The Association Between Ambient Air Pollution and Atrial Fibrillation
A Systematic Review and Meta-Analysis

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Summary
Atrial fibrillation (AF) is the most common cardiac arrhythmia; it has been known to increase the risk of stroke and heart failure. The association between air pollutants and AF has remained to be controversial. Thus, in this study, we sought to undertake a systematic review and meta-analysis in order to assess the short- and long-term effects of ambient air pollution on AF.

We searched PubMed, Web of Science, Embase, and Ovid for all related studies up to October 2019. We used the random-effects model to estimate the excess risk percentage (ER%) and confidence intervals (CI) for particulate matter with diameter ≤2.5 (PM$_{2.5}$) and ≤10 μm (PM$_{10}$), sulfur dioxide (SO$_2$), nitrogen dioxide (NO$_2$), ozone (O$_3$), and carbon monoxide (CO). Results were further analyzed by subgroups according to location, age, outcome, and gender.

In total, 18 studies were included in our meta-analysis: 5 evaluated for long-term effects, 12 for short-term effects, and 1 for both long- and short-term effects. For the short term, ER per 10 μg/m$^3$ increase of pollutants was 1.8% (0%-3.7%) for PM$_{2.5}$ and 1.1% (−0.2%−2.4%) for PM$_{10}$ per 10 parts per billion (ppb) increment of gaseous pollutions was 3.2% (0.6%-5.8%) for NO$_2$, 2.9% (0.3%-5.7%) for SO$_2$, 0.5% (−3.4%-4.7%) for O$_3$, and 2.0% (−1.3%-5.4%) for CO per 1000 ppb change. The subgroup analysis showed the short-term effect was significantly different by region, gender, outcome, and age. Meanwhile, in the long term, except for O$_3$, a statistically significant association was noted between AF incidence and all pollutants.

Our meta-analysis suggests that short-term exposure to part of pollutants (PM$_{2.5}$, SO$_2$, and NO$_2$) increases AF attack. Further, long-term exposure to air pollution can significantly contribute to the incidence of AF in a healthy population.

Key words: Cardiac arrhythmia, Particulate matter, Gaseous pollutions

Atrial fibrillation (AF) has been identified as the most common cardiac arrhythmia occurring in the general population and is one of the major causes of stroke, cardiac morbidity, and mortality. The underlying mechanisms for AF are complex, including inflammation, atrial fibrosis, electrical remodeling, autonomic dysfunction, calcium-handling abnormalities, and oxidative stress. A previous study has shown that advanced age, male sex, hypertension, and diabetes were well-estimated risk factors of AF. In addition, obesity, hyperuricemia, and alcohol abuse have been shown to be important contributors to AF.

Air pollution is recognized as one of the largest environmental health risks worldwide. The Global Burden of Disease, Injuries, and Risk Factor study 2017 (GBD 2017) estimated that air pollution, especially ambient particulate matter (PM) pollution, was responsible for nearly 4.9 million premature deaths globally. Previous studies suggested that air pollution is associated with an increased risk of pneumonia and stroke. Moreover, a recent study demonstrated that PM$_{2.5}$ is associated with an approximated 16% increase in the risk of heart disease mortality. A large body of literature shows that the effects of acute exposure to air pollution are thought to be mediated through oxidative stress, inflammation, and disturbance of autonomic function.

Given the putative pathophysiologic mechanisms, there seems to be a mechanistic link between air pollution and AF. Short-term exposure to air pollutants may increase AF attack in patients with AF history or those who are considered as high risk; further, long-term exposure may change electrophysiological characteristics of atria, which can result in the development of AF in healthy population. However, the findings of those studies that have evaluated the effect of ambient air pollutants on the AF remain inconsistent. Accordingly, we aim to provide a comprehensive meta-analysis to evaluate the short-term and long-term effects of air pollution on AF.

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Methods

Search strategy: We conducted searches indexed in PubMed, Embase, and Web of Science to identify all relevant observational studies, published until October 2019, and to further evaluate the relationship between short-term or long-term effects of outdoor air pollutants and AF. The search was restricted to studies conducted in human subjects, and there was no language restriction. Medical subject headings and free text words were combined, and the detailed search strategy was shown in the supplemental material (Supplemental Text).

