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Independent and combined effects of long-term air pollution exposure and genetic predisposition on COVID-19 severity: A population-based cohort study

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The relationships between air pollution, genetic susceptibility, and COVID-19-related outcomes, as well as the potential interplays between air pollution and genetic susceptibility, remain largely unexplored. The Cox proportional hazards model was used to assess associations between long-term exposure to air pollutants and the risk of COVID-19 outcomes (infection, hospitalization, and death) in a COVID-19-naive cohort (n = 458,396). Additionally, associations between air pollutants and the risk of COVID-19 severity (hospitalization and death) were evaluated in a COVID-19 infection cohort (n = 110,216). Furthermore, this study investigated the role of host genetic susceptibility in the relationships between exposure to air pollutants and the development of COVID-19-related outcomes. Long-term exposure to air pollutants was significantly associated with an increased risk of COVID-19-related outcomes in the COVID-19 naive cohort. Similarly, in COVID-19 infection cohort, hazard ratios (HRs) for COVID-19 hospital admission were 1.23 (1.19, 1.27) for $PM_{2.5}$ and 1.22 (1.17, 1.26) for PM_{10}, whereas HRs for COVID-19 death were 1.28 (1.18, 1.39) for $PM_{2.5}$ and 1.25 (1.16, 1.36) for PM_{10}. Notably, significant interactions were found between $PM_{2.5}$/PM_{10} and genetic susceptibility in COVID-19 death. In COVID-19 infection cohort, participants with both high genetic risk and high air pollutants exposure had 1.86- to 1.97-fold and 1.91- to 2.14-fold higher risk of COVID-19 hospitalization and death compared to those with both low genetic risk and low air pollutants exposure. Exposure to air pollution is significantly associated with an increased burden of severe COVID-19, and air pollution–gene interactions may play a crucial role in the development of COVID-19-related outcomes.

COVID-19 | air pollutants | cohort study

Significance

To date, no study has investigated the relationships between air pollutants and the progression of COVID-19, nor the potential role of genetic susceptibility on the associations. This large population-based cohort study investigates the associations between air pollutants and genetic susceptibility, both individually and in combination, with the risk of COVID-19-related outcomes. It involves 458,396 participants from UK Biobank and demonstrates that air pollutants interact with host genetic susceptibility in both multiplicative and additive manners, thereby influencing the risk of COVID-19 severity. This study with cutting-edge methods provides robust evidence for the interplay between environmental and genetic factors on COVID-19 outcomes.

Air pollution is a major contributor to the global burden of disease, including cardiovascular diseases (CVDs) and respiratory diseases (1). According to the World Health Organization (WHO) 2019 report (2), over 90% of the global population still lives in environments that do not meet the air quality guidelines set by the WHO. Despite that there is a wealth of literature on the impact of acute and prolonged environmental air pollution exposure on chronic respiratory diseases, evidence regarding the incidence or severity of acute respiratory infections due to long-term air pollution exposure is limited (3–5).

The coronavirus disease in 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mainly presenting as an acute respiratory infection (6). Since its initial documentation in humans in December 2019, the virus has resulted in over 6.8 million deaths globally, making it one of the most lethal viruses in human history (7). The existing literature has identified several risk factors for exacerbation of the condition and mortality among infected patients, such as age, male gender, and chronic comorbidities (8–10). Besides, ambient air pollutants pose a potential risk factor for COVID-19 susceptibility and severity. Evidence suggests that air pollutants can compromise lung defenses against infections and potentially increase the expression of SARS-CoV-2 receptors in the pulmonary system (11–13). A large-scale review study summarizes the evidence of the relationships between exposure to outdoor air pollutants and elevated risk of COVID-19 outcomes but found that the majority of current studies are ecological studies (134/139) (14). The inherent ecological fallacy in these studies will affect the inference of the real relationship between exposure and outcome (15). While some prospective cohort studies have explored the relationships between long-term air pollutants exposure and the risk of COVID-19 hospitalization or mortality, there are some limitations to consider, including a potential exposure misclassification bias, single

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The authors declare no competing interest.

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outcome measures, or inconsistent results (16–19). Additionally, almost all available studies started their research based on participants free of COVID-19 infection, ignoring the effects of air pollutants on COVID-19-infected individuals. Of note, these risk factors alone cannot explain all the variations in individual susceptibility and severity of COVID-19. If the contribution of genetic factors is also taken into account, it may provide biological insights into the pathogenesis of COVID-19 (20). However, to date, no study has investigated the associations between long-term air pollutants exposure, genetic susceptibility, and the risk of COVID-19 events from the perspective of gene–environment interactions.

