Original research

Associations between air pollution and the risk of first admission and multiple readmissions for cardiovascular diseases

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ABSTRACT

Objectives We aimed to investigate the associations between air pollutants and the risk of admission and multiple readmission events for cardiovascular disease (CVD).

Methods A total of 285 009 participants free of CVD at baseline from the UK Biobank were included in this analysis. Four major cardiovascular admission events were identified during the follow-up: chronic ischaemic heart disease (CIHD), cerebrovascular disease, atrial fibrillation and heart failure. We used Prentice, Williams and Peterson-Total Time model to examine the association between ambient air pollution and first admission, as well as multiple readmissions for these CVDs.

Results During a median follow-up of 12 years, 17 176 (6.03%) participants were hospitalised with CVDs, and 6203 (36.11%) patients with CVD had subsequent readmission events for CVDs. We observed significant associations between air pollution and both first admission and readmission for CVDs, with generally stronger associations on readmission for cardiovascular events. For example, the adjusted HRs for the first admission and subsequent readmission for cerebrovascular disease were 1.130 (95% CI 1.070 to 1.194) and 1.270 (95% CI 1.137 to 1.418) for each IQR increase of particulate matter with a diameter ≤2.5 µm. The corresponding HRs for CIHD were 1.060 (95% CI 1.008 to 1.114) and 1.120 (95% CI 1.070 to 1.171). Sex stratified analyses showed that the associations were generally more pronounced among females than males.

Conclusion This study provides evidence that ambient air pollutants might play an important role in both first admission and readmission for cardiovascular events. In addition, patients with pre-existing CVDs may be more vulnerable to air pollution compared with healthy population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ambient air pollution has been regarded as an important preventable risk factor of cardiovascular diseases (CVDs).
⇒ Although the majority of previous studies have focused on the incidence risk of CVD, there have been few investigations on the association between air pollution and the risk of readmission for CVD.

WHAT THIS STUDY ADDS

⇒ During a median follow-up of 12 years, we found ambient air pollutants might play an important role in both first admission and readmission for cardiovascular events.
⇒ In addition, patients with pre-existing CVDs may be more susceptible to air pollution as compared with individuals who are healthy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Considering the significant burden from CVD globally, further compounded by decreased rate of CVD due to advancements in medical care, the findings of this study may have important implications for implementing effective prevention measures for CVD and for guiding environmental regulatory decisions.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of disability and mortality globally, accounting for 40% of all deaths among the elderly population,[1] and its prevalence is expected to rise in the future. With the progress made in the diagnosis and treatment of CVDs, the survival rate has improved, but individuals who have been affected by CVDs are at an increased risk of experiencing recurrent CVD events. Therefore, it is crucial to examine the modifiable risk factors of the recurrent CVD events among the patients with CVD.

Ambient air pollution has been regarded as an important preventable risk factor of CVDs.[2] The health effect of air pollution could be explained by the inflammation and oxidative stress, which can result in cardiac automatic dysfunction.[3] Furthermore, studies have reported that air pollution is relevant for incident CVD events and for CVD events that occur in subsequent years.[4]

Although most previous studies have focused on the association between air pollution and the incidence risk of CVDs, there has been little research into the association between air pollution and the risk of recurrence for CVDs.[5] From both clinical and preventive perspectives, individuals who have suffered from a non-fatal CVD might be more likely