Selection criteria: The inclusion criteria were as follows: (1) studies examining the short- or long-term effects of ambient air pollutants (PM_{2.5}, PM_{10}, nitrogen dioxide, sulfur dioxide, carbon monoxide, and ozone) on AF; (2) studies examining the short-term association must be time-series or case-crossover studies; (3) studies providing the relative risks (RR), odds ratios (OR), or hazard ratio (HR) and the corresponding 95% confidence intervals.

The exclusion criteria were as follows: (1) studies that do not include AF as an endpoint; (2) review articles or letters; and (3) conference abstract.

Two independent (CM and ZJQ) reviewers screened the retrieved records based on the title and abstract. Then, the full texts of all potentially relevant articles were examined to assess for compliance with the inclusion criteria. Any disagreement between the two reviewers was resolved by consensus after discussing or calling upon a third reviewer (ZLR) to reach a final decision.

Data extraction: Data from each article were abstracted independently by two investigators. The extracted data elements included citation information (author and year of publication), the study design, study location or country, study period, study population, sample size, data source of outcomes, air pollutant level, and study outcomes (RR, OR, or HR and the corresponding 95% CI). All conflicts were decided by consensus between the reviewers.

Quality assessment: The quality assessment was performed using Newcastle-Ottawa Scale. To fit this study, we also took into account the similarities between the study groups on daily air level measured, methods of the studies, and covariates in the models. While abstracting the data for the analysis, CM and ZJQ independently performed the quality assessment.

Statistical analyses: Meta-analysis was performed across available studies to separately evaluate the evidence for or against an association between each air pollution (PM_{2.5}, PM_{10}, nitrogen dioxide, sulfur dioxide, carbon monoxide, and ozone) and outcome (trigger or incidence of AF). We have chosen those studies, which used either time-series or case-crossover analyses into our meta-analysis because both methods are widely used to assess the short-term effect of air pollution on the daily health condition.

Some studies have published various lags, models (single- or multi-pollution models), or subgroups by different factors. In order to avoid over-representation of a single study, we chose only one result from each study in the pooled estimate according to the following rules: (1) if the study provided several lags, the shortest one was selected; (2) if there were no single lag estimates, we used cumulative lags; (3) if results from both single- and multi-pollutant models were available, only the results from multi-pollutant models were included; (4) if results were reported for multiple seasons or temperatures, we selected an overall effect estimate.

We pooled RR or HR for a standardized increment in pollutant concentration: 10 μg/m^3 for PM_{2.5} and PM_{10}, 10 ppb for NO, SO2, and O3, and 1 part per million (ppm) for CO. In case of small relative risk or the OR value using conditional logistic regression models, the odds ratio and RR can be considered the same. As previously reported,7 we used the following formula to calculate the RR standardized or HR standardized (RR_{U} or HR_{U} is reported in the original research, and U is the increment used in the original research):

\[ \text{RR(HR)}_{\text{standardized}} = \frac{\text{RR(hR)}_{0}}{U} \]

Forest plots were then conducted to evaluate the summary of RR (HR) and 95% CI of individual studies by using random-effects models. Heterogeneity was evaluated through the I^2 statistic derived from the chi-square test.13 An I^2 > 50% indicates high statistical heterogeneity. Then, the sensitivity analysis was conducted by repeating meta-analysis, which excluded study one by one to assess the consistency of the main results.16 Funnel plots and Egger’s regression test were performed to determine any publication bias. Further, we analyzed the results by subgroups according to the location, outcome, age, and gender.

The overall effect estimates are reported as the percent change (ER% = (RR-1) × 100%) with 95% CI in the occurrence of AF per increment in air pollution. All statistical analyses were conducted using Stata 13 (Stata Corp LP, College Station, TX, USA). A two-tailed P-value of <0.05 was considered statistically significant.

Results

Our initial literature search yielded 1487 records. After reviewing the titles and abstracts, majority of these records (n = 1457) were discarded, mostly because the articles were not relevant and were reviews or letters. Subsequently, the remaining 30 full-text studies were closely evaluated, and 12 studies were further excluded. Thus, in total, 18 studies were included in our meta-analysis: 5 evaluated the long-term relationship,5-19 12 evaluated the short-term relationship,20-31 and 1 both evaluated the long- and short-term relationship.32 A flowchart summarizing the literature search progress is shown in the supplemental material (Supplemental Figure 1).

