Long-term exposure of fine particulate matter air pollution and incident atrial fibrillation in the general population: A nationwide cohort study

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ABSTRACT

Background: Although many studies have linked elevations in fine particulate matter ($PM_{2.5}$) air pollution to adverse cardiovascular outcomes, long-term exposures of $PM_{2.5}$ on air pollution-related incident atrial fibrillation (AF) in general population have not yet been investigated well.

Methods: We included 432,587 subjects of general population not diagnosed with AF from the Korean National Health Insurance Service-National Sample Cohort from 2009 to 2013. Medical records were screened from January 2002 to investigate the subjects' disease-free baseline period. They were followed until December 2013. We matched subjects' residential ZIP code with hourly measurements of air pollutant (particulate and gaseous) concentrations and meteorological (temperature and humidity) data during the study period.

Results: During 1,666,528 person·years, incident AF was observed in 5825 subjects (350/100,000 person·year). We found significant associations between incident AF and long-term average concentrations of $PM_{2.5}$ (HR = 1.179[1.176–1.183] for 10 μg/m³ increments, $p < 0.001$), PM_{10} (HR = 1.034[1.033–1.036] for 10 μg/m³ increments, $p < 0.001$), and gaseous air pollutants during the study period. When dividing subjects into subgroups, these long-term exposures of $PM_{2.5}$ effects were more profound in males (HR = 1.187[1.183–1.192], $p < 0.001$), older subjects (aged ≥ 60 years; HR = 1.194[1.188–1.200], $p < 0.001$), those who were obesity (body mass index ≥ 27.5 kg/m², HR = 1.191[1.183–1.199], $p < 0.001$), subjects with previous myocardial infarction (HR = 1.203[1.186–1.221], $p < 0.001$), and history of hypertension (HR = 1.191[1.185–1.197], $p < 0.001$) (each interaction $p < 0.05$ compared to the opposite subgroup).

Conclusions: Even in the Asian general population, long-term exposure of $PM_{2.5}$ is associated with the increased incidence of new-onset AF. It is more profound in obese male subjects > 60-year old and who have a history of hypertension or previous myocardial infarction.

1. Introduction

Epidemiological studies have suggested that elevated ambient particulate matter (PM) <2.5 μm ($PM_{2.5}$) or <10 μm (PM_{10}) in aerodynamic diameter are consistently associated with adverse cardiac events [1–4]. Although many studies for these adverse cardiovascular outcomes have been performed [5,6], some studies did not show correlations between short-term exposures of $PM_{2.5}$ and incident atrial fibrillation (AF) [7,8]. However, these studies were performed in European society and United States, where air pollution levels were much lower compared to Asian

countries; therefore, the effect sizes could be low in these areas. Moreover, the effects of long-term exposure to $PM_{2.5}$ on air pollution-related incident AF in the general population or even in healthy subjects with less comorbidities from the general population have not yet been well-investigated. Because AF is associated with multiple life-threatening conditions, such as ischemic stroke, and also has numerous risk factors of its own (such as hypertension in general population which had been known to be affected by air pollution [9]), accurately identifying the risk factors and allocating the right amount of attention and resources to the underlying conditions is crucial for successful patient care and prophylaxis. A previous retrospective study pointed to a possible association between AF with rapid ventricular responses and air pollution. That study was limited by the large proportion of patients who had single-chamber implantable defibrillators, which will only detect AF episodes that cause a rapid ventricular response [10]. Other studies have hinted at an association between air pollution

and AF, in that air pollution has been associated with some electrophysiological predictors of AF [11], and also with atrial premature beats [12]. Therefore, we conducted a large, comprehensive, cohort study using a Korean adult general population in an attempt to identify a direct association between long-term exposures of air pollution and new-onset AF. Furthermore, because the risks imposed by baseline characteristics can depend on regional and ethnic differences [13,14], we also focused on the endemic relevance of air pollution related to new-onset AF by using a Korean nationwide cohort.

2. Methods

This nationwide cohort study was about the relationships between long-term exposures of air pollution and incident AF and was performed according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement reporting guidelines (Supplementary Table 1) [15].