Therefore, considering the above-mentioned study gaps, the primary objective of our study is to prospectively estimate the associations between long-term air pollutants exposure and COVID-19 events in both COVID-19 naive cohort and COVID-19 infection cohort. Furthermore, utilizing findings from the latest genome-wide association study (GWAS) (21), which identified single nucleotide polymorphisms (SNPs) associated with critical COVID-19, we employed a polygenic risk score (PRS) to map a general picture of the genetic characteristics of COVID-19. Therefore, the second objective of our study is to investigate the combined effect of air pollutant exposure and genetic factors on COVID-19 severity.

Method

Study Design and Population. Participants from the UK Biobank consist of over a half million individuals living in communities across England, Scotland, and Wales, aged between 37 and 73 at baseline recruitment during 2007 to 2010 (22). It contains comprehensive biological and medical data primarily collected using touchscreen questionnaires, interviews, and physical assessments. Follow-up information is obtained through linkage to multiple external electronic health records and COVID-19-related data are specifically provided by Public Health England (PHE), Public Health Scotland, and Secure Anonymized Information Linkage, respectively. All participants provided written informed consent during the recruitment process for the cohort. UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 16/NW/0274). The present analyses were conducted under UK Biobank application number 69741.

Analytical Cohort. From the initial 502480 UK Biobank participants, patients were excluded if they had missing genetic data (n = 15,183), prestudy infection, hospital admission, or death (on 16th March 2020, n = 28,832), and absent air pollution data (n = 69). A total of 458,396 participants were finally included in the subsequent analysis. We then divided the included participants into two cohorts (*SI Appendix*, Fig. S1): the COVID-19 naive cohort (n = 458,396) and the COVID-19 infection cohort (n = 110,216).

Air Pollution Data. The Department for Environment, Food and Rural Affairs (DEFRA) supplies the high-resolution near-surface air pollution data in the UK (https://uk-air.defra.gov.uk). The DEFRA employed an air dispersion model, integrating data from the national atmospheric emissions inventory, secondary inorganic aerosol measurements, and dust resuspension sources to estimate near-surface concentrations of air pollutants. This was further refined by calibrating the estimates with measurement concentrations obtained from background stations within the DEFRA's Automatic Urban and Rural Network. As a result, a gridded dataset of air pollutants with a resolution of 1 × 1 km was generated for the period from 2006 to 2021. To assess the model's reliability, the DEFRA conducted a series of comparisons between the modeled annual average pollutant concentrations and the measured values, revealing a high degree of consistency between the two datasets. More specific information can be found at https://uk-air.defra.gov.uk/data/pcm-data. The air pollution concentration data from DEFRA are widely employed in many published papers (23–25). According to the method employed in a previous study (26), we evaluated individual-level exposure to ambient $PM_{2.5}$, PM_{10}, NO_2, and NO_x for 2019 (the first time COVID-19 was recorded in humans) based on information on residential address and residential mobility provided by the UK Biobank.

Polygenic Risk Score for Severe COVID-19. Relevant details regarding the genotyping process and quality control for participants in the UK Biobank can be found in prior studies (27). We calculated the PRS using SNPs associated with COVID-19 severity, identified in the largest and most recent meta-analysis of GWAS (21). A total of 39 independent SNPs were used to construct COVID-19-related PRS (*SI Appendix*, Table S1). The comprehensive methodology for computing the PRS is detailed in *SI Appendix*, *Supplementary Text* S1. Based on the calculated PRS, participants were categorized into three groups–low, intermediate, and high genetic risk–using tertiles.

Definition of COVID-19-Related Outcomes. The COVID-19 test results data have been updated biweekly since 16 March 2020 and are linked to UK Biobank using a validated algorithm (28). Record details include the date of specimen collection, type of specimen (e.g., nasal, nasopharyngeal, throat, sputum), results of the polymerase chain reaction test, and the processing laboratory. COVID-19 hospital inpatient data obtained from Hospital Episode Statistics data include information on hospital admissions and discharges, admission types, and other details associated with the entire inpatient record. Patients hospitalized due to COVID-19 were identified using ICD-10 code U07.1 and U07.2 for each hospital admission. Similarly, COVID-19 death cases were ascertained through death register data, which provide the date of death and primary and secondary causes of death, based on the same ICD-10 codes.