The short-term effects of air pollution on atrial fibrillation: Among those studies examining the short-term impact of air pollutants on AF, nine used a case-crossover approach, and four used a time-series analysis. The main features of the studies included in the meta-analysis are shown in Table I. Those short-term studies were conducted in North America (n = 3), Asia (n = 7), and Europe (n = 3). Most of the studies defined the outcomes by using the International Classification of Diseases (ICD) version 9 (code 427.3) or ICD10 (code 148); three studies defined the AF episodes according to the definition of the
American Heart Association, the American College of Cardiology, and the Heart Rhythm Society. All of them adjusted for seasonality, long-term time trends, and meteorological variables, such as mean temperature; most studies also adjusted for relative humidity, whereas only half of the studies adjusted for barometric pressure (Supplemental Table I).

Daily mean pollution levels reported in short-term studies varied widely for PM$_{2.5}$ (range 8.4-91.4 μg/m$^3$), PM$_{10}$ (20.0-121.0 μg/m$^3$), NO$_2$ (11.7-28.4 ppb), SO$_2$ (1.1-

### Table 1. Main Characteristics of All Studies Included in the Meta-Analysis

| Record | Author | Year | Location | Period       | Study design                  | Population | Outcome                                                                 | Number of events |
|--------|--------|------|----------|--------------|-----------------------------|------------|-------------------------------------------------------------------------|------------------|
| 1      | Rich   | 2006 | USA      | 1995–2002    | Case-cross-over             | Patients implanted ICD* at the Tufts-New England Medical Center | ICD*-recorded episode of PAF | 91               |
| 2      | Bunch  | 2011 | USA      | 1994–2006    | Case-cross-over             | People lived on the Wasatch Front | Hospital admissions for AF | 10457           |
| 3      | Link   | 2013 | USA      | 2006–2010    | Case-cross-over             | ICD* patients followed at the Tufts Medical Center | ICD*-recorded episode of AF | 328              |
| 4      | Milojevic | 2014 | UK       | 2003–2008    | Case-cross-over             | Emergency admissions made to NHS hospitals in England and Wales | Emergency visits for AF (ICD**-9: 427.3) | 310568            |
| 5      | Sade   | 2015 | Israel   | 2006–2010    | Case-cross-over             | Patients hospitalized in Soroka University Medical Center | Hospitalizations for new AF onset (ICD**-9: 427.3) | 1458             |
| 6      | Vaduganathan | 2016 | Italy    | 2004–2007    | Case-cross-over             | Patients hospitalized in Brigham and Women’s Hospital Heart and Vascular Center | Emergency visits for AF (ICD**-9: 427.3) | 830              |
| 7      | Solimini | 2017 | Italy    | 2001–2014    | Time-series                 | Emergency visits in 51 Emergency Departments of hospitals in Rome | Emergency visits for AF (ICD**-9: 427.3) | 79892            |
| 8      | Li     | 2018 | China    | 2013–2017    | Case-cross-over             | Hospital admission in all hospitals in Beijing | Hospital admissions for AF (ICD**-10: 148) | 24455            |
| 9      | Liu    | 2018 | China    | 2012–2013    | Case-cross-over             | CIED patients followed in Peking Union Medical College Hospital | CIED-recorded episode of AF | 353              |
| 10     | Amsalu*| 2019 | China    | 2013–2017    | Time-series                 | Hospital admission in all hospitals in Beijing | Hospital admissions for AF (ICD**-10: 148) | 24455            |
| 11     | Amsalu*| 2019 | China    | 2013–2017    | Time-series                 | Hospital admission in all hospitals in Beijing | Hospital admissions for AF (ICD**-10: 148) | 24455            |
| 12     | Kwon†  | 2019 | Korea    | 2002–2015    | Time-series/ cohort†         | Individuals recruited from the general population in Seoul | Emergency visits for AF/first AF occurrence (ICD**-10: 148) | 1137/1903        |
| 13     | Saifipour | 2019 | Iran     | 2010–2012    | Case-cross-over             | Hospitalization due to cardiovascular and respiratory diseases in Isfahan City | Hospital admissions for AF (ICD**-10) | 451              |
| 14     | Carey  | 2016 | UK       | 2005–2011    | Cohort                      | Individuals within the area bounded by the orbital M25 motorway around London | Developed atrial fibrillation (ICD**-10: 146-149) | 208 049          |
| 15     | Monrad | 2017 | Denmark  | 1997–2011    | Cohort                      | Individuals recruited from the general population in Copenhagen or Aarhus | Cases with a first diagnosis of AF (ICD**-10) | 2700             |
| 16     | Stockfelt | 2017 | Sweden   | 1990–2011    | Cohort                      | Individuals recruited from the general population in Gothenburg | New onset of AF (ICD**-9 or ICD**-10) | 1712             |
| 17     | Kim    | 2019 | Korea    | 2009–2013    | Cohort                      | Individuals who were not diagnosed with non-valvular AF in South Korea | Cases with a first diagnosis of AF (ICD**-10: 148) | 5624             |
| 18     | Shin   | 2019 | Canada   | 2001–2015    | Cohort                      | Individuals who were not diagnosed with AF in South Korea | Cases with a first diagnosis of AF (ICD**-9 or ICD**-10) | 313,157          |