2.1. Study cohort

(**Data Source** was described in detail on Supplementary Methods)
The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University College of Medicine. This study was based on the Korean National Health Insurance Service (NHIS)-National Sample Cohort (NSC) database from 2002 to 2013 [16]. Among an entire population in South Korea (about 47 million people in 2002), 96.6% were registered in NHIS. Adults ($n = 506,805$) over 18 years of age who received National Health Examination at least once between 2009 and 2013 among the total population ($n = 1,025,340$) included in the NHIS-NSC (NHIS-2016-2-189) [16]. Each was followed from health examination day to 31 December 2013, and was screened from January 2002 (>7 years) to assess the past medical history (2002–2008: disease-free baseline period). Further, the subjects who were matched with the exclusion criteria as follows were excluded (Fig. 1): (i) those under the age of 18, (ii) those diagnosed with AF (diagnoses based on the 10th revision of the International Classification of Disease (ICD-10) codes: ICD-I48) before undergoing a health examination, (iii) those with valvular AF, such as mitral valve stenosis or prosthetic valve disease (ICD-I050, I052, I342), (iv) who changed abode to another region in 2009–2013 (who cannot be matched with the regional air pollution information consistently during this period due to migration), and (v) those missing data regarding their residential ZIP code or the questionnaires for smoking status and alcohol intake given at the health examinations. Then, 432,587 subjects were finally included as the study population (overall general population, Fig. 1). For sensitivity analysis, we additionally excluded those with heart failure, hypertension, diabetes mellitus, stroke, myocardial infarction, peripheral vascular disease, and heavy alcoholic tendencies (those who drinks > 504.0 g/week of alcohol), which were known as AF-related comorbidities [17]. After that, a population of 307,106 healthy subjects was included in the sensitivity analysis to investigate the robustness of our main analysis (Supplementary Fig. 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 2), as likely a diagnosis of AF [18–20]. The cohort was followed to the time of an AF incidence, or to the condition disqualifying of the NHIS (death or emigration), or the end of the study (31 December 2013).

2.2. Air pollution measurements

Fine particle mass and gaseous air pollution ($PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3), plus temperature and humidity were measured hourly at the 313 sites of the Korean Nationwide Meteorological Observatory by the Korean Department of Environmental Protection during the study period. The entire Korean area was divided into 256 residential ZIP codes and has 74 codes with metropolitan area (average 73 km^2). To assess long-term exposures of air pollution effects, the nearest monitor of each residence was identified and used to assess an average annual pollutant concentrations to each study subject [5]. Geographically-based long-term average concentration of each air pollutant during the study period was measured hourly by the monitoring facilities [21], and 256 residential ZIP codes were matched with the nearest monitoring facilities. Meteorological variables (temperature and humidity) were included as geographically-based long-term average of hourly measured temperature and humidity for each subject during the follow-up period. Long-term average (during the total study period for each subject) air pollutant concentrations and meteorological measurements (temperature and humidity) were calculated from these hourly measurements for each site. Korean national air quality standards and measurement methods of each air pollutant are described in Supplementary Table 3.

2.3. Life-style factors and other clinical variables

Past medical histories were analyzed using medical claim data with ICD codes (Supplementary Table 2), and questionnaires regarding disease history and measurement of blood pressure and fasting blood glucose levels collected during health examinations.
The frequency (and proportion) of AF was described depending on age (15-year interval age groups), sex, and comorbidities. Further, Cox regression analyses were used to analyze the association between the life-style factors (smoking status and alcohol intake) and AF incidence. Models adjusting for the clinical variables were used to assess these associations.
Subjects were classified as non-, <20 pack·years or ≥20 pack·years (former- or current-) smokers, and the amount of the alcohol intake was classified as 0–220.5 g/week or ≥220.5 g/week. The primary outcome was the incidence of atrial fibrillation (AF) according to each air pollutant concentration. The incidence of AF was determined by counting the number of cases of new-onset AF, diagnosed either during a subject's first hospital admission, emergency department visits without subsequent hospital admissions, or during at least two different outpatient visits (with an interval of three months or more), and the number of deaths that occurred with a diagnosis of AF, as determined by an ICD-10 code of I48 [18–20]. To validate the accuracy of AF diagnosis in the NHIS database, we performed the validation study [19]. The cohort was followed up to the time of an AF incident, disqualification from the National Health Insurance Service
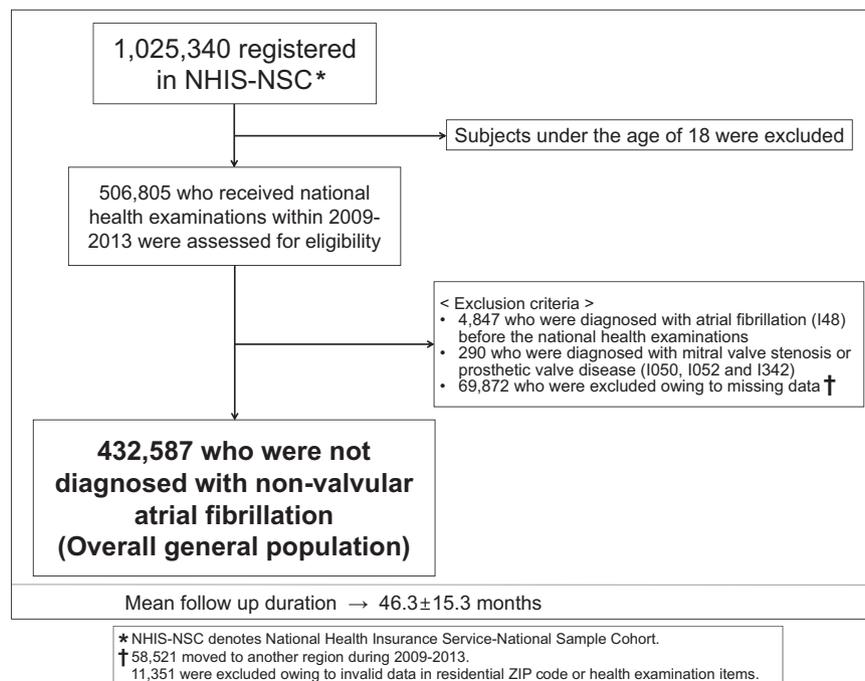