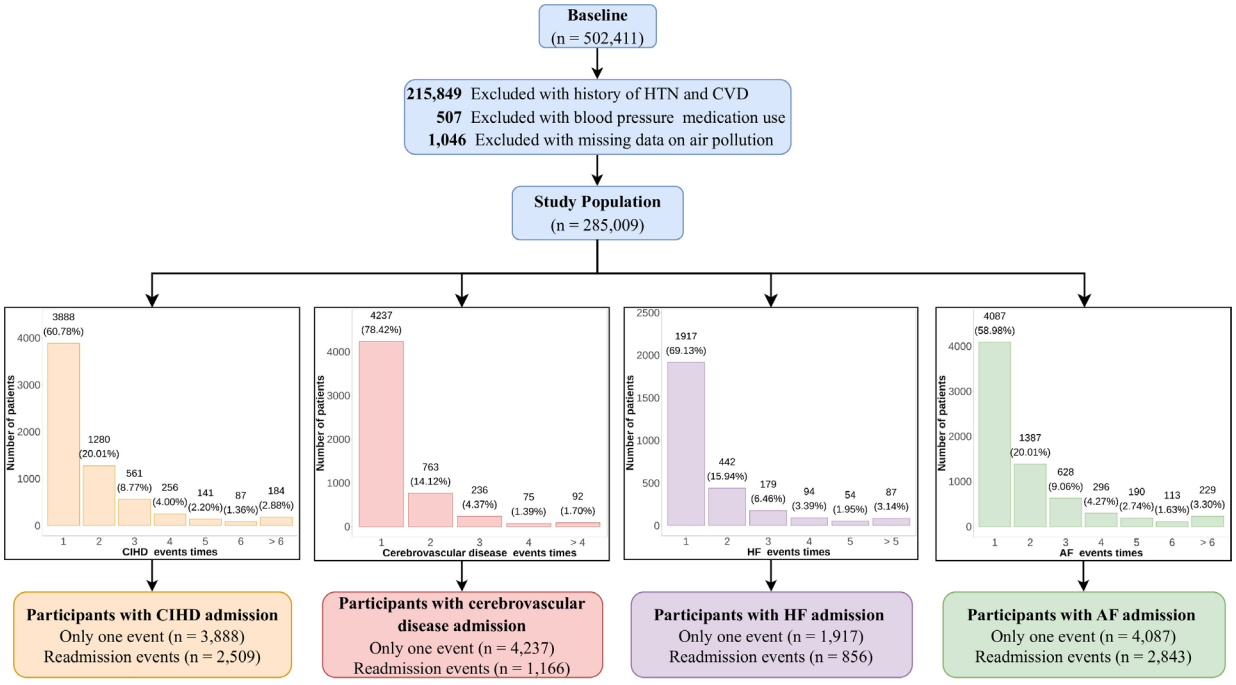

Figure 1 Flow chart of the participant selection and the numbers of admission events for cardiovascular diseases (CVDs). AF, atrial fibrillation; CIHD, chronic ischaemic heart disease; HF, heart failure; HTN, hypertension.

to experience the same events again, compared with individuals who have not.[6] Thus, neglecting the subsequent recurrent events may result in an incomplete understanding of the disease burden experienced by an individual over time.[7]

To address this research gap, we conducted this study to explore the potential relationship between air pollution and both initial and subsequent readmission for cardiovascular events. This study will contribute important evidence to guide future research on the cardiovascular risk posed by air pollution, and help to shed light on the long-term impact of exposure to air pollution on cardiovascular health.

METHODS

Study population

The UK Biobank is a national prospective cohort study in the UK. Between 2006 and 2010, over half a million participants aged 40–70 years were recruited at 22 assessment centres. Participants completed questionnaires on their lifestyle, environment and medical history at the beginning of recruitment. Among the 502 411 initially recruited participants, 215 849 and 507 were excluded due to a history of CVDs and blood pressure medication. A total of 286 055 participants were finally included in this analysis (figure 1).

Follow-up and outcome ascertainment

Non-elective hospital admissions of the participants were obtained from England's Hospital Episode Statistics database, the Scottish Morbidity Record and the Patient Episode Database for Wales. Data on disease ascertainment during the follow-up were available up to 14 years. Mortality data for England and Wales were obtained from the National Health Service (NHS) Digital, and for Scotland from the NHS Central Register. All the participants were followed-up for the hospital admissions started at the recruitment date and ended at the date of death, loss to follow-up or the last date with available data, whichever came first. Total admission events were defined as admission events for CVDs during follow-up, including the first admission event and subsequent readmission CVD events.

Diagnosis of CVDs was ascertained according to Tenth Revision of the International Classification of Diseases (ICD-10). We focused on four major cardiovascular events: chronic ischaemic heart disease (CIHD), cerebrovascular disease, heart failure (HF) and atrial fibrillation (AF). CIHD was defined as ICD-10 codes I25; cerebrovascular disease was coded as ICD-10 codes I60-I69; HF was defined as ICD-10 codes I50 and AF was defined as ICD-10 codes I48.

Air pollution exposure assessment

The annual mean concentrations of air pollutants were obtained from the UK's Department for Environment, Food & Rural Affairs, which provides high-resolution (1 km×1 km grid cells) near-surface air pollution data. The air pollutants included particulate matter with a diameter ≤2.5 µm ($PM_{2.5}$), PM_{10}, nitrogen oxides (NO_x) and nitrogen dioxide (NO_2). Exposure assessments were based on geocoded residential address history of the participants. We then matched the annual air pollution concentrations to each participant's residential locations using bilinear interpolation. The average estimate of air pollutant exposure in the first 3 years of recruitment was calculated by weighting the time spent at each location.

Covariates

A directed acyclic graph (online supplemental figure 1) was developed to identify potential covariates.[8] We selected the following covariates in the multivariate models: age, sex, relative humidity, ambient temperature, ethnicity, physical activity, income, and education. Individual exposure of relative humidity and ambient temperature was assessed based on the Met Offices' HadUK-Grid dataset using a bilinear interpolation method. Multiple imputation with the method of chained equations was performed to impute missing covariate values to make full use

Table 1 The general characteristic of the study population in the UK Biobank (original data)