The initiation date of this study is 16th March 2020, which coincides with the initiation of national-scale administration, processing, and reporting of COVID-19 tests by PHE. We designated 30th September 2022 as the end date of this study.

Covariate Assessment. We included a broad range of covariates as informed by existing literature and expert knowledge (29, 30). These include age (years), sex (men/women), body mass index (BMI, kg/m^2), education (degree level education/non-college education), employment (employment/retirement/unemployment), alcohol consumption status (never-drinking/former or current drinking), tobacco consumption status (never-smoking/former or current smoking), family income (less than £31,000/greater than or equal to £31,000), ethnicity (white Europeans/non-white Europeans), physical activity (never activity/low activity/medium activity/high activity) (26), chronic or oncological morbidities (yes/no), such as hypertension, other CVDs, diabetes, dyslipidemia, chronic obstructive pulmonary disease (COPD), asthma, and lung cancer (*SI Appendix*, Table S2). Participants with missing values for covariates were assigned to a separate category.

Statistical Analysis. Cohort characteristics were presented as mean (SD) for continuous variables and frequency (percentage, %) for categorical variables. This analysis was conducted separately in two stages and among different cohorts (see *SI Appendix*, Fig. S1 for more details). In stage I, we analyzed all included participants by starting follow-up from the beginning of the pandemic (16th March 2020) when all people were free of COVID-19 infection. We used a multivariable-adjusted Cox proportional hazards model to assess associations of air pollutants exposure (both in continuous and categorical forms) with the risk of COVID-19 infectious, hospital admission, and death. Covariates mentioned in the Covariate assessment section were incorporated into model. Dose–response relationships between exposure to air pollutants and COVID-19-related outcomes were explored using the restricted cubic splines (RCS) model. For genetic susceptibility analyses, the population was limited to individuals of European ancestry, with further adjustment for the first 10 genetic principal components and the genotyping batch in the model. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

The interaction between genetic susceptibility and air pollution exposure on COVID-19 hospital admission and death risk was analyzed on multiplicative and additive scale. A multiplicative term was included and the *P* for interaction was estimated using Cox proportional hazards model. We also calculated the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) to examine additive interactions, with 95% CIs derived using the Bootstrap method (31). The formulas of additive interaction were as follows:

$$\mathrm{RERI} = \mathrm{HR}_{11} - \mathrm{HR}_{10} - \mathrm{HR}_{01} + 1,$$

$$\mathrm{AP} = \mathrm{RERI} / \mathrm{HR}_{11},$$

HR_{11} refers to individual exposed to both air pollution and genetic risk; HR_{10} denotes individuals exposed to air pollution with low genetic risk; and HR_{01} indicates individuals exposed to genetic risk with low air pollution exposure (Q1).

Moreover, we investigated the joint associations of long-term exposure to air pollutants and host genetic susceptibility on COVID-19 hospital admission and death. In stage II, analyses were limited to COVID-19-infected participants and replicated using the same methods as in stage I.

Several sensitivity analyses were conducted to test the robustness of our primary findings. First, to ensure the balance of potential confounding effects across exposure groups and to enable causal inference, this study employed the marginal structural Cox model (MSCM) and instrumental variable (IV) analysis. MSCM was employed to construct a weighted pseudopopulation, simulating a randomized controlled trial, in which confounding factors were balanced across exposure groups, thereby ensuring that the effect estimates reflected a causal relationship (32, 33). In brief, stable inverse probability weighting is employed to assign weights to study participants, thereby constructing a weighted pseudopopulation that ensures the balance of potential confounding effects across exposure groups (34–36). The fundamental principle of IV analysis lies in the use of an IV that is related to the exposure of interest but not directly associated with the outcome (37). This approach allows for a more precise estimation of the causal relationship between the exposure and the outcome. This study built upon prior relevant literature to select wind speed as an instrumental variable and employs it to fit the model (38–40). Second, we examine persistence of associations at low air pollutant exposure levels by restricting to participants exposed to low levels of $PM_{2.5}$ (<10 $\mu g/m^3$), PM_{10} (<20 $\mu g/m^3$), NO_2 (<40 $\mu g/m^3$), and NO_x (<40 median) according to the WHO air quality guideline. Third, we excluded participants with chronic comorbidities mentioned in Table 1. Fourth, we used multiple imputation to deal with missing covariates and conducted analyses using the imputed dataset. Finally, we accounted for the population density of the home area in the regression model. Analyses were performed by R (version: 4.2.1) and Plink (version: 1.90).

