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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Joint exposure to various ambient air pollutants and incident heart failure: a prospective analysis in UK Biobank

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Aims Little is known about the relation between the long-term joint exposure to various ambient air pollutants and the incidence of heart failure (HF). We aimed to assess the joint association of various air pollutants with HF risk and examine the modification effect of the genetic susceptibility.

Methods and results This study included 432 530 participants free of HF, atrial fibrillation, or coronary heart disease in the UK Biobank study. All participants were enrolled from 2006 to 2010 and followed up to 2018. The information on particulate matter (PM) with diameters ≤2.5 μm ($PM_{2.5}$), ≤10 μm (PM_{10}), and between 2.5 and 10 μm ($PM_{2.5–10}$) as well as nitrogen oxides (NO_2 and NO_x) was collected. We newly proposed an air pollution score to assess the joint exposure to the five air pollutants through summing each pollutant concentration weighted by the regression coefficients with HF from single-pollutant models. We also calculated the weighted genetic risk score of HF. During a median of 10.1 years (4 346 642 person-years) of follow-up, we documented 4201 incident HF. The hazard ratios (HRs) [95% confidence interval (CI)] of HF for a 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2, and NO_x were 1.85 (1.34–2.55), 1.61 (1.30–2.00), 1.13 (0.80–1.59), 1.10 (1.04–1.15), and 1.04 (1.02–1.06), respectively. We found that the air pollution score was associated with an increased risk of incident HF in a dose–response fashion. The HRs (95% CI) of HF were 1.16 (1.05–1.28), 1.19 (1.08–1.32), 1.21 (1.09–1.35), and 1.31 (1.17–1.48) in higher quintile groups compared with the lowest quintile of the air pollution score (P trend <0.001). In addition, we observed that the elevated risk of HF associated with a higher air pollution score was strengthened by the genetic susceptibility to HF.

Conclusion Our results indicate that the long-term joint exposure to various air pollutants including $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2, and NO_x is associated with an elevated risk of incident HF in an additive manner. Our findings highlight the importance to comprehensively assess various air pollutants in relation to the HF risk.

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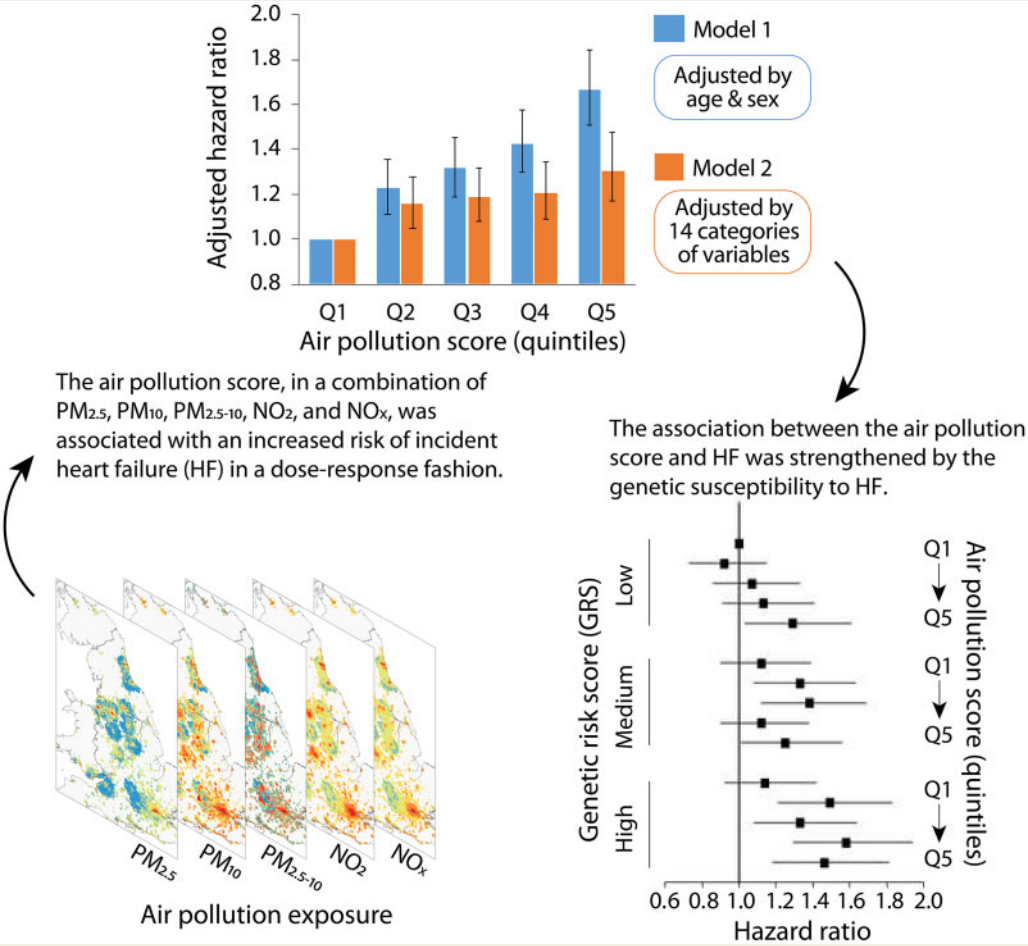
Graphical Abstract