ICD* indicates implantable cardioverter-defibrillator; CIED, cardiac implantable electronic devices; ICD**, International Classification of Diseases. *There two different studies researched by Amsalu et al. †This study evaluates both short- and long-term relationship.
Figure. Forest plot for the short-term effect of ambient air pollution (PM$_{2.5}$, PM$_{10}$, SO$_2$, O$_3$, NO$_2$, and CO) on AF. Relative risks (RRs) are for an increase of 10 μg/m$^3$ of PM$_{2.5}$ and PM$_{10}$; 10 ppb of SO$_2$, NO$_2$, and O$_3$; and 1000 ppb of CO.

A random-effects summary estimate of the short-term effect of air pollutant on AF is presented in the Figure. ER per 10 μg/m$^3$ increase of pollutants was 1.8% (0%–3.7%) for PM$_{2.5}$ and 1.1% (−0.2%–2.4%) for PM$_{10}$. These studies were significantly heterogeneous; the degree of I$^2$ was determined to be large in pooled estimates for PM$_{2.5}$ (79.8%) and PM$_{10}$ (83.2%). Moreover, the ER per 10 ppb increment of gaseous pollutants was 3.2% (0.6%–5.8%) for NO$_2$, 2.9% (0.3%–5.7%) for SO$_2$, 0.5% (−3.4%–4.7%) for O$_3$, and 2.0% (−1.3%–5.4%) for CO per 1000 ppb change.

The outcomes of subgroup analysis were presented in Table II. As per our findings, the effect of PM$_{2.5}$ and SO$_2$ on AF attack varied by geographic locations, with Asia showing statistically significant positive associations. Besides, it suggests that the effects of air pollution on AF were different between patients with ICDs and the general population. Besides, a few studies reported the effect estimates for multiple age groups and gender; we pooled the estimate by age (< 65 and ≥ 65 years) and gender. The analyses revealed that pooled estimates from males were larger than females. Similarly, results suggested that the
Table II. Subgroup Analysis of the Associations of All Pollutants with Atrial Fibrillation