Results

Our study encompassed a total of 458,396 participants who were alive at the commencement of this study (the COVID-19 naive cohort, Table 1). During a median follow-up of 2.07 y, there were 110,216 laboratory-confirmed cases of COVID-19 infection. At subsequent follow-up, there were 6,499 hospital admission and 1,135 deaths. All included participants in the COVID-19 naive cohort had an average age of 69.32 (8.12) y. Women constituted a larger proportion (55.10%) of the participants compared to men, and the study population was primarily of white Europeans (94.13%). In the COVID-19 infection cohort, there were 5,972 hospital admission and 1,135 deaths. The baseline characteristics of participants in the COVID-19 infection cohort are presented in *SI Appendix*, Table S3. *SI Appendix*, Fig. S2 and Table S4 exhibit the distribution and Pearson's correlation of air pollutants exposure concentrations. The mean (SD) concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x were 8.85 (1.72) $\mu g/m^3$, 13.77 (2.50) $\mu g/m^3$, 14.51 (5.43) $\mu g/m^3$, and 20.74 (9.77) $\mu g/m^3$, individually.

There were positive associations between long-term exposure to air pollutants and COVID-19-related outcomes in the COVID-19 naive cohort (Table 2). For each interquartile range (IQR) increase in air pollutants exposure concentration, the HRs (95% CIs) of COVID-19 infection were 1.04 (1.03, 1.05) for $PM_{2.5}$, 1.04 (1.03, 1.05) for PM_{10}, 1.03 (1.02, 1.04) for NO_2, and 1.02 (1.02, 1.03) for NO_x, respectively. In the COVID-19 infection cohort, we also observed positive associations between all air pollutants exposure and the risk of COVID-19 severity ($P < 0.001$). The HRs (95% CIs) of COVID-19 hospital admission and death, for per IQR increase, were 1.23 (1.19, 1.27) and 1.28 (1.18, 1.39) for $PM_{2.5}$, 1.22 (1.17, 1.26) and 1.25 (1.16, 1.36) for PM_{10}, 1.15 (1.12, 1.19) and 1.18 (1.10, 1.26) for NO_2, and 1.13 (1.10, 1.16) and 1.14 (1.08, 1.21) for NO_x, respectively. Similar associations were also identified when we fitted models using categorical air pollutant exposure. Fig. 1 clearly illustrates that the participants in high-exposure groups have larger HRs of COVID-19-related outcomes compared to those in low-exposure groups (P for trend < 0.001). As well, the dose–response relationship curves showed a similar trend (*SI Appendix*, Figs. S3–S7). The risk of COVID-19-related outcomes showed a rapidly increasing trend at lower concentrations of air pollutants, while at higher concentrations, the increase in risk tended to slightly level off.

In Table 3, we found that PRS (per IQR increase) was associated with the risk of COVID-19 hospital admission [1.25 (1.21, 1.29)] and death [1.42 (1.32, 1.54)]. When exploring the interactions of genetic susceptibility and air pollutants exposure with the risk of COVID-19 hospital admission and death in the COVID-19 naive cohort (*SI Appendix*, Table S5 and Table 4), we identified only significant multiplicative interactions between particulate matter and genetic susceptibility in relation to COVID-19 death ($P = 0.006$ for $PM_{2.5}$ and $P = 0.003$ for PM_{10}). As shown in Table 4, for additive interactions, the RERIs and APs were 1.31 (0.77, 1.87) and 57% (37%, 77%) for $PM_{2.5}$ in the fourth quantile and 1.11 (0.60, 1.59) and 55% (32%, 76%) for PM_{10} in the fourth quantile. The effect estimates in *SI Appendix*, Table S5 were smaller, with the RERIs and APs of 0.41 (0.16, 0.66) and 19% (7%, 30%) for $PM_{2.5}$ in the fourth quantile and 0.39 (0.13, 0.64) and 18% (6%, 29%) for PM_{10} in the fourth quantile. When analyses were restricted in the COVID-19 infection cohort (Table 5 and *SI Appendix*, Table S6), significant multiplicative and additive interactions between air pollutants exposure and genetic risk were observed for the risk of COVID-19 death, but not for the risk of COVID-19 hospital admission. In Table 5, the RERIs and APs were 1.06 (0.57, 1.56) and 52% (29%, 73%) for $PM_{2.5}$ in the fourth quantile, 0.96 (0.46, 1.46) and 50% (25%, 73%) for PM_{10} in the fourth quantile, 0.59 (0.03, 1.11) and 28% (2%, 52%) for NO_2 in the fourth quantile, and 0.62 (0.05, 1.15) and 29% (3%, 53%) for NO_x in the fourth quantile, respectively. For the joint associations of long-term air pollutants exposure and host genetic susceptibility with the risk of COVID-19-related outcomes, we found that participants with both the high genetic risk and high level of air pollutants exposure (fourth quantile) had the highest risk of COVID-19 events (*SI Appendix*, Figs. S8–S11).