Keywords Air pollution • Heart failure • Joint association • Cohort

Introduction

Long-term ambient air pollution exposure remains a major public health threat worldwide.[1] Numerous studies have associated air pollution with increased risks of cardiovascular diseases and related mortality.[2,3] Of note, the hazard of air pollution on patients with chronic coronary syndromes has been included in 2019 European Society of Cardiology (ESC) Guidelines for the first time.[4] In particular, heart failure (HF) is a highly prevalent clinical syndrome that contributes to a common cause of mortality from cardiovascular diseases.[5,6] Several epidemiological studies have shown that short-term exposure to air pollution is associated with an increased risk of mortality and rates of hospitalization due to HF. In addition, patients with congestive HF are at greater risks of pollution-related hospitalizations for ischaemic heart disease[7] and chronic obstructive pulmonary disorders.[8] However, the evidence on the relation between long-term exposure to air pollution and the incidence of HF remains lacking.[9,10]

Notably, the limited previous studies assessing the association between air pollution and the risk of HF were mainly focused on individual air pollutants, including particulate matter (PM) with diameters ≤2.5 μm ($PM_{2.5}$), ≤10 μm (PM_{10}), and nitrogen dioxide (NO_2).[11,12] In reality, ambient air pollution consists of a mixture of particles and gaseous pollutants, and their combined health effects may differ from those of the individual air pollutants.[13,14] However, no prospective cohort study has jointly examined various air pollutants in relation to the risk of incident HF.

In addition, it has been established that both genetic and environmental factors may contribute to HF. In recent years, emerging evidence has revealed that the genetic susceptibility might interact with environmental factors on cardio-metabolic outcomes.[15,16] Importantly, several studies have indicated that the association

between ambient air pollution exposure and cardiovascular diseases could be modified by genetic variations.[17] However, whether the genetic predisposition may modify the association between the joint exposure to various air pollutants and HF remains unknown.

Therefore, taking advantage the comprehensive information of air pollution and genetic variations in the UK Biobank study, we newly proposed an air pollution score to assess the joint exposure to a combination of air pollutants including $PM_{2.5}$, PM_{10}, and PM with diameters between 2.5 and 10 μm ($PM_{2.5–10}$) as well as nitrogen oxides (NO_2 and NO_x). We tested the association of the air pollution score with the risk of incident HF and further investigated the joint association of the air pollution score and genetic susceptibility with HF and explored the potential gene-air pollution interaction.

Methods

Study design and participants

The UK Biobank is a population-based prospective cohort study, with the study protocol being described in detail previously.[18] Briefly, about 0.5 million residents aged 40–69 years were enrolled from 2006 through 2010 across the UK. The baseline summary characteristics of the cohort are provided on the UK Biobank's website (www.ukbiobank.ac.uk). The information on lifestyle and health data, physical measurements, and biological samples were collected. The UK Biobank study was approved by the North West Multicenter Research Ethical Committee. All participants provided informed written consent.

Among the 502 506 participants with available data in the current study, we excluded those with HF, atrial fibrillation, or coronary heart disease at baseline. A total of 432 530 participants who had complete data for exposure to air pollution were included in the final analysis. In addition, only participants of European descent were included in the genetic analysis ($n = 327\,151$).

Assessment of outcomes

Prevalent HF was defined based on self-reported information and hospital inpatient records (Supplementary material online, *Table S1*).[19] Date and diagnosis for hospital admissions were determined through record linkage to Health Episode Statistics in England and Wales and the Scottish Morbidity Records in Scotland. Incident HF was ascertained as a hospital admission with International Classification of Diseases, Tenth Revision codes of I11.0, I13.0, I13.2, I50.0, I50.1, and I50.9.

Air pollution estimates

The annual average concentrations of $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2, and NO_x were estimated with a Land Use Regression (LUR) model developed from the European Study of Cohorts for Air Pollution Effects project.[20,21] The spatial variations of annual average air pollutant concentrations were calculated using the LUR model including the geospatial predictor variables generated from the Geographic Information System such as traffic, land use, and topography. Air pollution exposures of all participants in the UK Biobank were linked to the records through residential addresses given at the baseline visit. The exposure data of $PM_{2.5}$, $PM_{2.5–10}$, and NO_x were collected in 2010, while annual concentration data of NO_2 and PM_{10} were available for several years (2005, 2006, 2007, and 2010 for NO_2 and 2007 and 2010 for PM_{10}). The averaged values of NO_2 and PM_{10} were included in the analysis. We made a comparison between air pollution exposures ($PM_{2.5}$, PM_{10}, NO_2, NO_x) in the current study and the spatial distributions of air pollutants from the pubic UK Air Information Resources (https://uk-air.defra.gov.uk/data/pcm-data). The results are shown in Supplementary material online, *Figure S1*. The distribution patterns of air pollution exposures in the current study are similar with the spatial distributions of air pollutants from the public UK Air Information Resources.

