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# Air pollution, genetic susceptibility, and the risk of atrial fibrillation: A large prospective cohort study

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**To date, no study has explored the extent to which genetic susceptibility modifies the effects of air pollutants on the risk of atrial fibrillation (AF). This study was designed to investigate the separate and joint effects of long-term exposure to air pollutants and genetic susceptibility on the risk of AF events. This study included 401,251 participants without AF at baseline from UK Biobank. We constructed a polygenic risk score and categorized it into three categories. Cox proportional hazards models were fitted to assess the separate and joint effects of long-term exposure to air pollutants and genetics on the risk of AF. Additionally, we further evaluated the effect modification of genetic susceptibility. The hazard ratios and corresponding 95% confidence intervals of incident AF for per interquartile range increase in particulate matter with an aerodynamic diameter smaller than 2.5 μm ($PM_{2.5}$) or 10 μm ($PM_{10}$), nitrogen dioxide ($NO_2$), and nitrogen oxide ($NO_x$) were 1.044 (1.025, 1.063), 1.063 (1.044, 1.083), 1.061 (1.042, 1.081), and 1.039 (1.023, 1.055), respectively. For the combined effects, participants exposed to high air pollutants levels and high genetic risk had approximately 149.2% ($PM_{2.5}$), 181.7% ($PM_{10}$), 170.2% ($NO_2$), and 157.2% ($NO_x$) higher risk of AF compared to those with low air pollutants levels and low genetic risk, respectively. Moreover, the significant additive interactions between $PM_{10}$ and $NO_2$ and genetic risk on AF risk were observed, with around 16.4% and 35.1% of AF risk could be attributable to the interactive effects. In conclusion, long-term exposure to air pollutants increases the risk of AF, particularly among individuals with high genetic susceptibility.**

air pollutants | atrial fibrillation | genetic risk

## Significance

Previous studies have typically concentrated on the independent associations between air pollutants or genetic susceptibility and the risk of atrial fibrillation (AF). However, these studies have largely ignored the joint effects or interactions of genetics and air pollutants. In addition to the joint effects of genetic factors and air pollutants, our study estimated the potential interactions and revealed additive interactions between genetic susceptibility and air pollutants exposure on the development of AF. Our findings suggest that improving air quality will benefit the entire population, especially those at high level of genetic risk, which has a potential guiding significance for the primary prevention of AF.

As the most common type of cardiac arrhythmia, atrial fibrillation (AF) accounts for more hospitalizations and longer hospital stays than any other arrhythmia, and has been shown to be associated with a wide range of cardiovascular diseases and even death (1, 2). According to the Framingham Heart Study, the incidence and prevalence of AF has increased rapidly over the past few decades and is expected to become an emerging health threat globally (3). The currently elucidated risk factors related to AF explain only about half of AF cases in the population, which poses a challenge for preventing AF effectively (4, 5). Therefore, identifying risk factors for AF remains a top priority.

The associations between exposure to ambient air pollutants [i.e., particulate matter with an aerodynamic diameter smaller than 2.5 ($PM_{2.5}$) or 10 um ($PM_{10}$), nitrogen dioxide ($NO_2$), and nitrogen oxide ($NO_x$) etc.] and elevated cardiovascular morbidity and mortality are well established, and remain a pressing public health issue globally (6, 7). Recent epidemiological studies have mainly focused on short-term air pollution exposure and have discovered that pollutants, such as $PM_{2.5}$, $PM_{10}$, $NO_2$, sulfur dioxide, ozone, and carbon monoxide, are positively associated with acute exacerbations of AF (8, 9). However, available evidence regarding the cumulative damage of long-term exposure to air pollutants on the onset of AF remains limited and inconclusive (*SI Appendix*, Table S1). A study comparing existing research on the health effect of acute or chronic air pollution exposure found that estimates of nonfatal health effect due to long-term air pollution exposure tend to be greater (10). Thus, it is necessary to figure out the links between long-term air pollutants exposure and the risk of AF.

Besides environmental exposure, genetic susceptibility has been demonstrated to be another important risk factor for AF. Early evidence from a twin study documented that genetic susceptibility plays a big part in the risk of AF for both male and female (11). While twin studies and family studies have their own advantages, a broad exploration of multiple variants in disease-related genes based on large genome-wide association studies (GWAS) may be more valuable (12). Recently, a large GWAS involving around 60,000 cases detected more than 140 loci related to AF (13). In this context, constructing the polygenic risk score (PRS) based on the aggregation of multiple variants has ability to identify high-risk individuals (14). Despite the available evidence of

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gene–air pollution interactions in the development of cardiovascular disease (15), no study has comprehensively explored the possible joint or interactive effects of genetic risk and air pollution on the risk of AF. Therefore, this study prospectively investigated the associations between long-term exposure to a series of air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_x$) and risk of developing AF. Meanwhile, this study comprehensively outlined the joint effects and the interactions of genetic factors and air pollutants exposure on the risk of AF based on the nationwide genetic data from UK Biobank.