	No CVDs admission event (n=267 833)	Single admission for CVDs (n=10 973)	Readmissions for CVDs (n=6203)	P value
Age of recruit (years, mean±SD)	54.26±8.07	59.21±7.28	60.19±7.13	<0.001
Male (n, %)	110 768 (41.36)	6266 (57.10)	3800 (61.26)	<0.001
Ethnicity (n, %)				<0.001
White	252 001 (94.09)	10 491 (95.61)	5924 (95.50)	
Missing	1491 (0.56)	68 (0.62)	58 (0.94)	
Air pollution (μg/m^3, mean±SD)				
$PM_{2.5}$	10.48±2.13	10.37±2.04	10.47±2.07	<0.001
PM_{10}	16.63±2.89	16.48±2.75	16.61±2.80	<0.001
NO_2	20.74±6.93	20.49±6.54	20.91±6.76	<0.001
NO_x	31.53±13.42	31.06±12.67	31.84±13.20	<0.001
Meteorological factors (mean±SD)				
Relative humidity (%)	80.65±2.34	80.70±2.57	80.68±2.13	0.124
Ambient temperature (°C)	10.56±0.74	10.52±0.73	10.54±0.71	<0.001
Educational attainment (n, %)				<0.001
High	97 800 (36.52)	3221 (29.35)	1558 (25.12)	
Intermediate	15 485 (5.78)	826 (7.53)	475 (7.66)	
Low	104 706 (39.09)	3832 (34.92)	2097 (33.81)	
Other	44 842 (16.74)	2819 (25.69)	1883 (30.36)	
Missing	5000 (1.87)	275 (2.51)	190 (3.06)	
Income (£) (n, %)				<0.001
>100 000	15 382 (5.74)	400 (3.65)	162 (2.61)	
52 000–100 000	55 580 (20.75)	1573 (14.34)	724 (11.67)	
31 000–51 999	64 849 (24.21)	2222 (20.25)	1185 (19.10)	
18 000–30 999	54 512 (20.35)	2524 (23.00)	1413 (22.78)	
<18 000	40 285 (15.04)	2449 (22.32)	1566 (25.25)	
Missing	37 225 (13.90)	1805 (16.45)	1153 (18.59)	
Physical activity (n, %)				<0.001
Low	38 526 (14.38)	1564 (14.25)	950 (15.32)	
Moderate	89 049 (33.25)	3381 (30.81)	1888 (30.44)	
High	90 747 (33.88)	3773 (34.38)	2030 (32.73)	
Missing	49 511 (18.49)	2255 (20.55)	1335 (21.52)	
BMI (n, %)				<0.001
Normal	106 520 (39.77)	3512 (32.01)	1835 (29.58)	
Obese	46 419 (17.33)	2452 (22.35)	1465 (23.62)	
Overweight	111 731 (41.72)	4864 (44.33)	2787 (44.93)	
Underweight	1790 (0.67)	64 (0.58)	42 (0.68)	
Missing	1373 (0.51)	81 (0.74)	74 (1.19)	
Drinking frequency (n, %)				<0.001
Never	18 641 (6.96)	910 (8.29)	579 (9.33)	
Occasional	58 894 (21.99)	2403 (21.90)	1329 (21.43)	
Moderate	136 583 (51.00)	5184 (47.24)	2841 (45.80)	
Heavy	52 912 (19.76)	2434 (22.18)	1419 (22.88)	
Missing	803 (0.30)	42 (0.38)	35 (0.56)	
Smoking status (n, %)				<0.001
Never	155 778 (58.16)	5356 (48.81)	2789 (44.96)	
Previous	82 723 (30.89)	3904 (35.58)	2229 (35.93)	
Current	27 911 (10.42)	1647 (15.01)	1116 (17.99)	
Missing	1421 (0.53)	66 (0.60)	69 (1.11)	

BMI, body mass index; CVD, cardiovascular disease; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter.

of the data. Five datasets including imputed data were generated and combined using Rubin's rules.[9]

Statistical analysis

Continuous variables were presented as mean±SD. Frequencies of categorical variables were computed. Comparisons among groups were conducted using t-test, Pearson's χ^2 test or Fisher's exact test, as appropriate. The time intervals between sequential readmission events for CVDs after first admission were graphically displayed using Kaplan-Meier survival curves.

We used the Prentice, Williams and Peterson total time (PWP-TT) model to estimate the associations between air pollution