| Air pollutants | Location | Gender | Age | Outcome | Hospital/ emergency admissions |
|----------------|----------|--------|-----|---------|---------------------------------|
|                | North America | Europe | Asia | Male | Female | < 65 years | ≥ 65 years | Devices |                   |
| PM2.5          | Number of studies | 3      | 2   | 4    | 5      | 4       | 3       | 3       | 6     |
|                | ER% (95% CI)       | 23.2 (−9.3–67.5) | 0.6 (−3.9–5.4) | 2.3 (0.1–5.2) | 6.5 (2.2–11.0) | 2.7 (1.0–4.5) | 9.5 (−0.4–20.5) | 4.8 (−0.5–10.4) | 23.8 (−7.3–65.4) | 1.8 (0–3.7) |
|                | F², %               | 78.3 | 92.9 | 77.4 | 82.4 | 68.5 | 83.6 | 77.9 | 75.7 | 76.4 |
|                | Interaction P-value | <0.001 | 0.006 | 0.048 |
| PM10           | Number of studies | —     | 3   | 4    | 2    | 2    | 1     | 1      | 1     | 6     |
|                | ER% (95% CI)       | —     | 2.0 | 1.0  | 2.4  | 1.3  | −0.9  | 0.8   | 2.7   | 0.8   |
|                | CI, %               | (−1.0–4.0) | (−1.0–3.0) | (0.1–4.6) | (0.1–2.5) | (−2.2–0.8) | (−2.3–3.3) | (0.6–4.8) | (−0.5–2.2) |
|                | F², %               | —     | 92.7 | 62.4 | 53.8 | 0.0  | —     | —     | —     | 83.5  |
|                | Interaction P-value | 0.096 | <0.001 | —     | —     | 0.096 |
| NO2            | Number of studies | 2     | 2   | 4    | 2    | 2    | 1     | 1      | 3     | 5     |
|                | ER% (95% CI)       | 16.8 (3.3–32.0) | 1.6 (0.4–2.8) | 10.1 (0.2–21.1) | 4.5 (−4.8–14.7) | 2.0 (−1.0–5.1) | 7.2 (0.9–14.3) | −1.9 (−7.2–3.6) | 14.8 (4.4–26.3) | 3.2 (0.6–5.8) |
|                | CI, %               | (3.3–32.0) | (3.3–32.0) | (3.3–32.0) | (3.3–32.0) | (3.3–32.0) | (3.3–32.0) | (3.3–32.0) | (3.3–32.0) |
|                | F², %               | 0.0   | 24.5 | 34.3 | 26.1 | 0.0  | —     | —     | 0.0   | 42.4  |
|                | Interaction P-value | 0.16 | 0.035 | —     | —     | 0.016 |
| SO2            | Number of studies | 2     | 1   | 5    | 2    | 2    | 2     | 3      | 2     |
|                | ER% (95% CI)       | 9.1 (−25.4) | 0.8 (−4.5–6.4) | 3.6 (0.5–6.7) | 10.9 (−11.1) | 3.8 (−5.3–13.8) | 5.5 (0.8–10.4) | 3.5 (−3.0–10.5) | 5.8 (−32.1) |
|                | CI, %               | (−25.4) | (−4.5–6.4) | (0.5–6.7) | (−11.1) | (−5.3–13.8) | (0.8–10.4) | (−3.0–10.5) | (−32.1) |
|                | F², %               | 0.0   | —    | 0.0  | 43.2 | 7.1  | 0.0   | 0.0    | 0.0   | 0.0   |
|                | Interaction P-value | 0.031 | 0.018 | 0.013 | —     | 0.031 |
| O3             | Number of studies | 2     | 1   | 4    | 1    | 1    | 1     | 1      | 3     | 4     |
|                | ER% (95% CI)       | 17.5 (−13.9) | −0.6 (−1.4–0.2) | −0.9 (−5.9–4.3) | 0.2 (−17.9) | 7.2 (−10.2) | −5.8 (−14.2–3.5) | −6.7 (−7.2–3.6) | −5.5 (−29.1) |
|                | CI, %               | (−13.9) | (−1.4–0.2) | (−5.9–4.3) | (−17.9) | (−10.2) | (−14.2–3.5) | (−6.7–3.6) | (−29.1) |
|                | F², %               | 79.2  | —    | 0.0  | —    | —    | —     | —     | —     | 62.3  |
|                | Interaction P-value | 0.796 | —     | —     | 0.796 |
| CO             | Number of studies | 1     | 1   | 5    | 2    | 2    | 2     | 2      | 2     |
|                | ER% (95% CI)       | −21.3 (−63.6) | −0.9 (−6.5–5.0) | 2.0 (−1.3–5.4) | 2.6 (−1.4–6.9) | 4.3 (0.8–8.7) | 7.3 (1.9–13.0) | 1.5 (−2.0–5.3) | 12.2 (−3.2) |
|                | CI, %               | (−63.6) | (−6.5–5.0) | (−1.3–5.4) | (−1.4–6.9) | (0.8–8.7) | (1.9–13.0) | (−2.0–5.3) | (−3.2) |
|                | F², %               | —    | 15.8 | 0.0  | 0.0  | 0.0  | 0.0   | 0.0    | 0.0   | 21.6  |
|                | Interaction P-value | 0.232 | 0.024 | 0.074 | 0.232 |

ER% indicates excess risk percentage.