In sensitivity analyses, there was no substantial change in the relationships between chronic exposure to air pollutants and the risk of COVID-19-related outcomes when conducting analyses within the causal framework (*SI Appendix*, Tables S7 and S8), or excluding participants with exposure levels to air pollutants higher than the WHO air quality guideline limits (*SI Appendix*, Table S9), or excluding participants with chronic comorbidities (*SI Appendix*, Table S10). In addition, our findings remain unchanged when conducting analyses with the imputed dataset (*SI Appendix*, Table S11) or further adjusting home area population density in the regression model (*SI Appendix*, Table S12).

Discussion

This study examines both the individual and combined contributions of air pollutants and genetic factors on progression of COVID-19 in the COVID-19 naive cohort and the COVID-19-infected cohort. Our findings reveal that both long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, and NO_x and host polygenic variations may independently be associated with the risk of COVID-19-related hospital admission and death. Furthermore, the study reveals that interactions between air pollutants and genetic factors play a role in the development of severe COVID-19 events.

Table 1. Baseline characteristics of participants in the COVID-19 naive cohort

Baseline characteristics	Total participants (n = 458,396)	Participants with low $PM_{2.5}$ exposure (n = 348,044)	Participants with high $PM_{2.5}$ exposure (n = 110,352)	Standardized mean difference
Age (years)	69.32 (8.12)	69.61 (8.05)	68.41 (8.27)	0.147
Sex (%)				0.002
Men	205,827 (44.90)	156,359 (44.93)	49,468 (44.83)	
Women	252,569 (55.10)	191,685 (55.07)	60,884 (55.17)	
Ethnicity (%)				0.441
White Europeans	431,511 (94.13)	337,964 (97.10)	93,547 (84.77)	
Non-white Europeans	24,755 (5.40)	9,007 (2.59)	15,748 (14.27)	
Missing	2,130 (0.46)	1,073 (0.31)	1,057 (0.96)	
BMI categories (%)				0.057
<25	152,561 (33.28)	113,568 (32.63)	38,993 (35.34)	
25 to 30	196,422 (42.85)	150,615 (43.27)	45,807 (41.51)	
>30	109,413 (23.87)	83,861 (24.09)	25,552 (23.15)	
Employment (%)				0.145
Employment	269,558 (58.80)	203,257 (58.40)	66,301 (60.08)	
Retirement	146,441 (31.95)	115,285 (33.12)	31,156 (28.23)	
Unemployment	37,490 (8.18)	26,561 (7.63)	10,929 (9.90)	
Missing	4,907 (1.07)	2,941 (0.85)	1,966 (1.78)	
Education (%)				0.138
Degree level education	174,363 (38.04)	126,757 (36.42)	47,606 (43.14)	
non-College education	203,854 (44.47)	159,189 (45.74)	44,665 (40.48)	
Missing	80,179 (17.49)	62,098 (17.84)	18,081 (16.38)	
Alcohol consumption status (%)				0.150
Never drinking	20,096 (4.38)	12,901 (3.71)	7,195 (6.52)	
Current or former drinking	437,174 (95.37)	334,670 (96.16)	102,504 (92.89)	
Missing	1,126 (0.25)	473 (0.14)	653 (0.59)	
Tobacco consumption status (%)				0.068
Never smoking	254,428 (55.50)	194,539 (55.89)	59,889 (54.27)	
Current or former smoking	201,716 (44.00)	152,205 (43.73)	49,511 (44.87)	
Missing	2,252 (0.49)	1,300 (0.37)	952 (0.86)	
Physical activity (%)				0.107
Never	28,251 (6.16)	20,093 (5.77)	8,158 (7.39)	
Low activity	30,211 (6.59)	22,763 (6.54)	7,448 (6.75)	
Medium activity	336,764 (73.47)	259,086 (74.44)	77,678 (70.39)	
High activity	60,406 (13.18)	44,379 (12.75)	16,027 (14.52)	
Missing	2,764 (0.60)	1,723 (0.50)	1,041 (0.94)	
Income (%)				0.070
<£31,000	184,173 (40.18)	142,491 (40.94)	41,682 (37.77)	
≥£31,000	208,067 (45.39)	156,687 (45.02)	51,380 (46.56)	
Missing	66,156 (14.43)	48,866 (14.04)	17,290 (15.67)	
Hypertension (%)	131,656 (28.72)	101,374 (29.13)	30,282 (27.44)	0.037
Other CVDs (%)	81,340 (17.74)	63,359 (18.20)	17,981 (16.29)	0.051
Diabetes (%)	33,729 (7.36)	24,986 (7.18)	8,743 (7.92)	0.028
Dyslipidemia (%)	101,476 (22.14)	75,984 (21.83)	25,492 (23.10)	0.030
COPD (%)	16,981 (3.70)	13,216 (3.80)	3,765 (3.41)	0.021
Asthma (%)	64,287 (14.02)	48,945 (14.06)	15,342 (13.90)	0.005
Lung cancer (%)	1,128 (0.25)	848 (0.24)	280 (0.25)	0.002