Definition of the air pollution score

We created a weighted air pollution score through adding concentrations of the five air pollutants, weighted by the multivariable-adjusted risk estimates (β coefficients) on HF in the present analysis. The equation was: air pollution score = $(\beta\,[PM_{2.5}] \times PM_{2.5} + \beta\,[PM_{10}] \times PM_{10} + \beta\,[PM_{2.5–10}] \times PM_{2.5–10} + \beta\,[NO_2] \times NO_2 + \beta\,[NO_x] \times NO_x) \times$ (5/sum of the β coefficients). The air pollution score ranged from 49.6 to 177.6, as a higher score indicating higher exposure to ambient air pollution. Participants were divided into five groups according to the quintiles of the air pollution score.

In the sensitive analysis, we further constructed a weighted air pollution score based on the four air pollutants without $PM_{2.5–10}$: air pollution score = $(\beta\,[PM_{2.5}] \times PM_{2.5} + \beta\,[PM_{10}] \times PM_{10} + \beta\,[NO_2] \times NO_2 + \beta\,[NO_x] \times NO_x) \times$ (4/sum of the β coefficients).

Definition of the genetic risk score

Detailed information about genotyping, imputation, and quality control in the UK Biobank study has been described previously.[22] We created a genetic risk score (GRS) for HF using 12 single-nucleotide polymorphisms (SNPs) based on a previous genome-wide association study (Supplementary material online, *Table S2*).[23] A weighted method was used to calculate the HF GRS. Each SNP was recoded as 0, 1, or 2 according to the number of risk alleles; and then multiplied by the risk estimate (β coefficient) on HF obtained from the previous study to calculate the GRS: GRS = $(\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_{12} \times SNP_{12}) \times$ (12/sum of the β coefficients).[24] The HF GRS ranged from 1.4 to 18.3, with a higher score indicating a higher genetic predisposition to HF. We classified participants into three groups of low (tertile 1), intermediate (tertile 2), and high (tertile 3) genetic risk of HF.

Measurements of covariates

We included age, sex, race, Townsend Deprivation index, smoking status, alcohol consumption status, physical activity, body mass index (BMI), healthy diet score, blood pressure levels, and prevalent diseases as potential confounders. The Metabolic Equivalent Task (MET) minutes based on items from short International Physical Activity Questionnaire (IPAQ) was adopted to assess physical activity. A healthy diet score was calculated based on the following diet factors: 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. Each one point was given for each favourable diet factor, and the healthy diet score ranged from 0 to 5. In addition, height and weight were measured by trained nurses during the baseline assessment centre visit, and BMI was calculated through dividing weight in kilograms by the square of height in meters. The history of hypertension, diabetes, and respiratory diseases (chronic obstructive pulmonary disease [COPD] and emphysema) was based on self-reported information and medical records. Self-reported information on medication use including cholesterol-lowering medication, blood pressure medication, and insulin was also collected. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at baseline using standardized procedures by trained nurses. The mean values of two automated or manual measurements were used.

Statistical analysis

Survival time for each participant was calculated as the duration from the response date of baseline survey through the time of incident HF, death, or date of censoring, whichever came first. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI). The proportional hazards assumption was tested using Schoenfeld residuals. Several potential confounders were adjusted in these models, including age (continuous), sex (male, female), race (white European, mixed, South Asian, black, others), UK Biobank assessment centre, Townsend Deprivation index (continuous), alcohol consumption status (current, former, never, missing), smoking status (current, former, never, missing), BMI (kg/m^2, continuous), physical activity (MET-minutes/week, continuous), healthy diet score (0, 1, 2, 3, 4, 5), SBP (continuous), DBP (continuous), prevalent diabetes (yes/no), and prevalent hypertension (yes/no). For analyses of genetic data, we further adjusted for the genotyping array and the first ten genetic principal components. In the analysis of individual air pollutants, a single air pollutant was included in the model. The linear trend test was performed by treating the variables continuously. Missing data were coded as a missing indicator category for categorical variables such as smoking and with mean values for continuous variables.

To validate our results, we performed a 10-fold cross-validation analysis.[25,26] The cohort was randomly divided into 10 batches. In each run, one of the 10 samples was used as the testing data and the remaining nine samples as training data. The Cox regression was applied to the training dataset to obtain the regression coefficient of each air pollutant for the risk of HF and the subsequent air pollution score. Then, the air pollution score was used in the testing dataset to calculate the HRs and 95% CI for HF risk. The process was repeated 10 times, with each of the 10 samples used once as the testing data. A fixed-effects meta-analysis was conducted to obtain the comprehensive HR of these 10 groups.