The short-term effect of air pollution was more prominent for the non-elderly. When we divided the population according to outcomes, it showed that the effects of PM2.5 and SO2 were more prominent among patients admitted to hospital or emergency departments. In contrast, the effect of NO2 was found to be more prominent in ICD patients.

The funnel plots and the outcomes of the Egger’s test suggested that there was no asymmetry of results for most air pollutants, except for NO2: (Egger’s test, P = 0.001) (Supplemental Figure 2). For most pollutants, the results of sensitivity analysis were largely consistent with the main analysis (Supplemental Table IV-IX).

The long-term effects of air pollution on atrial fibrillation: The evidence of the long-term association between air pollutants and AF is limited; in total, six studies were included in this meta-analysis. Among those studies, two
were conducted in Asia, three in Europe, and one in North America (Table I). They used Cox proportional hazards models to estimate the long-term associations between exposures to air pollutants and the incidence of AF, and all of them were adjusted to common variables including sex, age, income, and smoking (Supplemental Table II). The range of daily mean pollution levels in long-term studies were 1.45-25 μg/m³ for PM$_{2.5}$, 13-49.1 μg/m³ for PM$_{10}$, 8.08-34 ppb for NO$_2$, 5.2-5.5 ppb for SO$_2$, 18.0-45.8 ppb for O$_3$, and 560-600 ppb for CO (Supplemental Table III). For the long-term effect, ER per 10 μg/m³ increase of pollutants was 11.6% (3.1%-20.7%) for PM$_{2.5}$ and 3.4% (3.2%-3.5%) for PM$_{10}$; per 10 ppb increment of gaseous pollution was 1.7% (0.1%-3.3%) for NO$_2$, 0.5% (0.4%-0.7%) for SO$_2$, 0.7% (-7.3%-9.4%) for O$_3$, and 2.0% (1.3%-2.2%) for CO per 1000 ppb change (Supplemental Figure 3).

Discussion

In recent years, there has been a well-documented association between air pollutants, especially PM, and increased risk of stroke, pediatric pneumonia, and cardiovascular diseases. However, there are only a few studies examining the relationship between air pollutants and AF risk. Thus, in this study, we analyzed both the short- and long-term effects of ambient air pollutants on AF. Our results suggested that higher concentrations of air pollution (PM$_{2.5}$, SO$_2$, and NO$_2$) may increase AF occurrence in the short term in patients with AF history or those who are considered high risk. There was a trend that PM$_{10}$ increased the risk of AF, but it was not statistically significant. In the long term, all pollutants (PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, and CO) were determined to be associated with AF incidence in healthy population, except for O$_3$. Our analysis confirmed that ambient air pollution was significantly associated with health problems.

Previously, Shao, et al. also did a meta-analysis on the association between air pollution and the development of AF, which only included four studies. Their results showed there was a statistically significant association between AF occurrence and all air pollutants (PM$_{2.5}$, SO$_2$, NO$_2$, O$_3$, and CO), which was partly different from our findings. The primary explanations for the difference may be the number of included studies; further, the different lags we selected may have also contributed to this discrepancy. Although we fail to find an apparent effect of short-term exposure to PM$_{10}$, O$_3$, and CO on AF, the results showed that ambient exposure to those pollutants increases the risk for atrial fibrillation development in the long term. The discrepancy might be explained by the different time windows, which addressed the cumulative effect of past exposures on outcomes. Time-series analyses usually capture the most immediate acute effect of a few days of exposure in the following days. In contrast, the cumulative long-term effect of air pollution is of a different order of magnitude compared to acute effects.

