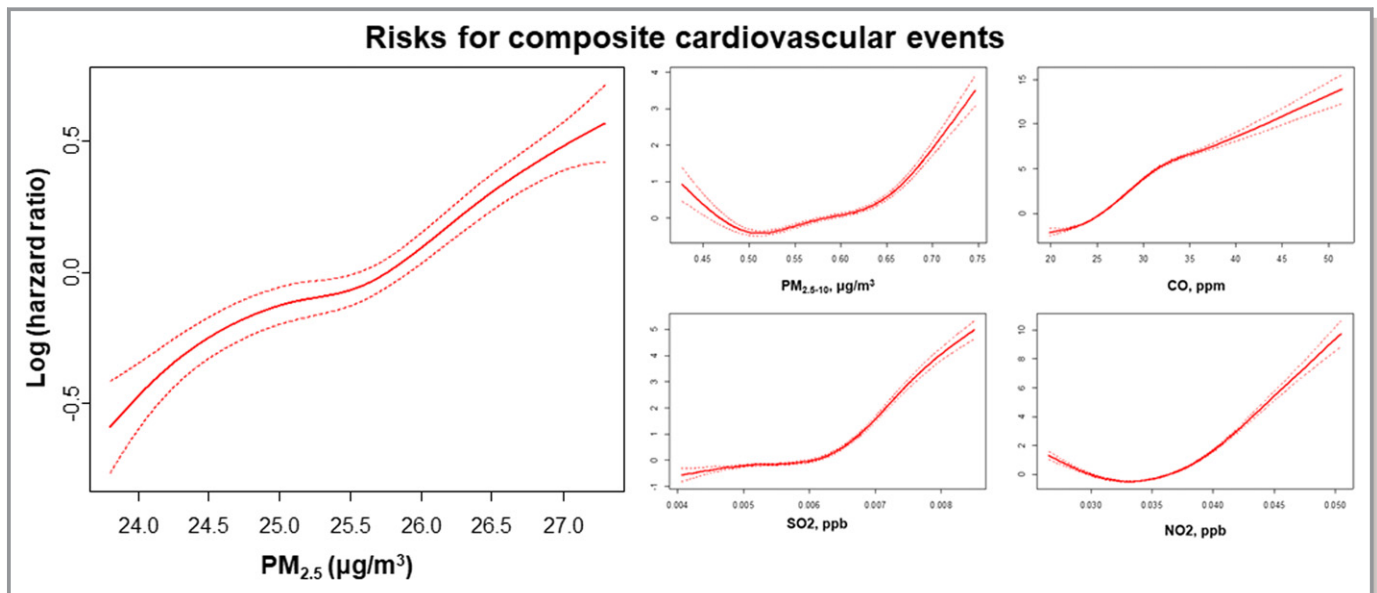
Figure 2. Relationship between long exposure to PM$_{2.5}$, PM$_{2.5-10}$, CO, SO$_2$, and NO$_2$ and composite cardiovascular events. Cox regression model for cardiovascular risk in response to PM$_{2.5}$ exposure was smoothed using penalized spline methods with 3 *df*. The *y*-axis represents the log hazard ratio (solid line). CO indicates carbon monoxide; NO$_2$, nitrogen dioxide: O$_3$, ozone; PM$_{2.5}$, fine particulate matter ≤2.5 μm in aerodynamic diameter; PM$_{2.5-10}$ indicates fine particulate matter ≤2.5 to 10 μm in aerodynamic diameter; SO$_2$, sulfur dioxide.

Table 2. Estimated HRs and 95% CIs for Cardiovascular Events According to Increased Exposure to Air Pollutants