To evaluate whether the genetic susceptibility of HF may modify the association between the air pollution score and HF incidence, we tested the gene–air pollution interaction by setting variable cross-product terms of the air pollution score with the HF GRS in the models.

Several sensitivity analyses were conducted to examine the robustness of our findings. First, since $PM_{2.5–10}$ was not significantly associated with the risk of incident HF, we excluded $PM_{2.5–10}$ and only incorporated $PM_{2.5}$, PM_{10}, NO_2, and NO_x in the air pollution score. We also additionally adjusted for average total household income (<£18 000, £18 000–£30 999, £31 000–£51 999, £52 000–£100 000, >£100 000, and 'do not know' or missing) and education years in the models. In addition, we further adjusted for the history of medication use including antihypertensive medication (yes/no), insulin (yes/no), and cholesterol-lowering medication (yes/no) as well as respiratory diseases (yes/no) at baseline. Moreover, we further adjusted for the average 24-h sound level of noise pollution (dB) in the model. Furthermore, we restricted incident HF cases to >2 years from the baseline survey to minimize the reverse causality effect on the observed associations. Finally, we conducted a sensitivity analysis including participants living in the current address for at least five years to assess the long-term effect of air pollution on HF.

All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and R software (version 3.5.1). All *P*-values for the tests were two-sided and *P*-values <0.05 were considered as statistically significant.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Table 1 Baseline characteristics of participants in the UK Biobank study

	Incident heart failure	
	Yes (*N* = 4201)	No (*N* = 428 329)
Characteristics		
Age (years)	61.6 (6.4)	56.2 (8.1)
Sex, male (%)	60.2	44.0
Race, white (%)	93.8	93.9
Body mass index (kg/m^2)	29.5 (5.9)	27.3 (4.7)
Townsend Deprivation index	-0.8 (3.3)	-1.4 (3.0)
Current drinkers (%)	86.4	92.0
Current smokers (%)	17.0	10.2
MET (min/week)	2478.9 (2283.5)	2666.8 (2437.3)
Healthy diet score (%)		
0–1	13.5	11.6
2–3	52.7	48.8
4–5	33.8	39.6
Prevalent diabetes (%)	15.2	4.5
Prevalent hypertension (%)	49.7	25.5
Systolic blood pressure (mmHg)	145.6 (20.0)	137.7 (18.6)
Diastolic blood pressure (mmHg)	83.7 (11.0)	82.4 (10.1)
$PM_{2.5}$ (μg/m^3)	10.2 (1.1)	10.0 (1.1)
PM_{10} (μg/m^3)	19.4 (1.9)	19.3 (2.0)
$PM_{2.5–10}$ (μg/m^3)	6.5 (0.9)	6.4 (0.9)
NO_2 (μg/m^3)	30.0 (9.1)	29.3 (9.3)
NO_x (μg/m^3)	46.1 (16.8)	43.9 (15.6)

Data are mean (SD) unless otherwise indicated. MET, Metabolic Equivalent Task; $PM_{2.5}$, particular matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particular matter with an aerodynamic diameter ≤10 μm; $PM_{2.5–10}$, particular matter with an aerodynamic diameter between 2.5 and 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

Results

The baseline characteristics of the participants according to incident HF are shown in *Table 1*. Participants who had incident HF were older, mainly males, and with high BMI and Townsend Deprivation index compared with those without incident HF. In addition, they were more likely to be current smokers but less likely to be current drinkers or have a healthy diet. Moreover, participants with incident HF had a higher prevalence of diabetes and hypertension as well as blood pressure levels at baseline. The mean (standard deviation [SD]) estimates of $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2, and NO_x were 10.2 (1.1), 19.4 (1.9), 6.5 (0.9), 30.0 (9.1), and 46.1 (16.8) μg/m^3, respectively, among participants with incident HF; and the corresponding concentrations were 10.0 (1.1), 19.3 (2.0), 6.4 (0.9), 29.3 (9.3), 43.9 (15.6) μg/m^3 for those without incident HF. The Spearman correlation coefficients among the five air pollutants are shown in Supplementary material online, *Table S3*.