Fig. 1. Study cohort and included subjects in NHIS-NSC (overall general population). NHIS-NSC, National Health Insurance Service-National Sample Cohort.

(death or immigration), or the end of the study (31 December 2013). For stroke history, we investigated the cerebral bleeding and infarction (ICD-10 code: I60-64), and excluded transient ischemic attacks (G45) or other kinds of thromboembolisms. To avoid an over-estimation of the risk of AF-related stroke, we used a blanking period of 4 weeks after the index date, and excluded events during this period which occurred immediately after the first diagnosis of AF [22]. The accuracy of the diagnosis of ischemic stroke in the NHIS database was also previously validated [16].

2.4. Statistical analyses

The multivariable model included age, sex, BMI, socioeconomic status, smoking status, and meteorological variable (relative humidity) [23,24]. To adjust potential confounders, we fit a multi-pollutant Cox-regression analysis [24] to assess the correlations between each pollutant and incident AF. Incident AF associated with exposure to each single pollutant was adjusted for exposure to other pollutants. New-onset AF 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 new-onset AF, disqualification (death or immigration), or the end of study in Cox-regression analysis.

We assumed the study subjects were exposed to ambient air pollution within their residential ZIP codes during the study period [24]. Individual subjects were matched with average air pollution concentrations and meteorological information during the study period from their nearest monitoring facilities according to their residential address. The relationship between incident AF and air pollutant concentration was analyzed by a Cox proportional-hazard model regression analysis using a generalized estimating equation approach with a random effects analysis [25,26].

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 healthy subjects (see Methods – Study cohort) to investigate the pure air pollution effect on AF incidence in these populations. Linear estimates of hazard ratio about concentration-response relationship between air pollution and incident AF were tested by log-linear model with a thin-plate splines for each air pollutant with adjusting age, sex, BMI, socioeconomic status, smoking status, and meteorological (temperature and humidity) variable (Fig. 2, Supplementary Figs. 2–4).

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. The AF incidences in Figs. 1–3 were represented as 'per person·year' to provide more accurate comparisons among groups because the follow-up time periods were not the same in all groups. We expressed a rate of events per 100,000 person·years. All statistical analyses were performed with SAS software (version 9.2, SAS Institute, Cary, NC, USA).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

3. Results

3.1. Baseline characteristics

In all, 1.3% of the study population developed new-onset AF during a mean follow-up of 3.9 ± 1.3 years. The risk of incident AF was higher in males than females, and increased with an advancing age (Supplementary Table 4, and Supplementary Table 5 for Sensitivity analysis – see Methods). Obesity [≥27.5 kg/m^2, hazard ratio (HR) 1.43 [1.16–1.76], p < 0.001] was associated with a higher risk of AF compared with a normal BMI (18.5 kg/m^2 ≤ BMI < 23.0 kg/m^2), and the population with heavy smoker (current- or former-, ≥20 pyrs, HR = 1.56 [1.45–1.68], p < 0.001), previous myocardial infarction (HR 1.73 [1.45–2.06], p < 0.001), heart failure (HR 2.16 [1.92–2.44], p < 0.001), stroke (HR 1.55 [1.41–1.72], p < 0.001), hypertension (HR 1.45 [1.30–1.61], p < 0.001), or diabetes mellitus (HR 1.38 [1.26–1.51], p < 0.001) had an increased risk of new-onset AF compared with the opposite population (Supplementary Tables 4 and 5).