Standardized mean difference <0.1 indicates that there is a good balance in the distribution of characteristics between the low- and high-exposure groups. Abbreviations: BMI, body mass index; CVDs, cardiovascular diseases; COPD, chronic obstructive pulmonary disease.

Table 2. Associations between air pollutants exposure (continuous variables) and the risk of COVID-19-related outcomes

Cohort	Air pollutants (per IQR increase)	COVID-19 infection		COVID-19 hospital admission		COVID-19 death	
		HRs (95% CIs)	*P* values	HRs (95% CIs)	*P* values	HRs (95% CIs)	*P* values
COVID-19 naive cohort (n = 458,396)	$PM_{2.5}$	1.04 (1.03, 1.05)	<0.001	1.27 (1.23, 1.31)	<0.001	1.31 (1.21, 1.42)	<0.001
	PM_{10}	1.04 (1.03, 1.05)	<0.001	1.26 (1.21, 1.30)	<0.001	1.28 (1.18, 1.39)	<0.001
	NO_2	1.03 (1.02, 1.04)	<0.001	1.16 (1.12, 1.19)	<0.001	1.19 (1.11, 1.27)	<0.001
	NO_x	1.02 (1.02, 1.03)	<0.001	1.13 (1.10, 1.16)	<0.001	1.14 (1.08, 1.21)	<0.001
COVID-19 infection cohort (n = 110,216)	$PM_{2.5}$	–	–	1.23 (1.19, 1.27)	<0.001	1.28 (1.18, 1.39)	<0.001
	PM_{10}	–	–	1.22 (1.17, 1.26)	<0.001	1.25 (1.16, 1.36)	<0.001
	NO_2	–	–	1.15 (1.12, 1.19)	<0.001	1.18 (1.10, 1.26)	<0.001
	NO_x	–	–	1.13 (1.10, 1.16)	<0.001	1.14 (1.08, 1.21)	<0.001

IQR of $PM_{2.5}$, PM_{10}, NO_2, and NO_x in the COVID-19 naive cohort was 2.28 μg/m^3, 3.34 μg/m^3, 6.28 μg/m^3, and 9.95 μg/m^3, respectively. IQR of $PM_{2.5}$, PM_{10}, NO_2, and NO_x in the COVID-19 infection cohort was 2.20 μg/m^3, 3.16 μg/m^3, 6.21 μg/m^3, and 9.90 μg/m^3, respectively. Cox regression models adjusted for age, sex, ethnicity, income, education, employment, alcohol consumption status, tobacco consumption status, physical activity, BMI, hypertension, other CVDs, diabetes, dyslipidemia, COPD, asthma, and lung cancer. Abbreviations: IQR, interquartile range; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; Q, quartile; BMI, body mass index; CVDs, cardiovascular diseases; COPD, chronic obstructive pulmonary disease.