During a median of 10.1 years (4 346 642 person-years) of follow-up, we documented 4201 incident HF. The associations between individual air pollutants and HF are shown in *Table 2*. We observed that $PM_{2.5}$, PM_{10}, NO_2, and NO_x each associated with an increased

Table 2 Adjusted hazard ratios[a] and 95% confidence interval for air pollution concentrations with the risk of incident heart failure in the UK Biobank study

	Air pollution concentrations (quintiles)					HR (95% CI) for a 10 μg/m^3 increase	*P* for trend
	Q1	Q2	Q3	Q4	Q5		
$PM_{2.5}$	1.00	1.00 (0.90–1.11)	1.05 (0.94–1.16)	1.16 (1.05–1.29)	1.14 (1.02–1.27)	1.85 (1.34–2.55)	<0.001
PM_{10}	1.00	1.17 (1.06–1.30)	1.24 (1.12–1.37)	1.16 (1.04–1.29)	1.31 (1.15–1.48)	1.61 (1.30–2.00)	<0.001
$PM_{2.5–10}$	1.00	1.03 (0.93–1.13)	1.07 (0.97–1.18)	1.04 (0.94–1.15)	1.02 (0.93–1.13)	1.13 (0.80–1.59)	0.48
NO_2	1.00	1.11 (1.00–1.23)	1.18 (1.06–1.30)	1.23 (1.10–1.37)	1.24 (1.09–1.42)	1.10 (1.04–1.15)	<0.001
NO_x	1.00	1.09 (0.98–1.21)	1.20 (1.08–1.33)	1.11 (1.00–1.24)	1.29 (1.16–1.45)	1.04 (1.02–1.06)	<0.001

CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particular matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particular matter with an aerodynamic diameter ≤10 μm; $PM_{2.5–10}$, particular matter with an aerodynamic diameter between 2.5 and 10 μm.
[a]Adjusted for age, sex, race (white European, mixed, South Asian, black, others), UK Biobank assessment centre, Townsend Deprivation index, alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), body mass index (kg/m^2), physical activity (MET-min/week), healthy diet score (0, 1, 2, 3, 4, 5), diabetes (yes/no), hypertension (yes/no), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg).

risk of HF in the models adjusted for age, sex, race, UK Biobank assessment centre, Townsend Deprivation index, alcohol consumption, smoking status, BMI, physical activity, healthy diet score, diabetes, hypertension, SBP, and DBP. The HRs (95% CI) of HF for a 10-μg/m^3 increase in $PM_{2.5}$, PM_{10}, NO_2, and NO_x were 1.85 (1.34–2.55), 1.61 (1.30–2.00), 1.10 (1.04–1.15), and 1.04 (1.02–1.06), respectively. In addition, we observed a non-significant elevated risk of HF associated with a 10-μg/m^3 increase in $PM_{2.5–10}$ (HR = 1.13, 95% CI, 0.80–1.59).

Table 3 shows the association between the air pollution score and HF. We found that the air pollution score was significantly associated with a higher risk of incident HF in the age, sex-adjusted, and multivariate-adjusted models. In the age- and sex-adjusted model, a 67% higher risk of incident HF was observed in the highest quintile vs. the lowest quintile of the air pollution score (*P* trend <0.001). After further adjustment for race, UK Biobank assessment centre, Townsend Deprivation index, alcohol consumption, smoking status, BMI, physical activity, healthy diet score, diabetes, hypertension, SBP, and DBP, the air pollution score was associated with an increased risk of incident HF in a dose–response fashion. The HRs (95% CI) of HF were 1.16 (1.05–1.28), 1.19 (1.08–1.32), 1.21 (1.09–1.35), and 1.31 (1.17–1.48) in higher quintile groups compared with the lowest quintile of the air pollution score (*P* trend <0.001). The results were largely unchanged after excluding $PM_{2.5–10}$ in the air pollution score (Supplementary material online, *Table S4*).

We further performed cross-validation analysis to evaluate the robustness of our findings. The results of the association between the air pollution score and the risk of HF in the cross-validation analysis are shown in the Supplementary material online, *Table S5*. The validation tests showed consistently significant results as in the current analysis.

The sensitivity analyses also showed that the association between the air pollution score and the risk of incident HF was robust with further adjustment for average total household income and education years or additionally adjustment for anti-hypertensive medication use, insulin use, cholesterol-lowering medication use, and history of respiratory diseases at baseline (Supplementary material online, *Table S6*). The results did not change appreciably after further adjustment for the average 24-hour sound level of noise pollution (Supplementary material online, *Table S6*). In addition, after limiting participants with a follow-up time of more than 2 years, the results did not alter appreciably (Supplementary material online, *Table S7*). Moreover, the results were robust when only participants living in the current address for at least five years were included (Supplementary material online, *Table S8*).

In the models adjusting for sex, age, assessment centre, genotyping batch, and the first ten genetic principal components, we observed a significant association of HF GRS with the risk of incident HF. The HF GRS was associated with a 173% higher risk of incident HF (95% CI, 105–262%). The association remained significant in the multivariable-adjusted model, as the HR (95% CI) of HF was 2.65 (1.99–3.53) for HF GRS (*Table 4*). We further assessed the joint association of the air pollution score and the HF GRS with the risk of incident HF. We found that participants with high GRS and air pollution score had the highest risk of HF, even though there was no statistically significant interaction between the air pollution score and genetic susceptibility to HF. Participants with high GRS and air pollution score had a 46% greater risk of HF (95% CI, 18%-81%) than participants with low GRS and air pollution score (*Figure 1*).