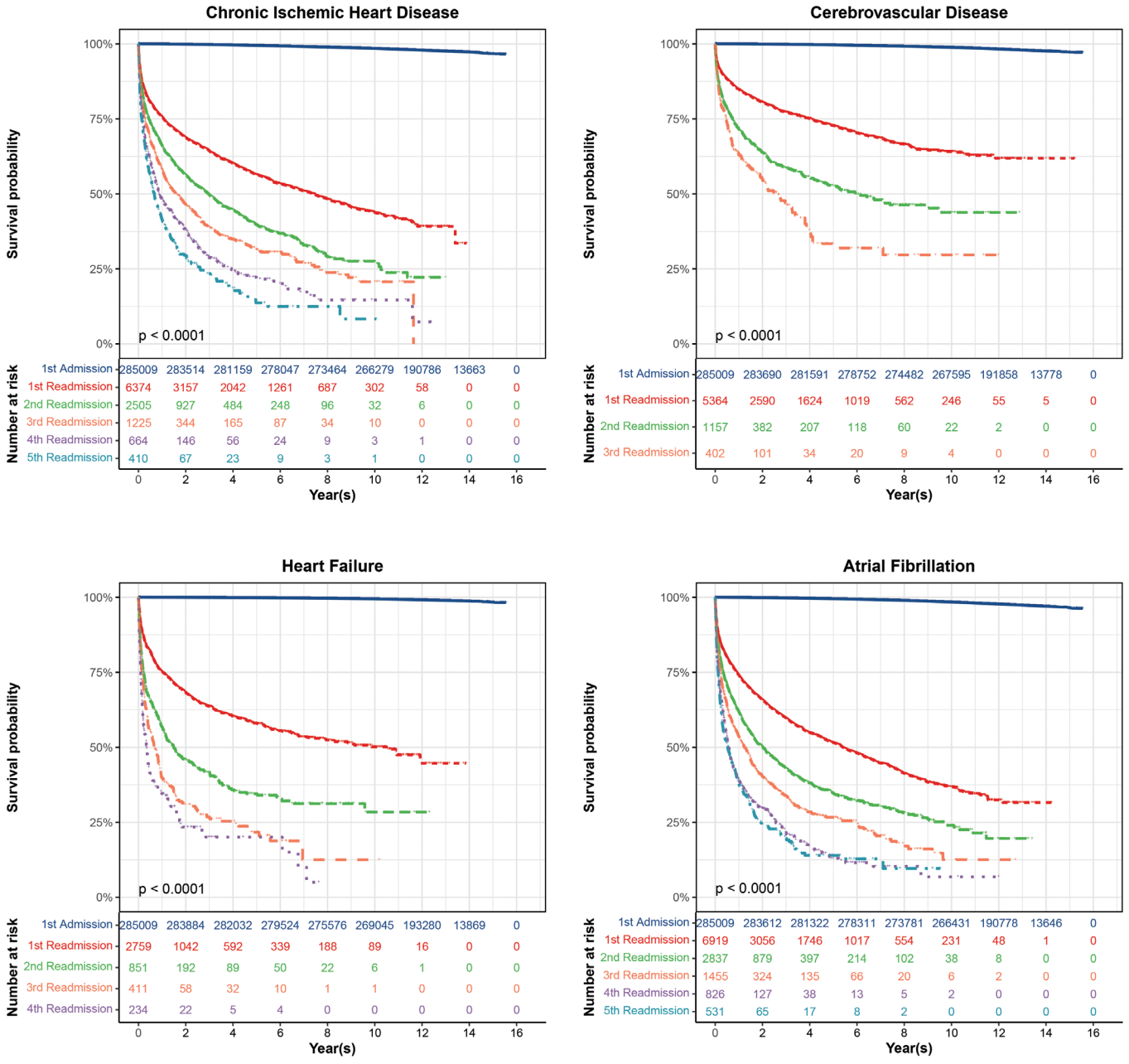

Figure 2 Kaplan-Meier survival curve for the time to each admission for four major cardiovascular diseases during follow-up.

and cardiovascular readmission events. The PWP-TT model is an extension of Cox proportional hazard model that allows investigating the first, and the subsequent multiple recurrent events. It is based on the assumption that recurrent events within the individual are related and an individual is at risk for the successive event only if he/she experienced a previous event.[10] Since the small number of events in a stratum might cause unreliable estimate, the readmission analysis was restricted to the stratum with the number of patients >1% of all the patients.[11] We conducted an additional analysis stratified by each time of readmission to explore the association between air pollution and cardiovascular events in different sequential risk sets. We modelled the associations between air pollutants and the risk of cardiovascular admission events in two steps with increasing adjustment for confounders: model 1 adjusting for age and sex, and model 2 additionally adjusting for relative humidity, ambient temperature, ethnicity, physical activity, income and education.

We used natural cubic spline function with df of 3 to graphically analyse the dose-response relationship between air pollution and the risk admission events for CVDs. We conducted stratified analyses by sex, ethnicity, education level, income, physical activity, body mass index (BMI), smoking status and drinking frequency to estimate the effect modification, and further examined the difference across each stratification by the two-sample z-test.[12]

Sensitivity analyses

To account for potential exposure misclassification resulting from residential mobility, we further conducted the analyses among participants who maintained a consistent residential