	Unadjusted		Age, Sex-Adjusted		Multivariable-Adjusted (1)*		Multivariable-Adjusted (2)†	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
$PM_{2.5}$, per 1 μg/m³								
Composite cardiovascular events	1.36 (1.29–1.43)	<0.001	1.37 (1.30–1.44)	<0.001	1.42 (1.33–1.51)	<0.001	1.41 (1.32–1.50)	<0.001
All-cause death	1.36 (1.29–1.43)	<0.001	1.38 (1.31–1.45)	<0.001	1.34 (1.23–1.44)	<0.001	1.32 (1.22–1.43)	<0.001
Cardiovascular death	1.24 (1.09–1.42)	0.0011	1.26 (1.11–1.44)	<0.001	1.38 (1.13–1.68)	0.002	1.36 (1.11–1.66)	0.003
Acute myocardial infarction	1.30 (1.16–1.46)	<0.001	1.33 (1.19–1.49)	<0.001	1.36 (1.19–1.56)	<0.001	1.36 (1.19–1.56)	<0.001
Congestive heart failure	1.39 (1.28–1.52)	<0.001	1.42 (1.31–1.55)	<0.001	1.46 (1.31–1.62)	<0.001	1.44 (1.29–1.61)	<0.001
Stroke	1.34 (1.25–1.43)	<0.001	1.35 (1.26–1.45)	<0.001	1.40 (1.28–1.52)	<0.001	1.39 (1.27–1.52)	<0.001
Ischemic stroke	1.37 (1.27–1.49)	<0.001	1.39 (1.28–1.51)	<0.001	1.46 (1.31–1.62)	<0.001	1.45 (1.31–1.61)	<0.001
Hemorrhagic stroke	1.18 (1.04–1.33)	0.011	1.19 (1.05–1.35)	0.005	1.23 (1.06–1.43)	0.008	1.22 (1.05–1.42)	0.009
$PM_{2.5-10}$, per 1 μg/m³								
Composite cardiovascular events	2.01 (1.97–2.04)	<0.001	1.76 (1.74–1.79)	<0.001	1.90 (1.85–1.95)	<0.001	1.91 (1.86–1.96)	<0.001
All-cause death	1.99 (1.96–2.03)	<0.001	1.67 (1.65–1.70)	<0.001	1.69 (1.65–1.74)	<0.001	1.68 (1.64–1.73)	<0.001
Cardiovascular death	1.98 (1.89–2.08)	<0.001	1.62 (1.56–1.69)	<0.001	1.64 (1.54–1.76)	<0.001	1.63 (1.53–1.75)	<0.001
Acute myocardial infarction	2.44 (2.33–2.55)	<0.001	2.16 (2.07–2.25)	<0.001	2.13 (2.01–2.25)	<0.001	2.14 (2.02–2.27)	<0.001
Congestive heart failure	1.39 (1.28–1.52)	<0.001	1.42 (1.31–1.55)	<0.001	1.46 (1.31–1.62)	<0.001	1.44 (1.29–1.61)	<0.001
Stroke	2.11 (2.07–2.16)	<0.001	1.85 (1.81–1.88)	<0.001	2.00 (1.94–2.06)	<0.001	2.02 (1.96–2.09)	<0.001
Ischemic stroke	2.12 (2.07–2.17)	<0.001	1.82 (1.78–1.86)	<0.001	1.98 (1.92–2.06)	<0.001	2.01 (1.94–2.08)	<0.001
Hemorrhagic stroke	2.57 (2.43–2.72)	<0.001	2.39 (2.26–2.52)	<0.001	2.42 (2.26–2.59)	<0.001	2.46 (2.28–2.64)	<0.001
CO, per IQR (0.25 ppm)								
Composite cardiovascular events	1.92 (1.77–2.09)	<0.001	1.83 (1.69–1.98)	<0.001	1.79 (1.62–1.98)	<0.001	1.79 (1.61–1.99)	<0.001
All-cause death	1.95 (1.79–2.12)	<0.001	1.83 (1.68–1.99)	<0.001	1.75 (1.54–1.97)	<0.001	1.72 (1.52–1.94)	<0.001
Cardiovascular death	2.51 (2.02–3.13)	<0.001	2.28 (1.84–2.81)	<0.001	3.07 (2.20–4.29)	<0.001	2.96 (2.12–4.14)	<0.001
Acute myocardial infarction	2.47 (2.06–2.97)	<0.001	2.32 (1.95–2.76)	<0.001	2.13 (1.73–2.61)	<0.001	2.12 (1.72–2.61)	<0.001
Congestive heart failure	1.88 (1.64–2.16)	<0.001	1.81 (1.58–2.08)	<0.001	1.84 (1.55–2.19)	<0.001	1.86 (1.56–2.21)	<0.001
Stroke	2.08 (1.86–2.33)	<0.001	1.99 (1.78–2.23)	<0.001	1.98 (1.72–2.28)	<0.001	2.00 (1.73–2.30)	<0.001
Ischemic stroke	2.06 (1.81–2.36)	<0.001	1.97 (1.73–2.24)	<0.001	1.88 (1.60–2.22)	<0.001	1.91 (1.62–2.25)	<0.001
Hemorrhagic stroke	2.04 (1.66–2.50)	<0.001	1.99 (1.62–2.43)	<0.001	2.22 (1.73–2.86)	<0.001	2.22 (1.73–2.87)	<0.001
SO_2, per IQR (2.54 ppb)								
Composite cardiovascular events	2.06 (1.93–2.20)	<0.001	1.97 (1.84–2.10)	<0.001	1.99 (1.83–2.17)	<0.001	1.94 (1.78–2.11)	<0.001
All-cause death	1.97 (1.83–2.11)	<0.001	1.84 (1.72–1.97)	<0.001	1.73 (1.56–1.93)	<0.001	1.73 (1.55–1.92)	<0.001
Cardiovascular death	2.02 (1.69–2.41)	<0.001	1.83 (1.55–2.17)	<0.001	1.48 (1.13–1.93)	0.004	1.50 (1.14–1.96)	0.00316
Acute myocardial infarction	1.81 (1.55–2.11)	<0.001	1.75 (1.51–2.04)	<0.001	1.83 (1.52–2.20)	<0.001	1.82 (1.52–2.19)	<0.001
Congestive heart failure	2.02 (1.80–2.26)	<0.001	1.95 (1.74–2.18)	<0.001	2.00 (1.73–2.31)	<0.001	2.00 (1.73–2.32)	<0.001
Stroke	2.25 (2.05–2.48)	<0.001	2.17 (1.97–2.38)	<0.001	2.25 (2.00–2.53)	<0.001	2.25 (2.00–2.54)	<0.001
Ischemic stroke	2.31 (2.07–2.58)	<0.001	2.20 (1.98–2.45)	<0.001	2.32 (2.02–2.66)	<0.001	2.33 (2.02–2.68)	<0.001
Hemorrhagic stroke	2.24 (1.89–2.66)	<0.001	2.19 (1.86–2.60)	<0.001	2.13 (1.73–2.62)	<0.001	2.13 (1.73–2.62)	<0.001
NO_2, per IQR (18.4 ppb)								
Composite cardiovascular events	2.17 (2.01–2.34)	<0.001	2.06 (1.91–2.22)	<0.001	2.30 (2.08–2.55)	<0.001	2.30 (2.08–2.55)	<0.001
All-cause death	2.05 (1.89–2.22)	<0.001	1.91 (1.76–2.07)	<0.001	1.80 (1.60–2.04)	<0.001	1.79 (1.59–2.03)	<0.001
Cardiovascular death	2.79 (2.26–3.45)	<0.001	2.47 (2.01–3.03)	<0.001	2.70 (1.96–3.72)	<0.001	2.67 (1.94–3.69)	<0.001