Discussion

In this prospective cohort study, we newly created an air pollution score to assess the joint exposure to various air pollutants including $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2, and NO_x through summing each pollutant concentration weighted by the regression coefficients with HF from single-pollutant models. We found that the air pollution score was associated with an increased risk of incident HF in a dose–response fashion, independent of traditional risk factors. In addition, we found that the association between the air pollution score and HF risk was strengthened by the genetic susceptibility to HF, even though there was no significant interaction between the air pollution score and HF GRS.

Previous epidemiological studies have associated HF with acute exposures to $PM_{2.5}$,[10,27] PM_{10},[10,28,29] and NO_2.[10,29] The publications with significant associations between short-term $PM_{2.5}$ exposure and HF are shown in Supplementary material online, *Figure S2*. An analysis

Table 3 Adjusted hazard ratios and 95% confidence interval for the air pollution score with the risk of incident heart failure in the UK Biobank study

	Air pollution score (quintiles)					*P* for trend
	Q1	Q2	Q3	Q4	Q5	
Cases/*N*	677/86506	819/86 506	850/86 506	890/86 506	965/86 506	
Model 1[a]	1.00	1.23 (1.11–1.36)	1.32 (1.19–1.46)	1.43 (1.30–1.58)	1.67 (1.51–1.84)	<0.001
Model 2[b]	1.00	1.16 (1.05–1.28)	1.19 (1.08–1.32)	1.21 (1.09–1.35)	1.31 (1.17–1.48)	<0.001

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, race (white European, mixed, South Asian, black, others), UK Biobank assessment centre, Townsend Deprivation index, alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), body mass index (kg/m^2), physical activity (MET-min/week), healthy diet score (0, 1, 2, 3, 4, 5), diabetes (yes/no), hypertension (yes/no), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg).

Table 4 Adjusted hazard ratios and 95% confidence interval for heart failure genetic risk score with the risk of incident heart failure in the UK Biobank study

	Heart failure genetic risk score (tertiles)				
	Low genetic risk	Medium genetic risk	High genetic risk	HR (95% CI) for the continuous variable	*P* for trend
Cases/*N*	869/106 248	1043/111 582	1147/109 321		
Model 1[a]	1.00	1.15 (1.05–1.26)	1.31 (1.20–1.43)	2.73 (2.05–3.62)	<0.001
Model 2[b]	1.00	1.15 (1.05–1.25)	1.30 (1.19–1.42)	2.65 (1.99–3.53)	<0.001

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, UK Biobank assessment centre, genotyping batch, and the first 10 genetic principal components.
[b]Adjusted for age, sex, race (white European, mixed, South Asian, black, others), UK Biobank assessment centre, Townsend Deprivation index, alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), body mass index (kg/m^2), physical activity (MET-min/week), healthy diet score (0, 1, 2, 3, 4, 5), diabetes (yes/no), hypertension (yes/no), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), genotyping batch, and the first ten genetic principal components.

using hospital admissions data of 11.5 million Medicare enrolees showed that $PM_{2.5}$ was associated with an increased risk for HF hospital admission.[30] Furthermore, a time series study in 184 major Chinese cities showed that an increase of 10 μg/m^3 in $PM_{2.5}$ was associated with a 0.27% increase in hospital admissions for HF.[31] $PM_{2.5}$ was also associated with mortality after cardiac transplantation, as the estimated HR per 10 μg/m^3 increment in annual exposure to $PM_{2.5}$ was 1.26 for mortality.[32] Moreover, a time-stratified case-crossover analysis in the Vietnamese population showed significant associations of $PM_{2.5}$ and PM_{10} with hospital admissions for cardiac failure.[33] In addition, PM_{10} and NO_2 were found to be associated with increased risks of hospital cardiac readmissions including HF among myocardial infarction survivors.[34] Of note, the associations between NO_2 and hospital admissions for HF showed evident heterogeneity across the previous studies.[9] Poloniecki *et al.*[35] did not find a significant association between NO_2 and emergency hospital admissions for HF, possibly due to a lack of controlling for confounders such as smoke and blood pressure in the models. However, these studies only assessed the short-term effect of air pollution on HF, the long-term association between air pollution and the incidence of HF is less established. Although several studies have assessed the associations of long-term exposures to $PM_{2.5}$,[36,37] PM_{10},[11,38] NO_2,[11,39,40] and NO_x[41] with the incidence of HF, most of the studies only conducted a secondary analysis on HF, while the investigations with HF as the primary outcome are still scarce. Even less studies have comprehensively assessed various air pollutants, and no study has assessed the joint association of different air pollutants with incident HF. In the current study, we comprehensively assessed the associations of long-term exposures to various air pollutants including $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2, and NO_x with HF risk and found that the estimated HR risks associated with the individual air pollutants were comparable with several prior investigations showing significant associations of air pollutants with the risk of HF. We have summarized the publications with significant associations between long-term $PM_{2.5}$ exposure and HF in Supplementary material online, *Figure S2*. In the present study, $PM_{2.5}$ showed the strongest association with the risk of HF, followed by PM_{10}, NO_2, and NO_x. However, we observed an elevated but non-significant risk for incident HF associated with $PM_{2.5-10}$. Although the reported associations between $PM_{2.5-10}$ and HF were heterogeneous,[37,39,42] we included $PM_{2.5-10}$ in the air pollution score to comprehensively assess the joint exposure to various air pollutants.