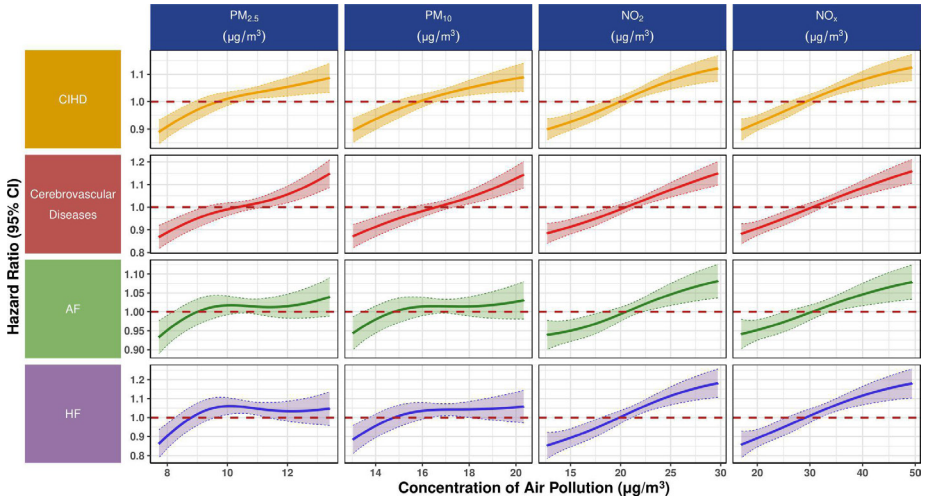

Figure 3 Dose-response curve of the association between air pollutants and the total admission events for cardiovascular diseases during follow-up. AF, atrial fibrillation; CIHD, chronic ischaemic heart disease; HF, heart failure; NO_x, nitrogen oxides; NO_2, nitrogen dioxide; PM, particulate matter.

address during the follow-up. The overlapped participants of four CVDs might lead to statistical selection bias,[13] we thus performed a sensitivity analysis for participants with only one of the four CVDs.

The results were presented as hazard ratios (HRs) per interquartile range (IQR) increase of air pollution with 95% Confidence interval CIs. Data management and analyses were performed using R V.4.0.1.

RESULTS

Among the 285 009 participants, 6397 (2.24%) developed CIHD, 6930 (2.43%) developed AF, 5403 (1.90%) developed cerebrovascular disease and 2773 (0.97%) developed HF during a median follow-up time of 12 years (figure 1). In summary, 39.22% of the patients with CIHD, 41.02% of the patients with AF, 21.58% of the patients with cerebrovascular disease and 30.87% of the patients with HF had subsequent recurrent events after the first admission.

Mean age of the participants without CVDs admission, with single CVDs admission and CVDs readmissions was 54.26 years, 59.21 years and 60.19 years, respectively. For participants with single CVDs admission, the mean concentrations of $PM_{2.5}$, PM_{10}, NO_2 and NO_x were 10.37 (SD 2.04) μg/m^3, 16.48 (SD 2.75) μg/m^3, 20.49 (SD 6.54) μg/m^3 and 31.06 (SD 12.67) μg/m^3, respectively. For participants with CVDs readmissions, corresponding concentrations were 10.47 (SD 2.07) μg/m^3, 16.61 (SD 2.80) μg/m^3, 20.91 (SD 6.76) μg/m^3 and 31.84 (SD 13.20) μg/m^3, respectively. In summary, compared with those without CVDs admission events during follow-up, patients with CVD were relatively older, more likely to be men and tended to have higher exposure levels of air pollution (table 1).

Kaplan-Meier survival curves displayed that patients who were readmitted more frequently had a significantly higher probability of subsequent readmissions compared with those who had fewer admissions (figure 2). A log-rank test showed statistically significant differences among the times of readmission for the