Continued

Table 2. Continued

	Unadjusted		Age, Sex-Adjusted		Multivariable-Adjusted (1)*		Multivariable-Adjusted (2)†	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Acute myocardial infarction	1.73 (1.45–2.06)	<0.001	1.68 (1.41–2.00)	<0.001	1.81 (1.46–2.25)	<0.001	1.81 (1.46–2.25)	<0.001
Congestive heart failure	2.12 (1.86–2.43)	<0.001	2.05 (1.79–2.33)	<0.001	2.40 (2.02–2.86)	<0.001	2.40 (2.02–2.85)	<0.001
Stroke	2.32 (2.07–2.59)	<0.001	2.24 (2.01–2.50)	<0.001	2.64 (2.29–3.05)	<0.001	2.65 (2.29–3.06)	<0.001
Ischemic stroke	2.48 (2.17–2.82)	<0.001	2.37 (2.09–2.70)	<0.001	2.73 (2.30–3.24)	<0.001	2.74 (2.31–3.24)	<0.001
Hemorrhagic stroke	2.02 (1.66–2.46)	<0.001	2.00 (1.64–2.43)	<0.001	2.43 (1.90–3.11)	<0.001	2.43 (1.90–3.12)	<0.001
O_3, per IQR (15.9 ppb)								
Composite cardiovascular events	0.65 (0.62–0.68)	<0.001	0.67 (0.64–0.70)	<0.001	0.63 (0.59–0.67)	<0.001	0.63 (0.63–0.73)	<0.001
All-cause death	0.66 (0.63–0.69)	<0.001	0.69 (0.65–0.72)	<0.001	0.68 (0.63–0.73)	<0.001	0.68 (0.63–0.73)	<0.001
Cardiovascular death	0.58 (0.52–0.66)	<0.001	0.62 (0.55–0.70)	<0.001	0.59 (0.49–0.71)	<0.001	0.59 (0.49–0.71)	<0.001
Acute myocardial infarction	0.73 (0.65–0.81)	<0.001	0.74 (0.67–0.83)	<0.001	0.72 (0.63–0.82)	<0.001	0.71 (0.63–0.82)	<0.001
Congestive heart failure	0.69 (0.63–0.74)	<0.001	0.70 (0.65–0.76)	<0.001	0.64 (0.58–0.71)	<0.001	0.64 (0.58–0.71)	<0.001
Stroke	0.63 (0.59–0.67)	<0.001	0.64 (0.60–0.69)	<0.001	0.60 (0.55–0.65)	<0.001	0.60 (0.55–0.65)	<0.001
Ischemic stroke	0.62 (0.57–0.66)	<0.001	0.63 (0.59–0.68)	<0.001	0.60 (0.54–0.66)	<0.001	0.60 (0.54–0.66)	<0.001
Hemorrhagic stroke	0.69 (0.62–0.78)	<0.001	0.70 (0.62–0.79)	<0.001	0.62 (0.53–0.71)	<0.001	0.62 (0.53–0.71)	<0.001