Infected participants with the high genetic risk and high levels of air pollutants had a 97% ($PM_{2.5}$), 90% (PM_{10}), 86% (NO_2), and 90% (NO_x) higher risk of COVID-19 hospital admission, and a 104% ($PM_{2.5}$), 91% (PM_{10}), 108% (NO_2), and 114% (NO_x) higher risk of death from COVID-19, compared to those with low risks in both factors.

Consistent with recent epidemiological research, our study found that long-term air pollutant exposure was associated with

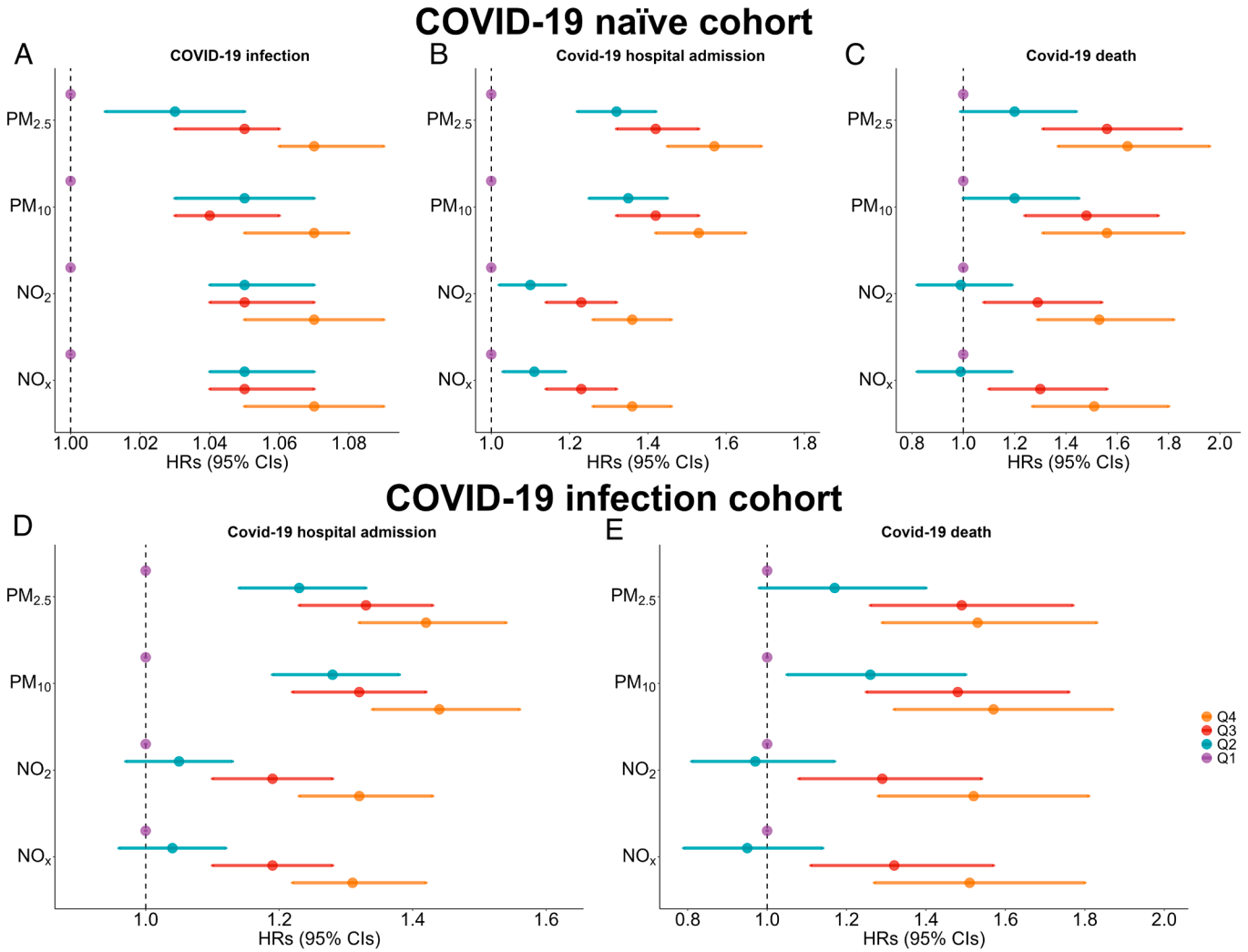

Fig. 1. Associations between air pollutants exposure (categorical variables) and the risk of COVID-19-related outcomes in the COVID-19 naive cohort (*A*–*C*) and the COVID-19 infection cohort (*D* and *E*). Cox regression models adjusted for age, sex, ethnicity, income, education, employment, alcohol consumption status, tobacco consumption status, physical activity, BMI, hypertension, other CVDs, diabetes, dyslipidemia, COPD, asthma, and lung cancer. Abbreviations: IQR, interquartile range; $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; Q, quartile; BMI, body mass index; CVDs, cardiovascular diseases; COPD, chronic obstructive pulmonary disease.