## Results

Table 1 exhibits the baseline characteristics of participants according to AF status. Of 401,251 participants, the average age was 56.142 (±8.105) y, and more than half were females (53.953%). During a median of 11.917 y of follow-up, we observed 17,731 incident AF cases. Participants with AF had higher measurement of body mass index (BMI), and higher prevalence of preexisting hypertension, hyperlipidemia, and diabetes, were more likely to be males, current smokers, and were less likely to be physically active. The distributions (mean, median, minimum, and maximum) and correlations of air pollutants are provided in *SI Appendix*, Table S2. The mean estimates of annual average concentrations for $PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_x$ were 9.991, 19.309, 29.236, and 43.997 $\mu g/m^3$, respectively.

The associations between air pollutants exposure and AF risk are presented in Table 2. In the Cox models, we observed that all air pollutants were positively associated with an increased risk of AF. The hazard ratios (HRs) (95% CIs) of AF per interquartile range (IQR) increase in $PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_x$ were 1.044 (1.025, 1.063), 1.063 (1.044, 1.083), 1.061 (1.042, 1.081), and 1.039 (1.023, 1.055), individually. In comparison with participants with the lowest air pollutants exposure (Q1), those with highest air pollutants exposure (Q5) had a multivariable adjusted HRs of 1.095 (1.045, 1.148) for $PM_{2.5}$, 1.165 (1.110, 1.223) for $PM_{10}$, 1.163 (1.108, 1.221) for $NO_2$, and 1.117 (1.065, 1.171) for $NO_x$ ($P$ for trend < 0.001 for all). Fig. 1 displays the dose–response curves of $PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_x$ concentrations with the occurrences of AF. Except for $PM_{2.5}$ (range: 8.170 to 13.150 $\mu g/m^3$, $P$ for nonlinearity < 0.05), we found a monotonic increase in the dose–response relationships between $PM_{10}$ (range: 12.865 to 24.580 $\mu g/m^3$), $NO_2$ (range: 8.863 to 58.045 $\mu g/m^3$), and $NO_x$ concentrations (range: 58.045 to 95.815 $\mu g/m^3$) and the risk of AF. There was some evidence (*SI Appendix*, Table S3) that the threshold model improved the model fit at $PM_{2.5}$, $NO_2$, and $NO_x$ concentrations of 10.5 $\mu g/m^3$ ($P < 0.05$), 32 $\mu g/m^3$ ($P < 0.05$), and 50 $\mu g/m^3$ ($P < 0.05$), respectively, as compared with the nonthreshold model.

For genetics-related analyses, we found a significant association between AF-related PRS and the risk of developing AF. Participants at medium or high genetic risk had an approximately 44.6% (38.8%, 50.7%) or 133.7% (124.9%, 142.8%) higher risk of AF compared to those at low genetic risk ($P$ for trend < 0.001; *SI Appendix*, Table S4). Moreover, we estimated the joint effects of air pollutants and AF-related PRS on the risk of AF (Fig. 2 and *SI Appendix*, Fig. S1). The combined effects of air pollutants and genetic risk on AF risk expressed in a dose–response manner. It was found that participants exposed to high air pollutants levels and high genetic risk had the greatest risk of AF [$PM_{2.5}$: 2.492 (2.290, 2.712), $PM_{10}$: 2.871 (2.579, 3.076), $NO_2$: 2.702 (2.475, 2.949), and $NO_x$: 2.572 (2.358, 2.805)] than those exposed to low air pollutants levels and low genetic risk. In terms of effect modification, the relative excess risk due to interactions (RERIs), attributable proportion due to interactions (APs), and synergy index (SI) were statistically significant, suggesting positive additive interactions of long-term $PM_{10}$ and $NO_2$ exposure with genetic susceptibility (Table 3). Notably, for participants with high air pollutants exposure and high genetic risk, the RERIs were 0.164 (0.027, 0.302) for $PM_{10}$ and 0.351 (0.133, 0.568) for $NO_2$, indicating the relative excess risk of AF onset in the context of genetic–air pollutants interactions of 0.164 and 0.351, respectively.

In the sensitivity analyses, the positive associations between air pollutants and the risk of incident AF were not materially changed after we controlled for the possible effects of the time-varying confounders by the time-varying Cox proportional hazards models (*SI Appendix*, Table S5). After we parsed out the short-term effects of air pollutants, the estimated effects of long-term air pollutants exposure on the risk of AF incidence remained virtually unchanged (*SI Appendix*, Table S6). We observed no significant difference in the HRs for AF after we excluded participants diagnosed with AF within the first 2 y of follow-up (*SI Appendix*, Table S7), excluded missing values for covariates (*SI Appendix*, Table S8), or further adjusted for the medication history of antihypertensive, hypoglycemic, and cholesterol lowering drugs (*SI Appendix*, Table S9). In addition, we did not observe any significant changes in the results of assuming that participants with unidentifiable lifestyle status had optimal status and fitting the models (*SI Appendix*, Table S10), restricting the analyses to those who had lived at their current address for more than 5 y (*SI Appendix*, Table S11), adding the average 24-h sound level of noise pollution into the models (*SI Appendix*, Table S12), fitting the two-pollutant model (*SI Appendix*, Table S13), considering the influence of competing events (*SI Appendix*, Table S14), or adjusting covariates selected by directed acyclic graph (DAG) in the models (*SI Appendix*, Fig. S2 and Table S15).