(**Air pollution and meteorological measurements** is described in detail on Supplementary Results)

3.2. Ambient particulate air pollution is associated with the increased incidence of new-onset AF

In Cox proportional-hazards models using covariates including age, sex, BMI, socioeconomic status, smoking status, and meteorological variables (temperature and humidity), an increase in PM$_{2.5}$ concentration by 10 μg/m^3 is independently associated with the increased risk of new-onset AF (HR = 1.179 [1.176–1.183], p < 0.001) (Table 1). PM$_{10}$ (by 10 μg/m^3 increase, HR 1.034 [1.033–1.036], p < 0.001) was also showed significant relationship (Table 1). We performed a sensitivity analysis to examine the robustness of our main results with healthy population, and overall results were consistent (Supplementary Table 7). Fig. 2 showed concentration-response relationship between long-term exposures of particulate air pollutants and incident AF tested by log-linear model with a thin-plate spline among overall general population with 432,587 subjects. It indicated significant and almost linear associations between particulate air pollutants and incident AF. Sensitivity analysis among 307,106 healthy subjects also showed consistent results (Supplementary Fig. 3).

3.3. Gaseous air pollution and the risk of new-onset atrial fibrillation

In Cox proportional-hazards models, an increase in SO$_2$ concentration by 10 ppb, NO$_2$ concentration by 10 ppb, and CO concentration by 1 ppm were each correlated with an increase in the incidence of AF, with HRs of 1.008, 1.016 and 1.022, respectively (p < 0.001 each) (Table 1). Even after adjusting for clinical and meteorological variables, an increase in SO$_2$ by 10 ppb, NO$_2$ by 10 ppb, and CO by 1 ppm was associated with an increased incidence of AF, with HRs of 1.005, 1.011, 1.017, respectively (p < 0.001 each) (Table 1; and Supplementary Table 7 for Sensitivity analysis). However, there was no association between O$_3$ concentration and incident AF. Supplementary Fig. 2 showed concentration-response relationship between long-term exposures of gaseous air pollutants and incident AF tested by log-linear model with a thin-plate spline among overall general population with 432,587 subjects. It indicated significant associations between gaseous air pollutants and incident AF except O$_3$. Sensitivity analysis among 307,106 healthy subjects also showed consistent results (Supplementary Fig. 4).

3.4. Subgroup analyses

Subgroup analyses revealed that men, subjects with an older age (≥60 years), those who were obese (BMI ≥ 27.5 kg/m^2), subjects with hypertension, and those with previous history of myocardial infarction had a higher estimated hazard of incident AF in association with PM$_{2.5}$ exposure (each interaction p-value < 0.05, respectively) (Fig. 3). In subjects who were male, of an older age (aged ≥ 60 years), obese (BMI ≥ 27.5 kg/m^2), and who have a history of hypertension or myocardial infarction, the rates of hazard ratio estimates for PM$_{2.5}$ were 1.01, 1.02, 1.01, 1.02, and 1.01 times higher, respectively, than those for the opposite population (Fig. 3).

4. Discussion

Even for the Asian general population, long-term exposures of air pollution were associated with the incidence of new-onset AF. After adjusting for clinical and meteorological variables, an increase in PM$_{2.5}$ and PM$_{10}$ by 10 μg/m^3 is associated with the increased risk of AF by 17.9% and 3.4%, respectively. Furthermore, the relationship between the incidence of AF and PM$_{2.5}$ and PM$_{10}$ exposure was more prominent in older (aged ≥ 60 years), obese (BMI ≥ 27.5 kg/m^2) subjects and who have a history of hypertension or myocardial infarction in this Asian general population. These findings suggest that subjects with conventional AF risk factors are more influenced by air pollution than subjects without conventional risk factors with regards to developing new-onset AF.