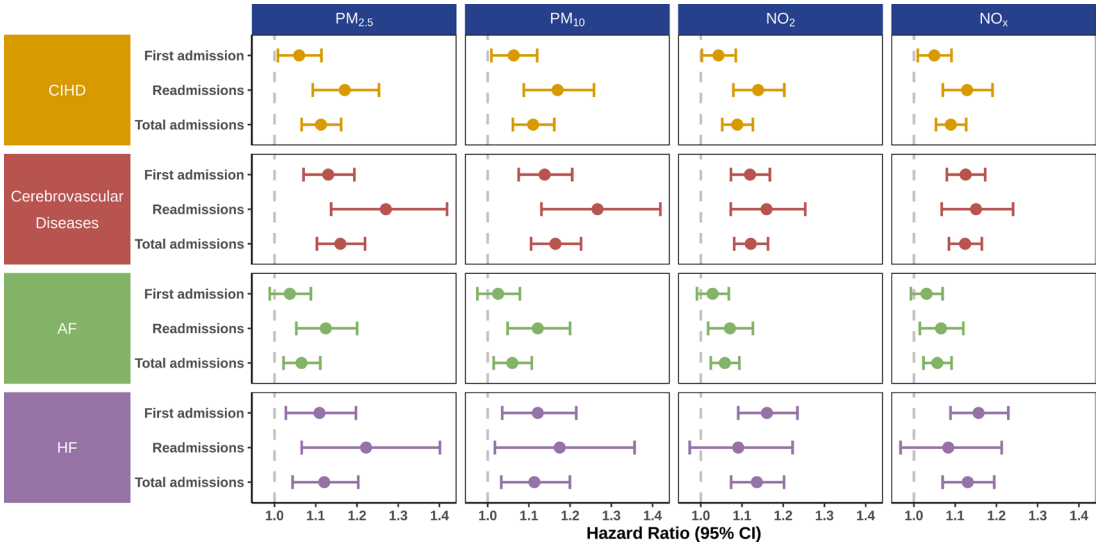

Figure 4 The associations of each IQR increase in air pollution with first admission, readmissions and total admissions for CVDs (HR and 95% CI). IQR increments are 2.79 μg/m^3 for $PM_{2.5}$, 3.81 μg/m^3 for PM_{10}, 8.15 μg/m^3 for NO_2 and 15.92 μg/m^3 for NO_x. AF, atrial fibrillation; CIHD, chronic ischaemic heart disease; HF, heart failure; NO_x, nitrogen oxides; NO_2, nitrogen dioxide; PM, particulate matter.

Table 2 HR with 95% CI for each IQR increase of air pollution on the total cardiovascular admissions during follow-up by using PWP-TT model

	CIHD		Cerebrovascular disease		AF		HF	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
$PM_{2.5}$	1.047 (1.017 to 1.077)	1.113 (1.066 to 1.162)	1.099 (1.064 to 1.135)	1.160 (1.103 to 1.219)	1.063 (1.034 to 1.093)	1.065 (1.022 to 1.111)	1.090 (1.043 to 1.140)	1.121 (1.044 to 1.203)
PM_{10}	1.046 (1.017 to 1.077)	1.110 (1.061 to 1.162)	1.102 (1.067 to 1.138)	1.164 (1.105 to 1.227)	1.062 (1.032 to 1.092)	1.060 (1.015 to 1.107)	1.088 (1.040 to 1.138)	1.113 (1.033 to 1.200)
NO_2	1.069 (1.042 to 1.097)	1.089 (1.052 to 1.126)	1.117 (1.087 to 1.147)	1.121 (1.081 to 1.163)	1.062 (1.035 to 1.088)	1.058 (1.024 to 1.093)	1.109 (1.067 to 1.153)	1.136 (1.074 to 1.202)
NO_x	1.072 (1.045 to 1.100)	1.090 (1.053 to 1.127)	1.119 (1.090 to 1.149)	1.124 (1.085 to 1.165)	1.061 (1.035 to 1.088)	1.057 (1.023 to 1.091)	1.107 (1.065 to 1.150)	1.130 (1.070 to 1.195)

Model 1 adjusted for age and sex; model 2 further adjusted for relative humidity, ambient temperature, ethnicity, physical activity, income and education. IQR increments are 2.79 μg/m^3 for $PM_{2.5}$, 3.81 μg/m^3 for PM_{10}, 8.15 μg/m^3 for NO_2 and 15.92 μg/m^3 for NO_x.
AF, atrial fibrillation; CIHD, chronic ischaemic heart disease; HF, heart failure; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter; PWP-TT, Prentice, Williams and Peterson-Total Time.

CVDs (p<0.0001). Compared with cerebrovascular disease and CIHD, HF and AF had higher likelihood of readmission (online supplemental table 1). For example, the cumulative probability without readmission after the first readmission at 3 years was 77.23%, 64.40%, 63.68% and 59.74% for cerebrovascular disease, CIHD, HF and AF, respectively.

The dose-response curves between air pollutants and first admission events (online supplemental figure 2), readmission events (online supplemental figure 3) and total cardiovascular events (figure 3) during follow-up were found to be monotonic and approximately linear. Exposure to air pollutants was positively associated with the increase of risk of total admission events for CVDs during follow-up. Consistently positive associations were observed on the first admission, readmission and total admission events for four major CVDs (figure 4, table 2, online supplemental tables 2,3 for specific HRs). The associations on the first admission for CVDs were generally smaller than the associations on multiple readmissions events and total admission events during follow-up in CIHD, cerebrovascular diseases, HF and AF; this was opposite for the associations between oxides of nitrogen (NO_2 and NO_x) and HF. Specifically, the adjusted HR of the first admission, readmission and total admission events for CIHD were 1.060 (95% CI 1.008 to 1.114), 1.120 (95% CI 1.070 to 1.171) and 1.113 (95% CI 1.066 to 1.162) for each IQR increase of $PM_{2.5}$, respectively. For cerebrovascular disease, these HRs were 1.130 (95% CI 1.070 to 1.194), 1.270 (95% CI 1.137 to 1.418) and 1.160 (95% CI 1.103 to 1.219), respectively. The associations between oxides of nitrogen and the first admission for HF were stronger than those in readmission for HF and total admissions for HF events during follow-up, with adjusted HR of 1.160 (95% CI 1.091 to 1.234), 1.091 (95% CI 0.973 to 1.223) and 1.136 (95% CI 1.074 to 1.202) for each IQR increase of NO_2, respectively.