## Discussion

This study evaluated the relationships between air pollutants and the risk of incident AF in the context of genetic susceptibility. We found that long-term exposure to air pollutants was pronouncedly associated with an increased risk of AF incidence. The dose–response functions of $PM_{10}$, $NO_2$, and $NO_x$ increased linearly. When we assessed the combined effects of genetic risk and air pollutants, a substantial relative increase in the risk of incident AF was observed in participants exposed to high air pollutants levels and high genetic risk. As well, our study provided evidence that genetic susceptibility interacts with $PM_{10}$ and $NO_2$ in an additive manner, leading to the initiation of AF.

Over the past several years, the American Heart Association and the U.S. Environmental Protection Agency have determined the causal relationship between particulate matter exposure and cardiovascular disease morbidity and mortality (16, 17). Yet, until now, only eight studies have specifically evaluated the relationships between long-term air pollutants exposure and AF risk in the cohort design (*SI Appendix*, Table S1), and the results were inconsistent. A Danish study indicated that residential traffic-related air pollutants in the concentration range of 5.8 $\mu g/m^3$ to 65.3 $\mu g/m^3$ ($NO_2$) and 10.3 $\mu g/m^3$ to 379.6 $\mu g/m^3$ ($NO_x$) were positively associated with an increased risk of AF among residents (18). Similarly, a positive association between $NO_2$ and AF has been discovered in residents of Korea, Canada, and the United States (19–21). As for particulate matter, the risk of incident AF increased with rising $PM_{2.5}$ level in three studies in Canada, Korea, and Denmark, where the average $PM_{2.5}$ concentration ranged from 9.8 to 32.2 $\mu g/m^3$ (20–22). Among the eight relevant studies, only one study from Korea (median concentration of $PM_{10}$:

**Table 1. Baseline characteristics of participants included in this study**

| | Total participants (n = 401,251) | Participants without AF (n = 383,520) | Participants with AF (n = 17,731) | *P* values |
|---|---|---|---|---|
| Age (year) | 56.142 (8.105) | 55.884 (8.090) | 61.722 (6.194) | **<0.001** |
| Sex (Female, %) | 216,486 (53.953) | 209,822 (54.710) | 6,664 (37.584) | **<0.001** |
| Ethnicity (%) | | | | **<0.001** |
| White | 375,776 (93.651) | 358,680 (93.523) | 17,096 (96.419) | |
| Mixed | 2,496 (0.622) | 2,440 (0.636) | 56 (0.316) | |
| Asian | 8,698 (2.168) | 8,458 (2.205) | 240 (1.354) | |
| Black | 7,074 (1.763) | 6,931 (1.807) | 143 (0.806) | |
| Other | 5,204 (1.297) | 5,105 (1.331) | 99 (0.558) | |
| Missing | 2,003 (0.499) | 1,906 (0.497) | 97 (0.547) | |
| BMI ($kg/m^2$) | 27.385 (4.746) | 27.312 (4.703) | 28.960 (5.352) | **<0.001** |
| Employment (%) | | | | **<0.001** |
| Employment | 236,652 (58.979) | 230,013 (59.974) | 6,639 (37.443) | |
| Retired | 126,465 (31.518) | 116,926 (30.488) | 9,539 (53.798) | |
| Unemployment | 33,657 (8.388) | 32,279 (8.417) | 1,378 (7.772) | |
| Missing | 4,477 (1.116) | 4,302 (1.122) | 175 (0.987) | |
| Education (%) | | | | **<0.001** |
| College or University degree | 173,074 (43.134) | 167,163 (43.587) | 5,911 (33.337) | |
| Non-college or other professional qualifications | 136,865 (34.110) | 131,164 (34.200) | 5,701 (32.153) | |
| None of the above | 91,312 (22.757) | 85,193 (22.213) | 6,119 (34.510) | |
| Alcohol consumption status (%) | | | | **<0.001** |
| Never | 17,805 (4.437) | 17,037 (4.442) | 768 (4.331) | |
| Previous drinkers | 13,853 (3.452) | 13,029 (3.397) | 824 (4.647) | |
| Current drinkers | 368,523 (91.844) | 352,438 (91.896) | 16,085 (90.717) | |
| Missing | 1,070 (0.267) | 1,016 (0.265) | 54 (0.305) | |
| Smoking (%) | | | | **<0.001** |
| Never | 220,842 (55.038) | 212,943 (55.523) | 7,899 (44.549) | |
| Previous smokers | 136,408 (33.996) | 128,701 (33.558) | 7,707 (43.466) | |
| Current smokers | 41,931 (10.450) | 39,932 (10.412) | 1,999 (11.274) | |
| Missing | 2,070 (0.516) | 1,944 (0.507) | 126 (0.711) | |
| Healthy diet score (%) | | | | 0.264 |
| 0 to 1 | 15,509 (3.865) | 14,814 (3.863) | 695 (3.920) | |
| 2 to 3 | 157,561 (39.267) | 150,503 (39.243) | 7,058 (39.806) | |
| 4 to 5 | 228,181 (56.867) | 218,203 (56.895) | 9,978 (56.274) | |
| Physical activity (%) | | | | **<0.001** |
| Never | 25,098 (6.255) | 23,592 (6.151) | 1,506 (8.494) | |
| Low activity | 27,258 (6.793) | 25,729 (6.709) | 1,529 (8.623) | |
| Medium activity | 293,461 (73.137) | 281,173 (73.314) | 12,288 (69.302) | |
| High activity | 52,721 (13.139) | 50,511 (13.170) | 2,210 (12.464) | |
| Missing | 2,713 (0.676) | 2,515 (0.656) | 198 (1.117) | |
| Hypertension (%) | 95,191 (23.724) | 88,629 (23.109) | 6,562 (37.009) | **<0.001** |
| Hyperlipidemia (%) | 43,248 (10.778) | 38,979 (10.163) | 4,269 (24.076) | **<0.001** |
| Diabetes (%) | 20,678 (5.153) | 18,747 (4.888) | 1,931 (10.891) | **<0.001** |
| Genetic risk category (%) | | | | **<0.001** |
| Low risk | 135,897 (33.868) | 132,011 (34.421) | 3,886 (21.916) | |
| Medium risk | 134,307 (33.472) | 128,810 (33.586) | 5,497 (31.002) | |
| High risk | 131,047 (32.660) | 122,699 (31.993) | 8,348 (47.081) | |