4.1. Clinical importance of the effects of air pollution on atrial fibrillation

Although some studies showed relationships between short-term exposures of air pollution and AF episodes in patients with known cardiac diseases [6,10], some studies from Western countries failed to show relationship between short-term exposures of PM$_{2.5}$ and incident AF [7,8]. However, these studies were performed in European society

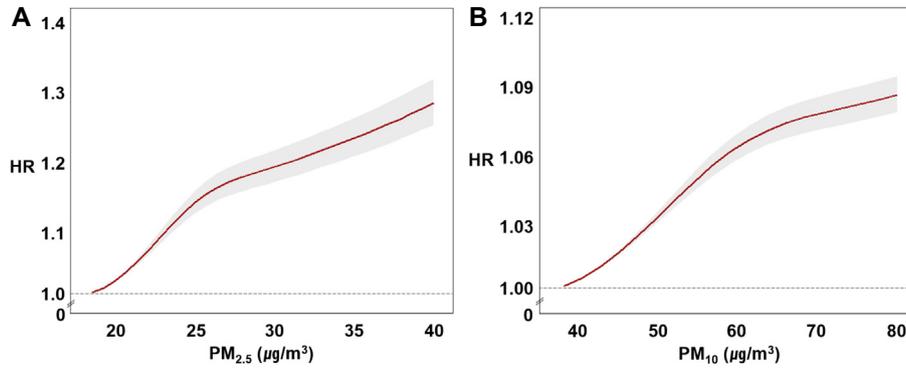## Particulate air pollutants and incident AF (Overall general population)

Fig. 2. Concentration-response relationships between long-term exposures of particulate air pollutants and incident AF tested by log-linear model with thin-plate splines (overall general population with 432,587 subjects). A, $PM_{2.5}$ and incident AF. B, PM_{10} and incident AF. AF, atrial fibrillation; HR, hazard ratio; $PM_{2.5}$, particulate matter < 2.5 μm in diameter; PM_{10}, particulate matter < 10 μm in diameter.

and United States, where air pollution levels were much lower compared to Asian countries; therefore, the effect sizes could be low in these areas. Moreover, the long-term exposure effects of $PM_{2.5}$ on incident AF in the general population have not yet been well-investigated. Cohort studies investigated the associations between long-term exposures of air pollution and incident AF; however, they did not investigate the correlations to $PM_{2.5}$ [27], and they did not show significant associations in relatively small populations [28]. This study showed an association between incident AF and exposure to particulate and gaseous air pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO), with the strongest relationship between $PM_{2.5}$ exposure and incident AF, in the general population and even in healthy subjects. A previous meta-analysis showed the pooled results of the studies which investigated the association

between air pollution and AF [29]; however, these associations have not been assessed in healthy subjects from the general population.

Exposure to ambient air pollution contributes to various adverse effects, including arrhythmias [3]. One suggested mechanism is the occurrence of myocardial repolarization abnormalities contributing to arrhythmias [30,31] caused by systemic inflammatory cytokines produced by pulmonary inflammatory responses after inhaling particles [32]. Another suggested mechanism includes alteration of the cardiac autonomic nervous system that occurs with the inhalation of particles [33] mediated by reactive oxygen species [34]. A previous study showed a decreased correlation between air pollution and arrhythmias in chronic lung disease [35]. Consistent with those findings, this study showed that former- or current-smokers who smoked ≥20 pack·years

$PM_{2.5}$ and incident AF according to subgroups (Overall general population)