Sex stratified analysis showed that the associations on total admission events for CIHD, AF and HF were generally stronger in females than males (table 3). For example, HRs for each IQR increase of NO_2 on total admissions for CIHD during follow-up were 1.109 (95% CI 1.051 to 1.171) and 1.071 (95% CI 1.026 to 1.117) in females and males, respectively. These HRs on total admissions for AF were 1.087 (95% CI 1.033 to 1.144) and 1.045 (95% CI 1.003 to 1.088) in females and males, respectively. In addition, the associations between $PM_{2.5}$, PM_{10}, NO_2 and NO_x and total admission for cerebrovascular disease in males were generally stronger than those in female. However, there were no significant disparity in the risk of total admission between sexes (p for difference >0.05). In addition, no significant effect modifications of ethnicity, education level, income or physical activity, BMI, drinking frequenct and smoking status were observed for any of the pollutants for the first admission and readmissions (online supplemental figures 4–7).

Additional analyses further examined the associations between air pollutants and specific stratum of each readmission event in four CVDs based on the PWP-TT stratified model (online supplemental tables 4–7). We observed that ambient air pollutants were associated with the first admission of each of the CVD, and subsequent readmission risk. For example, HRs for per IQR increase of $PM_{2.5}$ on the first, second, third, fourth and fifth readmission for CIHD were 1.084 (95% CI 1.005 to 1.168), 1.157 (95% CI 1.031 to 1.299), 1.125 (95% CI 0.966 to 1.310), 1.018 (95% CI 0.836 to 1.240) and 1.015 (95% CI 0.787 to 1.309), respectively.

The overlapped participants of four CVDs were shown in a Venn Diagram (online supplemental figure 8). The results of the analysis conducted for those participants with only one of

Table 3 Sex stratified HR with 95% CI for each IQR increase of the air pollution on the total cardiovascular events during follow-up by using PWP-TT model

	CIHD		P	Cerebrovascular disease		P	AF		P	HF		P
	Female	Male	value*	Female	Male	value*	Female	Male	value*	Female	Male	value*
$PM_{2.5}$	1.069 (0.993 to 1.150)	1.128 (1.072 to 1.188)	0.23	1.145 (1.063 to 1.234)	1.170 (1.094 to 1.253)	0.67	1.055 (0.988 to 1.125)	1.085 (1.029 to 1.144)	0.66	1.149 (1.024 to 1.289)	1.112 (1.019 to 1.213)	0.51
PM_{10}	1.079 (1.000 to 1.166)	1.119 (1.060 to 1.182)	0.45	1.139 (1.054 to 1.231)	1.183 (1.103 to 1.269)	0.47	1.058 (0.989 to 1.132)	1.073 (1.016 to 1.134)	0.43	1.159 (1.028 to 1.307)	1.090 (0.994 to 1.196)	0.75
NO_2	1.109 (1.051 to 1.171)	1.071 (1.026 to 1.117)	0.32	1.086 (1.030 to 1.144)	1.150 (1.093 to 1.209)	0.12	1.087 (1.033 to 1.144)	1.045 (1.003 to 1.088)	0.54	1.160 (1.064 to 1.264)	1.120 (1.041 to 1.205)	0.23
NO_x	1.106 (1.050 to 1.166)	1.074 (1.029 to 1.120)	0.38	1.092 (1.037 to 1.150)	1.150 (1.095 to 1.207)	0.16	1.086 (1.033 to 1.142)	1.044 (1.002 to 1.086)	0.60	1.151 (1.057 to 1.254)	1.117 (1.041 to 1.199)	0.22

Model adjusted for relative humidity, ambient temperature, age, ethnicity, physical activity, income and education. IQR increments are 2.79 μg/m^3 for $PM_{2.5}$, 3.81 μg/m^3 for PM_{10}, 8.15 μg/m^3 for NO_2 and 15.92 μg/m^3 for NO_x.
*Estimated using the two-samplie z-test.
AF, atrial fibrillation; CIHD, chronic ischaemic heart disease; HF, heart failure; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM, particulate matter; PWP-TT, Prentice, Williams and Peterson-Total Time.

the four CVDs were consistent with the main analysis (online supplemental table 8). In addition, out of the 285 009 participants, >70% of them did not change their residential address during the follow-up (online supplemental table 9). The associations between air pollution and admission events for the CVDs during follow-up in participants who did not change their residential addresses remain stable (online supplemental table 10).

DISCUSSION

In this study, the relationship between air pollutants exposure and total cardiovascular events during follow-up was investigated. CIHD, cerebrovascular disease, AF and HF were the most common recurrent cardiovascular events in the study population of 286 055 middle-aged and older participants. Ambient air pollutants exposure was significantly associated with the first admission and readmission risk of these four CVDs. Sex did not appear to significantly modify the associations between exposure to air pollution and the recurrent CVD events, except for the associations of HF.