Abbreviation: BMI, body mass index.
Bold represents statistical significance (*P* <0.05).

**Table 2. Associations of air pollutants with the risk of incident AF among participants in UK Biobank**

| Air pollutants | HRs (95% CIs) for continuous (per IQR† increase) | Air pollutants (quantile) | | | | | *P* for trend |
|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q5 | |
| $PM_{2.5}$ | **1.044 (1.025, 1.063)*** | 1 (Ref.) | 0.965 (0.921, 1.011) | 0.984 (0.939, 1.031) | 1.002 (0.956, 1.049) | **1.095 (1.045, 1.148)*** | **<0.001** |
| $PM_{10}$ | **1.063 (1.044, 1.083)*** | 1 (Ref.) | **1.053 (1.005, 1.103)*** | 1.044 (0.996, 1.094)+ | **1.127 (1.076, 1.181)*** | **1.165 (1.110, 1.223)*** | **<0.001** |
| $NO_2$ | **1.061 (1.042, 1.081)*** | 1 (Ref.) | 0.993 (0.948, 1.041) | 1.024 (0.977, 1.073) | **1.087 (1.037, 1.139)*** | **1.163 (1.108, 1.221)*** | **<0.001** |
| $NO_x$ | **1.039 (1.023, 1.055)*** | 1 (Ref.) | 0.975 (0.930, 1.022) | 1.014 (0.968, 1.063) | 1.027 (0.980, 1.077) | **1.117 (1.065, 1.171)*** | **<0.001** |

†IQR of $PM_{2.5}$ is 1.28 μg/m$^3$; IQR of $PM_{10}$ is 2.34 μg/m$^3$; IQR of $NO_2$ is 10.96 μg/m$^3$; IQR of $NO_x$ is 16.58 μg/m$^3$.
HRs and 95% CIs in bold represent significance at $P < 0.05$ (*). *P* slightly higher than 0.05 are recognized as suggested significant (+).
Cox regression models adjusted for age, sex, ethnicity, education, employment, alcohol consumption status, smoking status, healthy diet score, physical activity, BMI, hypertension, hyperlipidemia, and diabetes.
Abbreviations: AF, atrial fibrillation; BMI, body mass index; HRs, hazard ratios; IQR, interquartile range; NO2, nitrogen dioxide; NOx, nitrogen oxides; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; $PM_{10}$, particulate matter with diameter <10 μm.

53.2 μg/m$^3$) reported a significant positive association of $PM_{10}$ with the risk of developing AF (20). Nevertheless, apart from the above studies, no study has identified significant associations between air pollutants and the risk of AF onset. For example, a Swedish study that examined the relationships between traffic-related exposure ($NO_2$) and particulate matter ($PM_{2.5}$ and $PM_{10}$) exposure, and the risk of AF using data from two cohort studies failed to reach significant results (23). In line with the findings of Stockfelt et al., studies based on the population from the United Kingdom and Korea also yielded nonsignificant results (24, 25).

The heterogeneity between the findings from various studies may be explained by the following reasons: First, the population profiles (including sample size, sociodemographic characteristics, population susceptibility, or exposure windows etc.) are different. Second, air pollutants levels are not consistent across study areas due to differences in geographic conditions or in the methods or models used to estimate individual exposures. Third, differences in the covariates incorporated in the models and unmeasured or unknown factors to some extent contribute to gaps in findings of studies. Last, particulate matter can absorb and retain various toxic compounds (i.e., polycyclic aromatic hydrocarbons or heavy metals) due to its large total surface area and porous surface (26). Thus, the discrepancies in chemical composition of particulate matter may lead to varying degrees of health hazards.