To our knowledge, this is the first prospective study to assess the association between the joint exposure to various ambient air pollutants and the risk of incident HF. Recently, the importance of evaluating the health effects of multi-pollutant exposures has been increasingly recognized; as the various air pollutants are highly correlated and may be from the same emission sources.[43,44] We found a

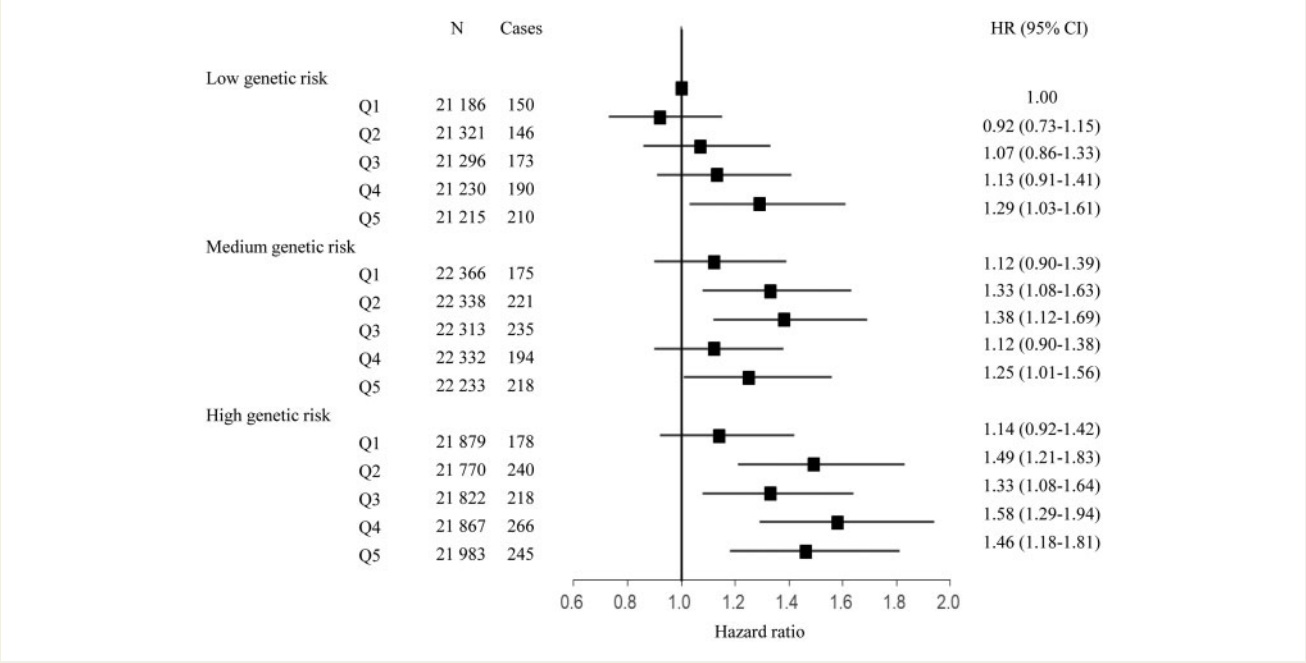


Figure 1 The joint association of the air pollution score (in quintiles) and heart failure genetic risk score with the risk of incident heart failure. The model was adjusted for age, sex, race (white European, mixed, South Asian, black, others), UK Biobank assessment centre, Townsend Deprivation index, alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), body mass index (kg/m^2), physical activity (MET-min/week), healthy diet score (0, 1, 2, 3, 4, 5), diabetes (yes/no), hypertension (yes/no), systolic blood pressure, diastolic blood pressure, genotyping batch, and the first 10 genetic principal components.

relatively stronger association between our newly developed air pollution score and the risk of HF compared with individual air pollutants. Thus, the air pollution score may reflect a more comprehensive measure of the joint exposure to various air pollutants. Previous studies have proposed similar methods by summing air pollutant concentrations to estimate the combined effects of multi-pollutant exposures on human health.[45,46] For example, Hong *et al.*[45] examined the combined effects of PM_{10}, NO_2, sulphur dioxide, and ozone through summing each air pollutant concentration divided by its mean and found that the combined index had a stronger association with total mortality than individual air pollutants. The use of the statistical approach by adding air pollutant concentrations allows estimating the combined effects of mixtures in the presence of correlation among them. In addition, similar algorithms have been used to assess the joint exposure to other environmental risk factors[47] and dietary factors.[48] The simple score algorithm makes epidemiological findings easier to be interpreted and may also facilitate public health preventive practice.