Proper assessment of the disease burden and implementation of effective preventive measures require comprehensive consideration of all subsequent events following the first occourance.[14] However, numerous studies have mainly reported the associations between air pollutants and incidence of CVDs,[15] only a few studies have examined their role in recurrent cardiovascular events.[6] These studies have only considered the effects of air pollution exposure on the first recurrent event among patients with a history of CVDs, rather than the multiple cardiovascular events since the first occurrence of CVDs.[16 17] This may be largely due to traditional statistical methods, which are only capable of focusing on single events. Therefore, we employed the PWP-TT model, a well-developed statistical tool for analysing recurrent event data, to accurately and comprehensively assess the relationship between the air pollution exposure and the total cardiovascular events that occur during the follow-up.[18] In addition, PWP-TT model is capable of estimating the association between air pollution and the risk of multiple sequential events simultaneously by taking accounts for the order of events.[19]

This study explored the associations between air pollutants and the dynamic progression of CVDs, suggesting that four air pollutants ($PM_{2.5}$, PM_{10}, NO_2 and NO_x) were associated with the increased risk of total admission events for CVDs. This result is consistent with previous studies that reported a significant effect of air pollution on the risk of CVDs in Europe.[20] Additionally, previous studies also proposed that individuals with existing CVDs might be more susceptible to the air pollution exposure.[21] Similarly, we observed a tendency towards an increase in the risk of readmission for CVDs in response to exposure to air pollutant, which is significantly higher than the risk associated with the first hospitalisation event. Previous studies had also found that the exposure to air pollution was associated with recurrent event of acute myocardial infarction,[22] and cerebrovascular disease.[21] However, few studies have focused on the role of air pollution on the multiple readmission events. This is the first study to investigate the association between air pollution and total admission events for CVDs during follow-up in middle-aged and elderly participants. More research is needed to further disentangle the relationship between air pollution and recurrent cardiovascular events.

Several biological mechanisms have been proposed to explain the observed associations. Among these mechanisms, oxidative stress and inflammation are considered the leading pathways by which air pollutants increase risk of CVDs.[23] Exposure to

air pollution can trigger the upregulation of pathways that generate reactive oxygen species and ultimately lead to endothelial dysfunction, atherosclerosis and thrombosis.[24] Moreover, individuals with poor physiological conditions are more likely to be exacerbated by exposure to air pollution, especially for the patients with pre-existing CVDs, air pollution exposure may accelerate thrombosis and thus increase the risk of the recurrence of CVDs.[25] Thus, early identification of these preventable risk factors in patients with pre-existing CVDs is of critical significance in the primary prevention efforts and public health policy.

There were generally stronger associations between air pollutants and total CVD events in females compared with males. However, sex differences were not statistically significant. Consistent results in previous studies regarding the sex-related cardiovascular effects of air pollution,[26] the following physiological differences may be the primary reason for the sexual differences in the susceptibility of CVDs. Elderly women have a higher incidence and severity of CVDs compared with men due to the decreased levels of sex hormones.[27] In addition, the key systems involved in the development of CVDs, such as immune system and sympathetic nervous system, are activated differently in males and females.[28] Furthermore, participants with abnormal BMI, smoking and drinking were associated with an increased risk of both first admission and readmission for CVDs triggered by air pollution,[29] although the degree of risk may vary among these factors.

Strengths and limitations

The main strength of this study is the large and well-characterised sample in UK Biobank, as well as the extensive linkages to health records derived from the national healthcare system with universal coverage and rigorous follow-up protocols. In addition, the health data collected by the UK Biobank spans over 14 years, providing extensive follow-up, which enabled the reliable identification of multiple CVD events of the participants.

There are limitations that warrant noting. First, indoor air pollution was not considered due to limited measurements of indoor air pollution exposure. Second, information on potential time-varying confounders were not available, therefore, residual confounding is another issue. However, air pollution emissions have been shown to be stable over decades remained relatively stable according to the UK official statistics.[30] Therefore, it is reasonable to believe that the exposure estimates of air pollutants at baseline could represent the long-term exposure. In addition, we did not consider the blood pressure medication during the follow-up due to the lack of the information, which might lead to bias in the estimated associations between air pollution and recurrent CVDs.

CONCLUSION

Our study provides evidence that ambient air pollutants might be an important risk factor for the first admission, and the subsequent multiple readmissions for CVD. Given the heavy CVD burden, compounded by decreased mortality of CVD due to medical advances, this study may have important implications for the carrying out prevention measures for CVD and for guiding environmental regulatory decisions.

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Data availability statement Data may be obtained from a third party and are not publicly available. This research was conducted using the UK Biobank resource under access application 69550. UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: http://www.ukbiobank.ac.uk/register-apply.

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