Several animal and human studies have explored the possible biological mechanisms underlying long-term exposure to air pollutants and the development of AF (27). One proposed mechanism is about the release of systemic inflammatory cytokines induced by inhaling particulate matter, which further lead to the occurrence of myocardial repolarization abnormalities and arrhythmias (28). Additionally, systemic inflammation and oxidative stress induced by air pollutants exposure are related to hypertension, which is an important risk factor for cardiac arrhythmias (4, 19). Another suggested mechanism is that inhaled air pollutants might induce alterations in the cardiac autonomic nervous system mediated by reactive oxygen species, thereby affecting heart rate variability (29).

Although the effect of genetic susceptibility on the risk of developing AF has been described in prior studies (30), no study to date has evaluated the joint effects of genetic factors and air pollutants

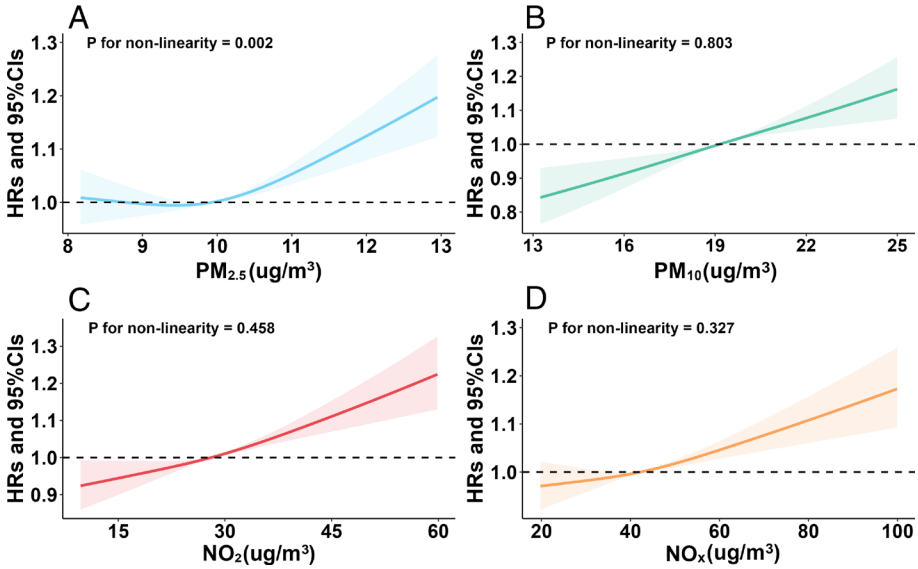


**Fig. 1.** Associations of long-term $PM_{2.5}$ (*A*), $PM_{10}$ (*B*), $NO_2$ (*C*), and $NO_x$ (*D*) exposure with the risk of AF among participants in UK Biobank. A RCS regression model with three knots (at the 10th, 50th, 90th percentiles) was used to estimate the dose–response relations between air pollutants and the risk of AF among participants. HRs (solid lines) and 95% CIs (shaded areas) were adjusted for age, sex, ethnicity, education, employment, alcohol consumption status, smoking status, healthy diet score, physical activity, BMI, hypertension, hyperlipidemia, and diabetes. Abbreviations: AF, atrial fibrillation; HRs, hazard ratios; BMI, body mass index; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; $PM_{10}$, particulate matter with diameter <10 μm; $NO_2$, nitrogen dioxide; $NO_x$, nitrogen oxides.