CI indicates confidence interval; CO, carbon monoxide; HR, hazard ratio; IQR, interquartile range; NO_2, nitrogen dioxide: O_3, ozone; $PM_{2.5}$, fine particulate matter ≤2.5 μm in aerodynamic diameter; $PM_{2.5–10}$ indicates fine particulate matter ≤2.5 to 10 μm in aerodynamic diameter; ppm, parts per million, 10^{-6}; ppb, parts per billion, 10^{-9}; SO_2, sulfur dioxide.
*Multivariable-adjusted model 1 was adjusted for age, sex, socioeconomic status, hypertension, diabetes mellitus, dyslipidemia, chronic renal failure, end-stage renal diseases, ischemic heart disease, peripheral arterial disease, chronic obstructive pulmonary disease, and malignancy.
†Multivariable-adjusted model 2 was adjusted for the variables listed above as well as body mass index, fasting blood glucose, total cholesterol, and hemoglobin. Composite cardiovascular events were a composite of cardiovascular death, acute myocardial infarction, congestive heart failure, and stroke.

10, CO, SO_2, NO_2, or O_3. In addition, the effects of other air pollutants with multipollutant models were also similar with those of single-pollutant models.

The cardiovascular risks associated with $PM_{2.5}$ exposure did not differ significantly across various subgroups (Figure 4). No significant interactions were observed with regard to sex, age, presence of cardiovascular risk factors, anemia, and malignancy.

Long-term exposure to a $PM_{2.5}$ concentration >25 μg/m^3—the mean daily concentration in Seoul during the study period—was responsible for 30.8% of the population-attributable risks for composite cardiovascular events (Table 3). Population-attributable risks were 23.7% for men and 39.0% for women. The burden attributable to air pollution was comparable to or greater than those from conventional major cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and obesity.

Discussion

We performed a large-scale population-based study evaluating the cardiovascular impact of long-term exposure to air pollution. In this study, we found that long-term exposure to high levels of air pollution was associated with increased risk of major adverse cardiovascular events as well as all-cause deaths. Every 1-μg/m^3 increase of long-term exposure to

$PM_{2.5}$ was associated with a 36% increase in cardiovascular risks including mortality, AMI, CHF, and stroke. Other pollutants such as $PM_{2.5–10}$, CO, SO_2, and NO_2 also had an adverse impact on cardiovascular events. This study also demonstrated that the burden from air pollution was as large as that of conventional cardiovascular risk factors such as hypertension and diabetes mellitus in this study population.

Particulate matter is a mixture of solid particles and liquid droplets suspended in the air. The size of particles is directly linked to their impact on human health.[16] $PM_{2.5}$, also known as fine particles, has a small diameter that enables particles to reach deep into the lungs and penetrate the alveolar–capillary epithelium.[17] Evidence suggests the effects are stronger for cardiovascular mortality than for other causes of mortality.[17–19] Although most previous studies on the long-term effects evaluated mortality risks, the major novel finding of this study is the association of air pollution with specific major cardiovascular diseases.