Remarkably, the short-term effect of ambient air pollutants on AF was different by region, with Asia showing a more prominent trend. This may be due to the different levels of air pollutants in different regions. Therefore, further investigation is needed to determine if there is a concentration-response function between the levels of air pollutant and AF risk. The individuals with ICDs or pacemakers represent different base populations concerning the baseline risk of AF. The subgroup analysis suggested the effect of air pollution on AF is different between patients with ICDs and the general population. Surprisingly, it showed that the effects of PM$_{2.5}$ and SO$_2$ were more prominent in patients admitted to hospitals or emergency departments. In contrast, the effect of NO$_2$ was more prominent among ICD patients. Patients with ICDs or pacemakers may have more underlying diseases, thus, having a higher rate of AF incidence compared to the general population. AF has been considered a heterogeneous disease, and the incidence of AF varies by age and gender, so we have to analyze the effect of air pollutants on AF in different population stratification by age or gender. Surprisingly, we found that the effect of air pollutants was more prominent among males and the non-elderly. It is possible that different populations have different sensitivities to air pollutants, but this mechanism is hypothetical and requires further research.

Although recent studies have shown that air pollution and air PM are associated with AF, the underlying mechanisms of this association remain to be unknown. There are several possible reasons that might explain this association. First, acute autonomic nervous system dysfunction has been demonstrated in air pollution study, which could lead to decreased heart rate variability, thus, AF may be triggered by autonomic imbalance. This mechanism was thought to be the most plausible reason for the short-term effect. Second, exposure to air PM can elicit an acute-phase response and an increase right heart pressure. Third, irritants can cross the pulmonary epithelium directly into circulation, which may affect blood coagulability. Besides, acute exacerbations of pulmonary diseases such as COPD during short-term exposure to air pollutants might potentiate the risk of arrhythmia. We believe these pathophysiologic changes can provide a good rationale for the hypothesis that short-term exposure to air pollutants can trigger AF in patients with AF history or those who are considered as high risk. The underlying mechanisms for AF are complex, mainly including atrial fibrosis, altered calcium homeostasis, inflammation, and oxidative stress. An increasing body of studies indicated that air pollutant involves several pathophysiology processes of AF such as inflammation, oxidative stress, and autonomic imbalance. Thus, long-term exposures to air pollutants might increase the risk of AF.

Study limitations: This study has several limitations. First, we found significant heterogeneity in the relationship between PM$_{2.5}$, PM$_{10}$, and AF, but we failed to decrease the heterogeneity in any subgroup analysis. The differences in other factors such as individual patient characteristics, sample size, and study design may be the cause of the observed heterogeneity. Second, data from monitoring sites represents the average levels of air pollutants of regions, so it did not reflect the personal exposure situation. Moreover, the source of air pollutants was different between regions where these studies were conducted. For example, PM$_{2.5}$ and NO$_2$ may mainly be used
as proxies for traffic-related air pollution in some regions. Third, most studies reported effect for single air pollutants, and only two studies provided the effect estimates for multiple pollutants model. Those single-pollutant models did not consider the potential additive effects of multiple pollutants, which may overestimate the effect of a single pollutant. However, most of these studies adjusted for meteorological factors, such as temperature, humidity, and seasonality. Fourth, although we did some subgroup analysis according to location, outcomes, age, and gender, the number of studies in some subgroup was too little. Thus, the results of our subgroup analysis need to be further confirmed in the future. Fifth, we did not perform a subgroup analysis according to different AF types because of insufficient data. Finally, those studies included in our meta-analysis were all observational studies. Thus, they may carry over uncontrolled biases such as selection bias and information bias.

Conclusion
Our meta-analysis indicated that short-term change in ambient air pollution, as measured by the concentrations of PM$_{2.5}$, NO$_2$, and SO$_2$, is associated with AF within days. Besides, it is suggested long-term exposure to air pollutants was found to be associated with the increased incidence of AF. To better understand those relationships and the related public health impact in the most polluted regions of the world, more high-quality studies are needed in the future.

Disclosure
Conflicts of interest: The authors declare no conflict of interest.

Authors’ Contributions: Liangrong Zheng conceived of the idea for this review. Miao Chen and Jianqiang Zhao independently did the literature search and data extraction. Miao Chen and Chengui Zhuo did the statistical analyses. Jianqiang Zhao interpreted the statistical analyses. Miao Chen wrote the first draft of the manuscript. All authors revised and approved the final manuscript.

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Supplemental Files

Supplemental Text
Supplemental Figures 1-3
Supplemental Tables I-IX

Please see supplemental files; https://doi.org/10.1536/ihj.20-523