	N	Incident AF : age-, sex- adjusted (per 100,000 person·year)		Adjusted HR (by 10μg/m³ of $PM_{2.5}$ increase)	P for interaction
Male	216,653	470 (455-485)		1.187 (1.183-1.192)	<0.001
Female	215,934	378 (365-392)		1.178 (1.174-1.182)	
Age≥60	96,114	1,225 (1,190-1,261)		1.194 (1.188-1.200)	<0.001
Age<60	336,473	194 (186-201)		1.173 (1.169-1.177)	
BMI <18.5 kg/m²	18,107	386 (340-436)		1.184 (1.168-1.200)	0.687
BMI 18.5-22.9 kg/m²	171,830	347 (333-362)		1.181 (1.177-1.185)	Ref
BMI 23.0-27.4 kg/m²	191,303	459 (444-475)		1.185 (1.181-1.190)	0.163
BMI ≥27.5 kg/m²	51,347	565 (532-600)		1.191 (1.183-1.199)	0.046
Smoking ≥20pyrs	56,551	640 (607-674)		1.178 (1.170-1.187)	0.164
Smoking <20pyrs	106,480	299 (282-316)		1.182 (1.176-1.189)	0.536
Non-smoker	269,556	421 (408-434)		1.187 (1.183-1.191)	Ref
Lower SES	170,809	404 (389-420)		1.185 (1.180-1.190)	0.332
Higher SES	261,778	438 (426-452)		1.180 (1.176-1.184)	
Previous MI (+)	4,396	3,764 (3,471-4,076)		1.203 (1.186-1.221)	0.001
Previous MI (-)	428,191	392 (383-402)		1.181 (1.178-1.184)	
Previous HF (+)	10,751	4,430 (4,226-4,642)		1.196 (1.184-1.211)	0.103
Previous HF (-)	421,836	327 (318-336)		1.181 (1.178-1.184)	
Previous Stroke (+)	16,731	2,139 (2,025-2,256)		1.194 (1.179-1.209)	0.071
Previous Stroke (-)	415,856	358 (349-368)		1.180 (1.177-1.184)	
HTN (+)	95,448	1,350 (1,313-1,388)		1.191 (1.185-1.197)	0.039
HTN (-)	337,139	164 (157-171)		1.178 (1.174-1.183)	
DM (+)	27,627	1,256 (1,188-1,326)		1.192 (1.179-1.205)	0.058
DM (-)	404,960	370 (360-380)		1.181 (1.177-1.185)	

1.0 1.17   1.19   1.21

Fig. 3. Effect of $PM_{2.5}$ exposure on the incidence of AF in different subgroups (overall general population with 432,587 subjects). The HR was adjusted for age, sex, BMI, SES, smoking status, and meteorological variables (temperature and humidity). 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.

Table 1
Ambient particulate and gaseous air pollution and incidence of atrial fibrillation in overall general population ($n = 432,587$).

Air pollutants[a]	Crude		Adjusted for clinical and meteorological variables[b]	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
$PM_{2.5}$ (by 10 μg/m^3 increase)	**1.192** (1.189–1.195)	**<0.001**	**1.179** (1.176–1.183)	**<0.001**
PM_{10} (by 10 μg/m^3 increase)	**1.040** (1.039–1.041)	**<0.001**	**1.034** (1.033–1.036)	**<0.001**
SO_2 (by 10 ppb increase)	**1.008** (1.007–1.009)	**<0.001**	**1.005** (1.003–1.006)	**<0.001**
NO_2 (by 10 ppb increase)	**1.016** (1.015–1.017)	**<0.001**	**1.011** (1.009–1.013)	**<0.001**
CO (by 1 ppm increase)	**1.022** (1.021–1.023)	**<0.001**	**1.017** (1.013–1.022)	**<0.001**
O_3 (by 10 ppb increase)	0.911 (0.834–1.027)	0.302	0.923 (0.834–1.055)	0.343

Bold: $p < 0.05$.
AF, atrial fibrillation; BMI, body mass index (kg/m^2); CI, confidence interval; CO, carbon monoxide; HR, hazard ratio; NO$_2$, nitrogen dioxide; O$_3$, ozone; PM$_{2.5}$, particulate matter <2.5 μm in diameter; PM$_{10}$, particulate matter <10 μm in diameter; ppb, parts per billion; ppm, parts per million; SO$_2$, sulfur dioxide.
[a] To adjust potential confounders, we fit a multi-pollutant Cox regression analysis to assess the correlations between each pollutant and incident AF. Incident AF associated with exposure to each single pollutant was adjusted for exposure to other pollutants.
[b] Clinical variables were age, sex, BMI, socioeconomic status, and smoking status. Meteorological variables indicate temperature and humidity.

had a lower association between PM$_{2.5}$ and PM$_{10}$ exposure and incident AF compared to smokers who smoked <20 pack·years.

4.2. Subjects with conventional AF risk factors are more influenced by PM$_{2.5}$ with regards to incident AF

In this study we analyzed from overall general population and we also performed a sensitivity analysis with excluding subjects with AF-related comorbidities with heart failure, hypertension, diabetes mellitus, stroke, vascular disease, or heavy alcoholics [17], to minimize the influence of conventional risk factors on incident AF. However, several risk factors, including old age, obesity, smoking, prehypertension and prediabetes, were not excluded [36]. Interestingly, air pollution is associated with the increased risk of incident AF in subjects who were male, older, obese, and who have a history of hypertension or myocardial infarction. A sensitivity analysis among healthy subjects also showed similar result (Supplementary Fig. 5). These findings suggest that there are susceptible patients to the effects of long-term exposure of air pollution with regards to incident AF.