The potential biological mechanisms explaining the association between air pollution and cardiovascular diseases include systemic inflammation caused by oxidative stress, autonomic imbalance, and the possible direct actions of pollutants reaching the systemic circulation.[4,5] Acceleration of atherosclerosis and vascular inflammation in response to long-term air pollution exposure was suggested in an animal model.[20] Recently, studies from the MESA Air (Multi-Ethnic
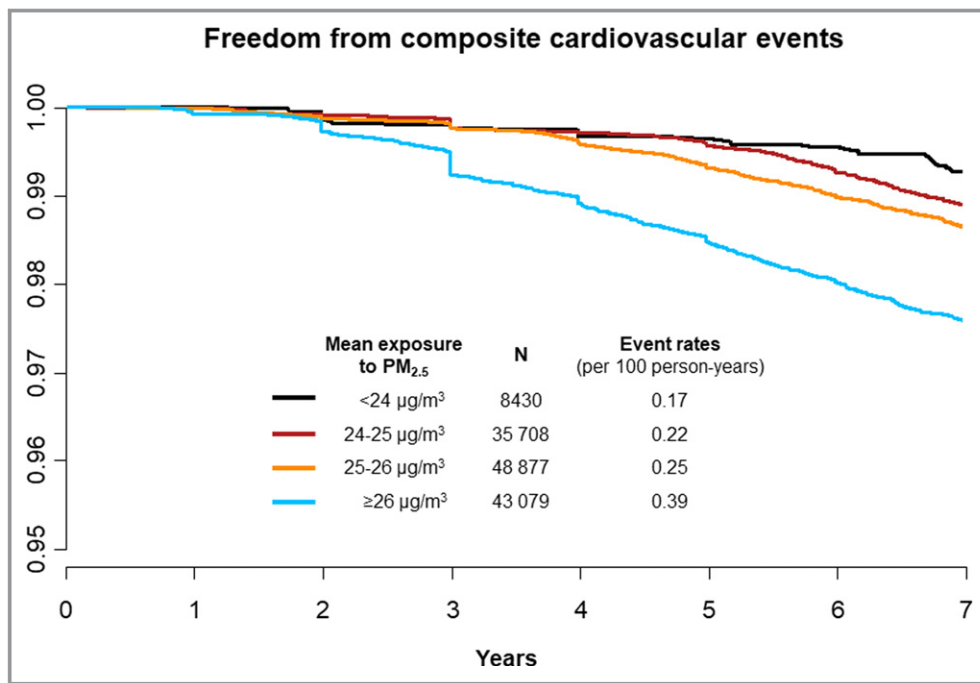
Figure 3. Kaplan–Meier survival curves for composite cardiovascular events in response to long-term exposure to ambient $PM_{2.5}$. $PM_{2.5}$ indicates fine particulate matter ≤2.5 μm in aerodynamic diameter.

Study of Atherosclerosis and Air Pollution) cohort have demonstrated that long-term $PM_{2.5}$ concentrations are associated with the progression of intima–media thickness on ultrasound examination and coronary calcification measured by cardiac computed tomography.[21,22] In addition, greater reductions in $PM_{2.5}$ were related to slower progression of intima–medial thickness progression. In the present study, we found that the impact of air pollution is not confined to atherosclerotic cardiovascular diseases such AMI and ischemic stroke but also affects CHF and hemorrhagic stroke.

The estimated risk of air pollution shown in the present study was larger than the risk reported in previous studies from the United States and Europe.[23–26] There may be several explanations for this difference. First, the level of air pollution in Seoul is higher than that in Western countries. The individual weighted mean concentration of $PM_{2.5}$ was 25.0 μg/m³ among the present study participants, who resided in Seoul between 2007 and 2013, whereas it is typically <15 μg/m³ in Western countries.[6,27] The impact of ambient $PM_{2.5}$ may differ with varying degrees of baseline $PM_{2.5}$ levels. Second, the composition and sources of the particles differ between East Asia and Western countries. Recent studies suggest that specific PM constituents play a more important role than the total mass concentration.[28] This geographic region is under rapid industrialization, and a large proportion of air pollution is suggested to be associated with fossil fuel combustion.[29] Third, individual $PM_{2.5}$ concentrations fell within a narrow range with an interquartile range of

1.5 μg/m³. Although Seoul has a large area of 605.21 km², it is also one of the most densely populated cities worldwide.[30] Fourth, there may be ethnic differences between study populations. Finally, although we performed rigorous adjustment for baseline cardiovascular risk factors, there could be unaccounted-for potential confounders.