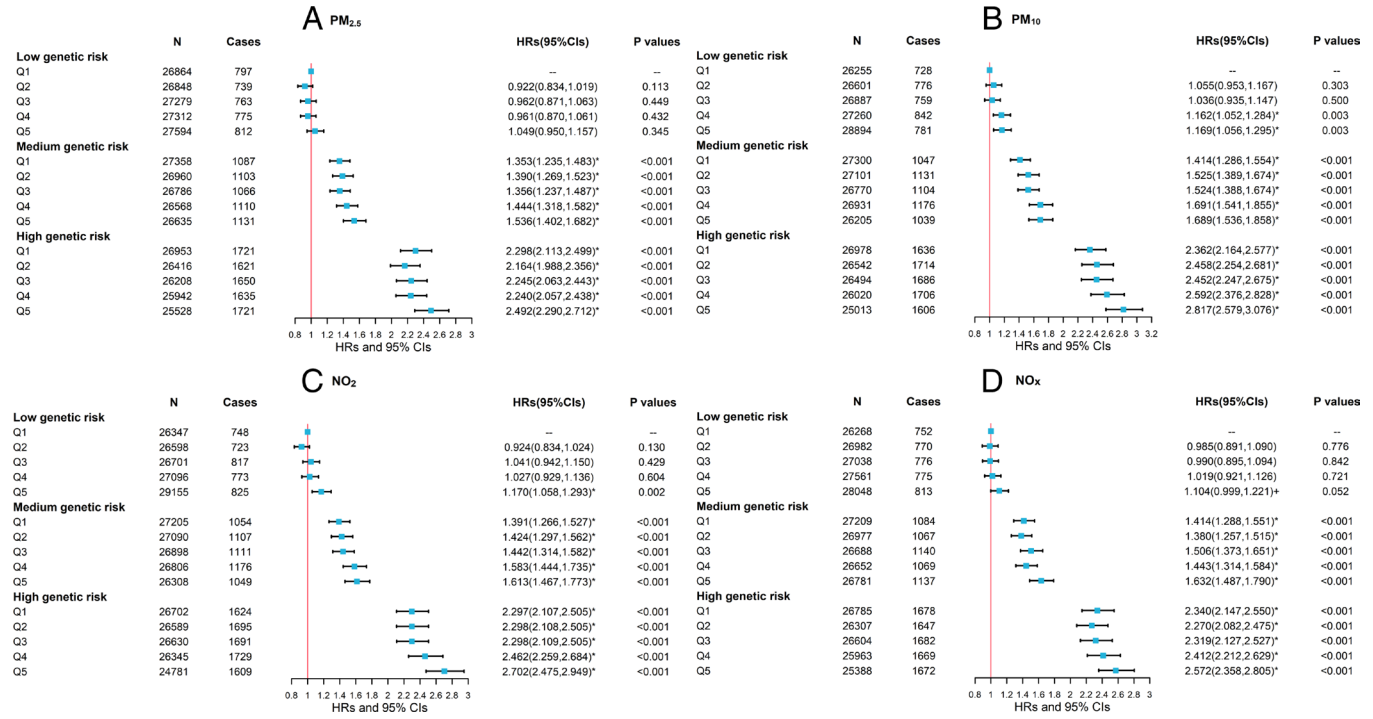


**Fig. 2.** The joint associations of long-term $PM_{2.5}$ (*A*), $PM_{10}$ (*B*), $NO_2$ (*C*), and $NO_x$ (*D*) exposure and PRS with the risk of incident AF. Cox regression models adjusted for age, sex, ethnicity, education, employment, alcohol consumption status, smoking status, healthy diet score, physical activity, BMI, hypertension, hyperlipidemia, diabetes, genotyping batch, and the first 10 genetic principal components. Abbreviations: PRS, polygenic risk score; HRs, hazard ratios; BMI, body mass index; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; $PM_{10}$, particulate matter with diameter <10 μm; $NO_2$, nitrogen dioxide; $NO_x$, nitrogen oxides.

exposure on AF incidence. Findings of our study revealed that the risk of AF increase monotonically with increasing genetic risk and air pollutants exposure levels. Furthermore, the additive interactions between air pollutants ($PM_{10}$ and $NO_2$) and PRS were identified in our study. Approximately 16.4 to 35.1% of AF risk can be explained by the additive effects of co-exposure to high air pollutants and high genetic risk, meaning that the combined effects of air pollutants and genetic risk were much greater than simply adding the two effects together. This finding has far-reaching implications for the field of environmental epidemiology, such as the provision of targeted preventive or medical care for the group of people at high genetic risk and exposed to severe levels of air pollutants.

This study has the following advantages: First, with the help of a large sample of follow-up data and biological information from UK Biobank, the current study has ability to obtain relatively robust results with high statistical efficiency. Second, findings on the role of genetic susceptibility in modifying the relationships between air pollutants exposure and AF risk provided the possibility of precise

**Table 3. Additive interactions between air pollutants and PRS on the risk of incident AF**

| | PRS | | | | | |
|---|---|---|---|---|---|---|
| | Medium genetic risk | | | High genetic risk | | |
| Air pollutants | RERIs (95% CIs) | APs (95% CIs) | SIs (95% CIs) | RERIs (95% CIs) | APs (95% CIs) | SIs (95% CIs) |
| $PM_{2.5}$ [*] | | | | | | |
| High pollution | 0.058 (−0.043, 0.159) | 0.038 (−0.028, 0.103) | 1.121 (0.909, 1.382) | 0.057 (−0.064, 0.178) | 0.023 (−0.026, 0.073) | 1.041 (0.954, 1.135) |
| $PM_{10}$ [†] | | | | | | |
| High pollution | 0.040 (−0.076, 0.155) | 0.024 (−0.046, 0.095) | 1.067 (0.880, 1.295) | **0.164 (0.027, 0.302)** | **0.062 (0.011, 0.113)** | **1.111 (1.015, 1.216)** |
| $NO_2$ [‡] | | | | | | |
| High pollution | 0.050 (−0.124, 0.225) | 0.032 (−0.077, 0.140) | 1.094 (0.800, 1.496) | **0.351 (0.133, 0.568)** | **0.127 (0.055, 0.200)** | **1.250 (1.091, 1.431)** |
| $NO_x$ [§] | | | | | | |
| High pollution | 0.048 (−0.052, 0.149) | 0.032 (−0.034, 0.097) | 1.100 (0.894, 1.353) | 0.056 (−0.065, 0.177) | 0.023 (−0.026, 0.072) | 1.040 (0.954, 1.134) |