In subgroup analysis, higher exposure to cigarette smoking showed smaller associations compared with non-smokers (Fig. 3), there might be the possible explanations that air pollution effects might be somewhat diminished in subjects with pulmonary diseases [35].

4.3. Study strengths compared with previous reports

There have been multiple studies on the association between atrial arrhythmias and certain air pollutants [32,33]; however, there are a limited number of studies on the effect of ambient particulate and gaseous air pollution on new-onset AF. Even the few studies on air pollution tended to be of a smaller scale with a few thousand subjects [32,33], of which a very small proportion develop AF, or were limited to a narrow age group of a particular sex [37,38]. In contrast, our study is (i) a large-scale adult cohort (≥18 years) of over 400,000 subjects who underwent a National Health Examinations that were enrolled in the Korean NHIS cohort and (ii) a long-term follow-up duration of more than a mean of 1,666,528 person-years, and (iii) we performed a sensitivity analysis with excluding those subjects with comorbidities to analyze the direct effect of air pollution on new-onset AF in healthy subjects from the general population, and it showed the robustness of the main results. Finally, (iv) these correlations also showed concentration-response relationships tested by log-linear model with thin-plate splines, it strengthens our results.

4.4. Clinical implications

Our study supported that air pollution has a significant association and a concentration-response relationship with new-onset AF in the general population and even in healthy subjects with less comorbidities.

Secondarily, controlling the air pollution, in the general population, may be an additional prophylactic measure for preventing new-onset AF.

4.5. Limitations

Our study, nonetheless, had its limitations. Because we set seven years (2002–2008) of disease-free baseline period and excluded subjects who diagnosed with AF previously, this also has selection bias. However, we performed the validation study for the accuracy of the AF diagnosis in the NHIS database [19]. Subjects with many important comorbidities have known to affect the occurrence of AF much more than air pollution were all included in our main analysis (overall general population of 432,587 subjects), and a sensitivity analysis with excluding these population to analyze the true air pollution effects in healthy population also showed consistent results. Although we excluded subjects who changed abode to another region within the study periods, this might not have fully reflected participants' specific locations or air pollutant exposure during the periods. In addition, since our study cohort was constituted with the National Health Insurance administrative claim data, we could not identify the exact hour of AF development. For this reason, the analysis for the acute exposure effects was thought as it may draw somewhat biased results with our cohort data, and further investigation is needed. Although we analyzed the air pollution effect on incident AF while adjusting age, sex, BMI, socioeconomic status, smoking status, and meteorological variables, some confounders (e.g. noise) [39] were not considered. Data for subjects using occasional recreational drug (which might be expected to have little portions in our country) were not available in our cohort, which were well-known risk factors for paroxysmal AF in younger population [40]. In sensitivity analysis, overall results were consistent among healthy population after excluding subjects with AF-related comorbidities (Sensitivity analysis: Supplementary Figs. 1 and 3–5). Because the air pollution data of different sources (such as diesel, benzene, or metal compounds) were not available, we could analyze with only measured air pollutants (PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO, and O$_3$). To estimate each air pollutant contribution to PM$_{2.5}$, we fit another multi-pollutant Cox regression analyses with mutual adjustment model to assess the correlation between PM$_{2.5}$ and incident AF (Supplementary Table 8). Because smoking history and alcohol intake behavior were obtained from the questionnaires during the national health examinations, careful interpretation of these results is needed, and so we used two models of Cox-regression analysis, overall results were also consistent (Table 1 and Supplementary Table 7). We did not investigate the associations between air pollution and myocardial repolarization, and thus the mechanism behind the relationship exposure of air pollution and AF remains unclear.

5. Conclusions

Even in the Asian general population or in healthy subjects, long-term exposure of PM$_{2.5}$ is associated with the increased incidence of new-onset AF. It may suggest that there are susceptible people who are more influenced by long-term exposure of PM$_{2.5}$ with regards to incident AF, especially obese male subjects who were older than 60 years of age. Although the relationships between air pollution and AF incidences are significant, the effect sizes were somewhat small, therefore, it is still important to manage the well-known cardiovascular risk factors of AF.

Conflicts of interest

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

Appendix A. Supplementary materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.048.

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