This study is the first investigation performed in the Asia–Pacific region regarding the long-term effects of air pollution. According to the Global Burden of Disease Study 2015, the mean $PM_{2.5}$ is 58.4 and 28.7 μg/m³ in China and South Korea, respectively.[2] A report from the Environmental Performance Index estimated that >50% of the populations of these countries are exposed to unsafe levels of fine particulate matter.[31] A recent study found that ≈17% of all deaths in China are attributable to air pollution.[32] This study adds to the current evidence that the cardiovascular burden of air pollution should be considered as important as conventional cardiovascular risk factors.

This study has several limitations. First, we estimated individual exposure to air pollution using the ambient concentrations measured by outdoor monitors. People who live in industrialized countries spend ≈90% of their time indoors.[33] A growing body of evidence indicates that exposure to air pollution indoors also has health impacts. Second, we linked the ZIP code of each study participant's residence to the location of the monitoring stations; however, many people may spend much of their time at their workplace, which may be far from their home. Conversely, using administrative data
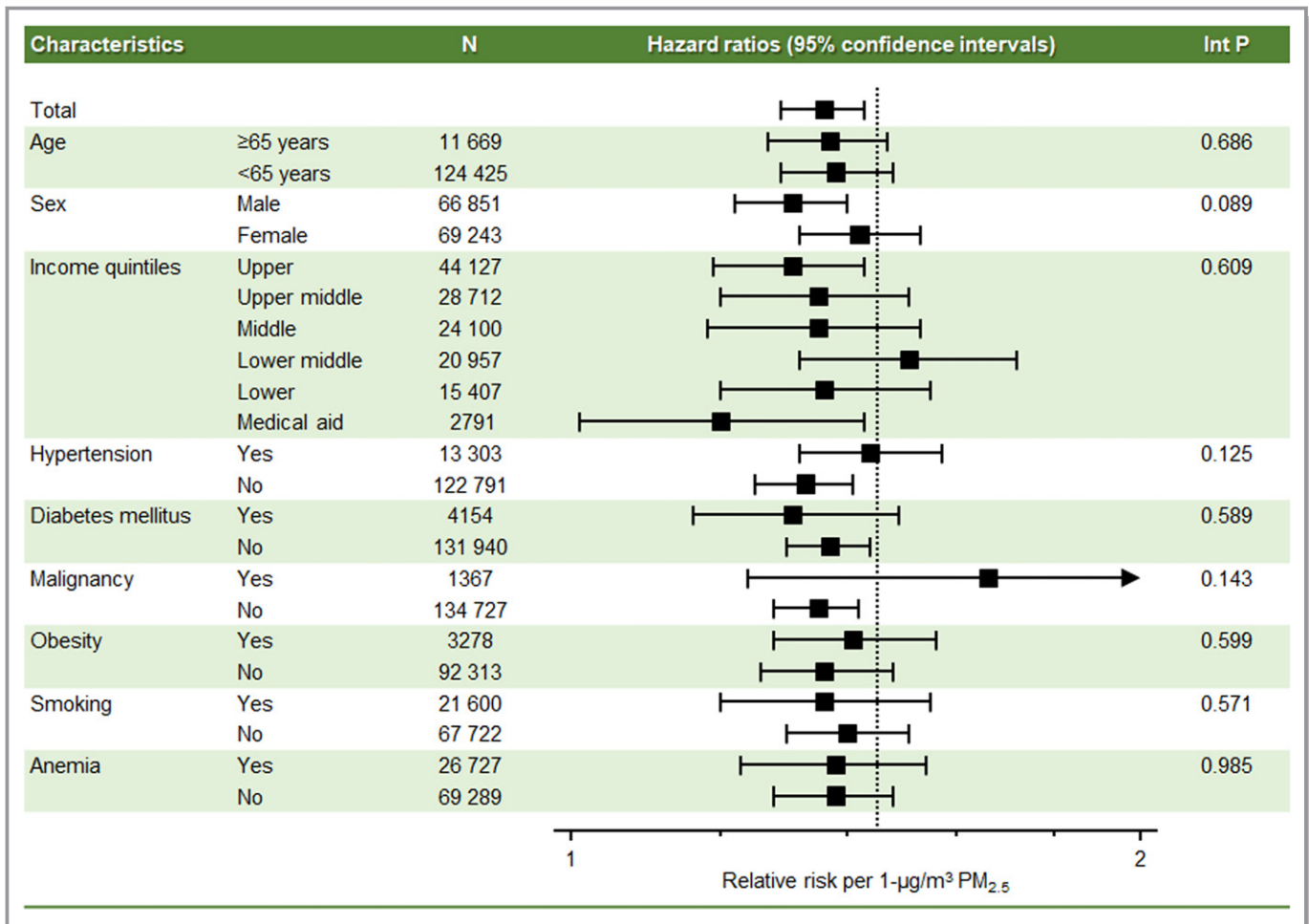
Figure 4. Subgroup analysis for cardiovascular risk of long-term exposure to PM$_{2.5}$. The *x*-axis represents hazard ratios with 95% confidence intervals. Int *P* denotes interaction *P* value; PM$_{2.5}$ indicates fine particulate matter ≤2.5 µm in aerodynamic diameter.