[*]Defined by WHO guideline value of $PM_{2.5}$: low (<10 μg/m$^3$) and high (>10 μg/m$^3$).
[†]Defined by WHO guideline value of $PM_{10}$: low (<20 μg/m$^3$) and high (>20 μg/m$^3$).
[‡]Defined by WHO guideline value of $NO_2$: low (<40 μg/m$^3$) and high (>40 μg/m$^3$).
[§]Defined by the median of $NO_x$: low (<42.20 μg/m$^3$) and high (>42.20 μg/m$^3$).
Bold represents statistical significance (*P* <0.05).
Cox regression models adjusted for age, sex, ethnicity, education, employment, alcohol consumption status, smoking status, healthy diet score, physical activity, BMI, hypertension, hyperlipidemia, diabetes, genotyping batch, and the first 10 genetic principal components.
Abbreviations: AF, atrial fibrillation; AP, attributable proportion due to interaction; BMI, body mass index; $NO_2$, nitrogen dioxide; $NO_x$, nitrogen oxides; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; $PM_{10}$, particulate matter with diameter <10 μm; PRS, polygenic risk score; RERI, relative excess risk due to interaction; SI, synergy index.

prevention strategies for high-risk populations. Nevertheless, we acknowledge that certain limitations still exist in this study: First, due to the lack of biomarker information related to pathogenesis in UK Biobank, we could not confirm the study results mechanistically. Second, since the participants in the UK Biobank were healthy volunteers, selection bias could not be completely avoided. Third, despite the World Health Organization has now released updated air quality guidelines, this study did not follow the latest version of the low-level definition of air pollutants exposure, as participants in UK Biobank were exposed to air pollutants at levels higher than the latest cutoff values. Fourth, the structure of the Land Use Regression (LUR) model is the same for each pollutant, and many of the predictor variables are the same for different pollutants. This may lead to a high correlation between pollutants. Finally, findings related to the interactions between air pollutants exposure and genetic susceptibility on AF should be interpreted with caution when generalizing to other populations, as the majority of participants in the current study were White Europeans.

In conclusion, our study used prospective data to validate the adverse chronic effects of various air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_x$) on the onset of AF. More importantly, we found a substantially increased risk of AF in participants with high genetic risk and high levels of air pollutants exposure, and additive interactions between $PM_{10}$ and $NO_2$ and genetic risk. Thus, appropriate strategies are urgently needed to effectively reduce air pollution and protect people from cardiovascular effects, especially for those with high genetic risk.

## Materials and Methods

**Study Design and Population.** As a large population-based cohort study, UK Biobank has recruited over 500,000 community dwelling participants aged 37 to 73 y from 22 centers across the United Kingdom (England, Scotland, or Wales) since 2006 (31). It has collected substantial biological and medical information through touch screen questionnaires, verbal interviews, health records, physical measurements, biological samples, and imaging.

**Air Pollution Estimates.** Annual average concentrations of air pollutants in UK Biobank were estimated by fitting a LUR model developed by the European Study of Cohorts for Air Pollution Effects project (32, 33). This model can calculate the spatial variations of annual average concentrations of air pollutants around the participants' home addresses via Geographic Information System-derived predictors. The performance of model was assessed by the leave-one-out cross-validations method, and the cross-validations $R^2$ for $PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_x$ were 77%, 88%, 87%, and 88%, respectively (32, 33). In UK Biobank, multi-year data are accessible for $NO_2$ (2005, 2006, 2007, and 2010) and $PM_{10}$ (2007 and 2010), while $NO_x$ and $PM_{2.5}$ data are only available for 1 y (2010). Consistent with previous studies, we used average concentrations of $NO_2$ and $PM_{10}$ for the analysis (33, 34).

Considering exposure data of air pollutants was estimated at baseline in UK Biobank, we further estimated the exposure to $PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_x$ during the follow-up at each participant's residential addresses using data from the UK's Department for Environment, Food and Rural Affairs based on a previous study (35). Then, we applied the Cox proportional hazards model with time-varying exposure to validate the robustness of results. The corresponding results were presented in the sensitivity tests.

**Genetic Data and PRS Calculation.** Genetic data were obtained from UK Biobank, and details of the single-nucleotide polymorphisms (SNPs) information regarding genotyping process, imputation, and stringent quality control have been described briefly in *SI Appendix*, *Text* S1. We selected 155 independent SNPs ($r^2 < 0.05$ or 1,000 Kb apart, without linkage disequilibrium) associated with AF at $P < 5 \times 10^{-8}$ and minor allele frequency >0.05 according to the recent published GWASs in populations of European ancestry (13, 36). *SI Appendix*, Table S16 provides the detailed information regarding the selected SNPs. PRS was constructed based on the selected SNPs. Detailed information on PRS construction is described in *SI Appendix*, *Text* S2. Participants were then categorized into low (tertile 1), medium (tertile 2), and high (tertile 3) genetic risk according to the PRS.

**Assessment of Outcomes.** In UK Biobank, the first occurrence records were used to ascertain incident AF (field ID 13151, category ID 1712, ICD-10 code I48) (36). The diagnosis of AF in the first occurrence records was obtained by using the Primary Care data (Category 3000), Hospital inpatient data (Category 2000), Death Register records (Field 40001, Field 40002), and Self-reported medical condition codes (Field 20002). Detailed information is available in https://biobank.ctsu.ox.ac.uk/crystal/exinfo.cgi?src=diag_xtabs_HES (last accessed date 19 Jul 2022).