Several potential mechanisms might be underlying the observed relations between air pollution and HF. For instance, exposure to air pollution can lead to oxidative stress, systemic inflammation, and autonomic imbalance and then increase blood pressure and decrease cardiac output.[12,49,50] Prolonged or repeated stimulation of these pathways may further result in the progression of endothelial dysfunction, atherosclerosis, diastolic dysfunction, left ventricular hypertrophy, and myocardial fibrosis,[50–52] which could eventually increase the risk of HF. In addition, a randomized controlled study of HF (the FILTER-HF Trial) showed that a filter intervention might reduce endothelial dysfunction and B-type natriuretic peptide increases associated with the short-term exposure to diesel exhaust exposure in patients with HF.[53] The mechanisms by which the combination of air pollutants might affect the risk of HF remain unclear. Since the association between the air pollution score and HF risk was stronger than those for the individual air pollutants, we assumed that the various air pollutants might have additive effects on the risk of HF through similar biological mechanisms such as oxidative stress and inflammation.[49,54]

We also assessed the joint association of air pollution and genetic susceptibility with the risk of incident HF. We observed that the risk of HF associated with a higher air pollution score was strengthened by high genetic risk, even though the test on the interaction between the air pollution score and genetic susceptibility was not significant. The proportion of HF risk explained by the variants was <10%, which may partially explain the negative interaction. Existing evidence suggests the potential mechanisms for the risk of HF associated with a higher air pollution score strengthened by a high genetic risk. The identified genetic loci for HF in the genome-wide association study were associated with risk factors and traits related to left ventricular structure and function. The genetic loci associated with reduced left ventricular systolic function or atrial fibrillation were also related to the processes of cardiac development, protein homoeostasis, and cellular senescence. In addition, the observed relations between air

pollution and HF might be through these aforementioned mechanical changes. Therefore, we assumed that air pollutants and genetic variations for HF risk might have additive effects on the risk of HF through at least certain overlapped biological mechanisms related to cardiac function.

Strengths and limitations

Several strengths of this study include the prospective design and large sample size. Our study is the first prospective study to assess the association between the joint exposure to various ambient air pollutants and the risk of incident HF. The novel findings on the relation between the combined air pollutants and HF may prompt the development of new prevention strategy by considering various air pollutants together. In addition, with HF as the primary disease outcome, the results might provide a global picture about the health effect of air pollution on HF. Moreover, we for the first time examined the joint association of air pollutants and the genetic susceptibility with HF. Furthermore, we conducted a cross-validation analysis and found the results were consistently significant in the validation tests, indicating the robustness of our findings. However, we acknowledge that investigations in other populations are warranted to further validate our findings. The current study also has several potential limitations. First, the results from our observational study were based on a retrospective sub-analysis of the data from the UK Biobank. Thus, the causality of the results should be interpreted with caution. Second, we estimated the weights (regression coefficients) of air pollutants by treating each as a continuous variable. However, air pollutants may not be linearly associated with HF. Although examining non-linearity relations in the single air pollutant models may provide more information, the construction of a simple weighted risk score would not be possible. Third, the air pollution score did not include all air pollutants, such as O_3 and ultrafine particles that might be also related to the risk of HF.[12,28,40] Fourth, the air pollution exposure might be over- or underestimated since air pollution exposure in work environment is unavailable in UK Biobank study. Moreover, only a single measurement of air pollution is available in UK Biobank since home addresses of the participants are unavailable during follow-up. Further studies with repeated measurements are needed to confirm the findings. In addition, although we adjusted for the major confounders, residual confounding from unknown or unmeasured factors might be still existing. Finally, the present study was based on UK Biobank and most of the participants were European descent; thus, the generalization of the gene–air pollution score interaction results to other populations should be interpreted with caution.

Conclusions

In summary, for the first time, our results indicate that the long-term joint exposure to various air pollutants including $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2, and NO_x, evaluated as an air pollution score, is associated with an elevated risk of incident HF in a dose–response fashion. Our findings suggest potential additive effects of different air pollutants on HF risk and highlight the importance to comprehensively assess various air pollutants in the prevention of cardiovascular diseases.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Contributors

M.W. and L.Q. conceived and designed the study, interpreted the data, and drafted and critically revised the manuscript. M.W., X.L., and Y.S. performed the statistical analysis. All authors contributed to the interpretation of the results and critical revision of the manuscript. All authors approved the final manuscript.

Data sharing

This research has been conducted using the public UK Biobank Resource (www.ukbiobank.ac.uk/).

Conflict of interest: none declared.

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