ensures reliable information on the individual residence with freedom from recall or nonresponse bias. Third, although PM$_{2.5}$ is a heterogeneous mixture of solid and liquid particles emitted from a variety of sources, we could not estimate the specific constituents and sources of the particles. Fourth, we used claims data to define covariates and outcomes.

Misclassification is a potential cause of bias in population-based studies using claims records.[34]

In conclusion, this study revealed that long-term exposure to air pollution increases the risk of major cardiovascular diseases such AMI, CHF, stroke, and mortality. Air pollutants including PM$_{2.5}$, PM$_{2.5-10}$, CO, SO$_2$, and NO$_2$, but not O$_3$,

Table 3. Population Attributable Risk Percentages and 95% CIs Associated With Selected Cardiovascular Risk Factors for Composite Cardiovascular Outcomes

		Sex		Age	
	Total	Men	Women	<65 y	≥65 y
PM$_{2.5}$ (>25.0 µg/m^3)	30.8 (24.1–37.5)	23.7 (16.9–30.6)	39.0 (30.9–47.2)	31.4 (23.5–40.3)	30.2 (23.5–37.1)
Hypertension	27.2 (24.1–30.4)	22.3 (18.6–26.1)	33.2 (30.1–36.3)	16.4 (13.9–18.8)	9.4 (2.5–16.4)
Diabetes mellitus	12.1 (10.2–14.1)	11.4 (9.2–13.7)	13.0 (10.3–15.7)	9.4 (7.4–11.4)	6.9 (3.9–9.9)
Dyslipidemia	10.9 (9.3–12.5)	9.1 (5.9–12.4)	13.0 (9.9–16.1)	9.2 (6.9–11.6)	−1.1 (−4.7 to 2.5)
Obesity	11.0 (5.9–16.0)	−0.7 (−7.0 to 5.7)	20.1 (14.7–25.4)	16.8 (11.7–21.9)	−4.8 (−10.9 to 1.4)

CI indicates confidence interval; PM$_{2.5}$, fine particulate matter ≤2.5 µm in aerodynamic diameter.

demonstrated positive relationships with cardiovascular risks, and the effects were consistent after adjusting for baseline risk factors and other pollutants. The attributable risk from air pollution was as large as that of conventional cardiovascular risk factors such as hypertension and diabetes mellitus.

Disclosures

None.

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Supplemental Material

Table S1. Summary statistics for air pollutions in Seoul, 2007–2013

Pollutants	Mean (SD*)	Quantiles					IQR†
		Min‡	25%	50%	75%	Max§	
$PM_{2.5}$, $\mu g/m^3$	25.03 (14.29)	2.79	15.04	21.92	31.00	121.10	15.96
$PM_{2.5\text{-}10}$, $\mu g/m^3$	25.23 (20.99)	2.00	13.52	21.21	30.04	367.30	16.52
CO, ppm‖	0.57 (0.24)	0.19	0.41	0.51	0.66	1.81	0.25
SO_2, ppb#	5.53 (2.30)	2.24	9.92	4.92	6.46	22.52	2.54
NO_2, ppb	34.45 (12.92)	6.44	24.52	32.32	42.92	92.35	18.4
O_3, ppb	19.93 (10.86)	1.84	11.18	18.75	27.08	71.12	15.9

*SD denotes standard deviation; †IQR, interquartile ranges; ‡min, minimum; §max, maximum; ‖ppm, parts-per-million, 10^{-6}. #ppb, parts-per-billion, 10^{-9};