**Ascertainment of Covariates.** The baseline questionnaire in UK Biobank provided information on sociodemographic factors, physical measurements, and medical history. According to prior literatures, we chose the following covariates: age (years), sex (male or female), ethnicity (White European, mixed, Asian, Black, and others), education (college or university degree, non-college or other professional qualifications, and none of the above), employment status (employment, retired, and unemployment), alcohol consumption status (never, former, or current drinkers), smoking status (never, former, or current smokers), healthy diet score (0, 1, 2, 3, 4, or 5), physical activity (never activity, low activity, medium activity, or high activity), BMI ($kg/m^2$), hypertension (yes or no), hyperlipidemia (yes or no), and diabetes (yes or no). Physical activity was divided into four types (none activity, low activity, medium activity, and high activity) according to questionnaire (37). A healthy diet score was derived from the self-reported diet information and ranged from 0 to 5. Each one point was added for each favorable diet factor: vegetable intake ≥ four tablespoons/day, fruit intake ≥ three pieces/day; fish intake ≥ twice/week, unprocessed red meat intake ≤ twice/week, and processed meat intake ≤ twice/week (38).

**Analytical Cohort.** Among the 487,241 participants with complete genetic data, we excluded participants with missing air pollutants exposure ($NO_2$, $NO_x$, $PM_{2.5}$, or $PM_{10}$, n = 41,215), and those with a history of AF, cancers, or other cardiovascular diseases at the baseline (n = 44,775). After exclusions, a total of 401,251 participants with complete data were included in the final analyses. All participants were followed up by registrants from the enrolment in the study to diagnosis of AF or death or the end of 16 March 2021.

**Statistical Analysis.** Sample characteristics were illustrated as mean (±SD) for continuous variables or frequency (percentage) for categorical variables. Missing data of variables (all < 5%) were coded as a missing indicator category. Continuous or categorical variables in different groups were compared by Student's *t* test, Mann–Whitney *U* test, or $\chi^2$ tests, as appropriate.

Cox proportional hazards model was performed to evaluate the associations of air pollutants (continuous or categorized by quintile), genetic risk categories (three categories with low risk as reference), and the combination of air pollutants and genetic risk (15 categories with low genetic risk and the lowest quintile of air pollutants as reference) with the risk of incident AF. The results were expressed by HRs and the corresponding 95% CIs. Schoenfeld residuals were used to test the proportional hazards assumption, and no violation was observed. The multivariable-adjusted models were fitted by incorporating several potential confounders: age, sex, ethnicity, education, employment, alcohol consumption status, smoking, healthy diet score, physical activity, BMI, hypertension, hyperlipidemia, and diabetes. In the analyses related to genetic data, we further adjusted the genotyping batch and the first 10 genetic principal components.

We fitted restricted cubic spline (RCS) model to examine dose–response relationships between air pollutants and risk of incident AF. The selection of knots was based on the Akaike information criterion and the location of knots was set according to Harrell's recommendation (*SI Appendix*, Table S17) (39). We also applied the threshold model to determine whether a threshold exists for the associations between exposure to air pollutants and the risk of AF. The model with the smallest −2*log likelihood value is the best-fit threshold model, and the corresponding air pollutants concentrations are the possible threshold estimates (40, 41). To examine whether genetic predisposition modifies the associations of air pollutants with AF incidence, we fitted models on an additive scale and calculated the RERI, the AP, and the SI. If 0 is outside the CIs of RERI and AP, or 1 is outside the CIs of SI, it means that there is an additive interaction.

We validated the findings through a series of sensitivity analyses: 1) Given that a portion of effects from long-term air pollutants exposure may be driven by acute exposure, we incorporated the short-term air pollutants deviations in the models (42). Detailed information on the calculation of short-term deviations can be seen in *SI Appendix, Text* S3. The air pollutants data used to estimate the short-term deviations were obtained from the Environmental Information Data Centre, which collects estimates of daily averaged $PM_{25}$, $PM_{10}$, and $NO_2$ at 3 * 3 $km^2$ grid in the UK from 2002 to 2021 (43). This dataset is output from the European Monitoring and Evaluation Programme model and is widely utilized in the existing literatures (44, 45). 2) We excluded participants who were diagnosed with AF within the first 2 y of follow-up. 3) We excluded participants with missing covariates. 4) We further adjusted the medication history of antihypertensive, hypoglycemic, and cholesterol lowering drugs in the Cox models. 5) We assumed that participants with unidentifiable lifestyle status as having optimal status and fitted the models. 6) We restricted our analyses to participants with more than 5 y of residence at their current address. 7) We further adjusted for the average 24-h sound level of noise pollution in the Cox models. 8) Considering the potential collinearity, we fitted the two-pollutant model for each air pollutant by adding another different type of pollutant to the model. 9) We employed Fine and Gray's subdistribution hazards regression model to avoid the possible influences of competing events (non-AF death). 10) We used a DAG to select covariates and adjusted them in the models. All analyses were performed by R program (version: 4.2.0).

**Data, Materials, and Software Availability.** Some study data available [Researchers can apply for data access directly from UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/register) (31)].

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