Table S2. Correlation matrix among air pollutants, in Seoul, 2007-2013

	$PM_{2.5}$	$PM_{2.5\text{-}10}$	CO	SO_2	NO_2	O_3
$PM_{2.5}$	-	0.58	0.84	0.75	0.69	0.67
$PM_{2.5\text{-}10}$	0.58	-	0.93	0.42	0.45	0.37
CO	0.84	0.93	-	0.62	0.62	0.55
SO_2	0.75	0.42	0.62	-	0.77	0.84
NO_2	0.69	0.45	0.62	0.77	-	0.68
O_3	0.67	0.37	0.55	0.84	0.68	-

Table S3. Incidence of cardiovascular events per 100 person-years in Seoul, 2007–2013

Event	Total	Sex	
		Male	Female
Major adverse cardiovascular events	1,856 (0.21)*	1001 (0.23)	855 (0.19)
All-cause death	1,658 (0.18)	998 (0.23)	660 (0.14)
Cardiovascular death	265 (0.03)	133 (0.03)	132 (0.03)
Acute myocardial infarction	354 (0.04)	208 (0.05)	146 (0.03)
Congestive heart failure	652 (0.07)	319 (0.07)	333 (0.07)
Stroke	934 (0.10)	522 (0.12)	412 (0.09)
Ischemic stroke	688 (0.08)	385 (0.03)	303 (0.07)
Hemorrhagic stroke	292 (0.03)	164 (0.04)	128 (0.03)

*Data were presented as number of events (incidence per 100 person-years).

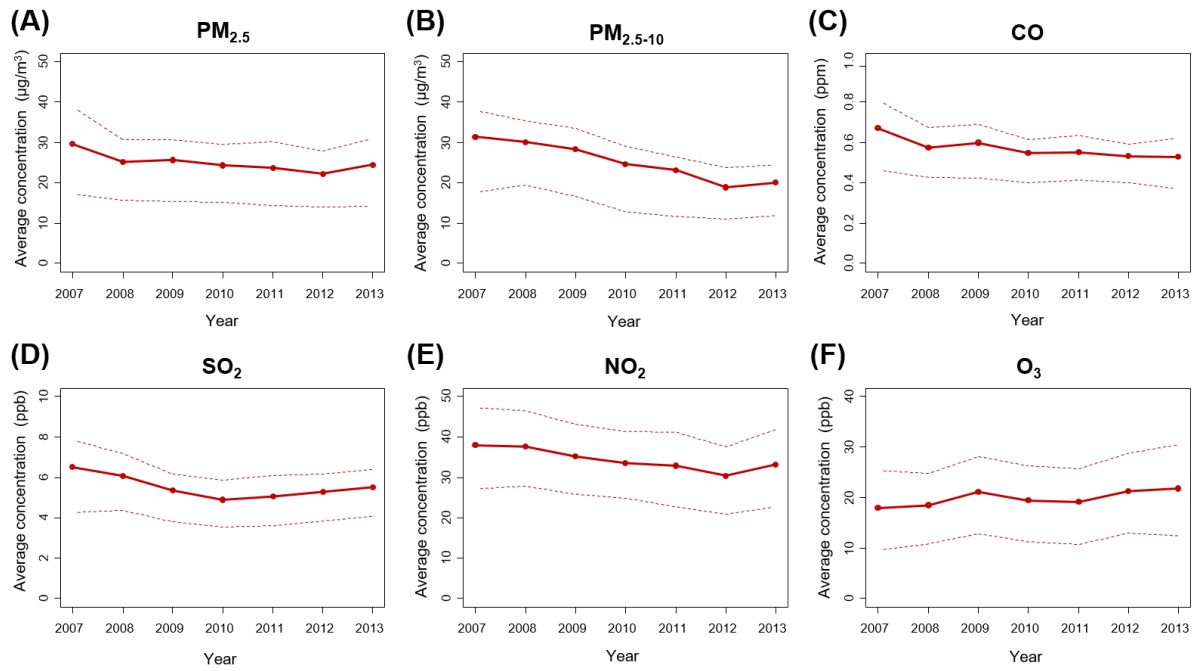**Figure S1.** The yearly trends of the average concentrations of air pollutants 2007-2013

Figure S2. Single, two-, and multi-pollutant models for cardiovascular risk of long-term exposure to $PM_{2.5}$. The y-axis denotes the hazard ratio (box) with 95% confidence intervals (line).