Table 3. Associations of polygenic risk score with the risk of COVID-19 hospital admission and death in the COVID-19 infection cohort

PRS	HRs (95% CIs)	*P* values	*P* for trend
COVID-19 hospital admission			
Categorical format			
Low genetic risk	Ref.	–	
Intermediate genetic risk	**1.20 (1.12, 1.28)**	**<0.001**	**<0.001**
High genetic risk	**1.46 (1.37, 1.56)**	**<0.001**	
Continuous format			
PRS, per IQR* increase	**1.25 (1.21, 1.29)**	**<0.001**	–
COVID-19 death			
Categorical format			
Low genetic risk	Ref.	–	
Intermediate genetic risk	**1.27 (1.08, 1.49)**	**0.004**	**<0.001**
High genetic risk	**1.75 (1.50, 2.04)**	**<0.001**	
Continuous format			
PRS, per IQR* increase	**1.42 (1.32, 1.54)**	**<0.001**	–

P values, HRs and 95% CIs in bold represent significance at $P < 0.05$. Cox regression models adjusted for age, sex, ethnicity, income, education, employment, alcohol consumption status, tobacco consumption status, physical activity, BMI, hypertension, other CVDs, diabetes, dyslipidemia, COPD, asthma, lung cancer, genotyping batch, and the first 10 genetic principal components. Abbreviations: $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; BMI, body mass index; CVDs, cardiovascular diseases; COPD, chronic obstructive pulmonary disease; PRS, polygenic risk score.
*IQR of PRS was 13.51.

the risk of COVID-19-related events in individuals who are naive to COVID-19. For instance, cohort studies from Switzerland (n = 28,540), UK (n = 313,657), California (n = 50,010), Catalonia (n = 4,660,502), and Danish (n = 3,721,813) found a significant association between $PM_{2.5}$, PM_{10}, and NO_2 with COVID-19 case severity (29, 41–44). Similarly, the latest review, chronic exposure to $PM_{2.5}$ and NO_2 was reported to be associated with elevated risk of COVID-19 mortality, with relative risks of 1.71 (1.40, 1.28) and 1.33 (1.07, 1.65), respectively (45). In addition, our study uniquely highlights that air pollutants exposure may increase the risk of COVID-19 hospital admission and death among those already infected. This finding suggests that long-term exposure to air pollutants is associated with both increased susceptibility to the disease in infected individuals and a faster progression in those individuals.

The findings of this study are biologically plausible, as studies conducted in multiple countries, including the United States, Poland, and China, have indicated that exposure to air pollution increases the risk of influenza incidence and hospitalization (relative risks range from 1.02 to 1.21) (46–48). Moreover, previous research has identified that ambient air pollution can trigger the dynamics of air pollution-to-human transmission mechanisms for viral infectivity, thereby affecting the incidence of infectious diseases (49). Our findings reinforce previous laboratory insights into potential mechanisms. Air pollutants exposure may impair host defense against SARS-CoV-2 through pulmonary barrier tissues and the mucociliary clearance process, weakening its ability to prevent invasion (5, 50). Moreover, exposure to particulate matters may enhance the expression of proteins, such as angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine type 2 (TMPRSS2), which are necessary for the entry of SARS-CoV-2 into host cells (13, 51). This upregulation could result in a higher viral load, thereby increasing host susceptibility to COVID-19 infection and severity (52). From the perspective of clinical mechanisms, air pollutant exposure has the potential to increase the risk of COVID-19 mortality by elevating the upstream risk of serious comorbidities (i.e., COPD, hypertension, as well as diabetes) following infection (11, 53, 54).

Of note, incorporating genetic factors in assessing the effects of air pollutant could offer insights into the pathogenesis of COVID-19. The results of the interactions between air pollutants and genetic susceptibility suggest that there is a complex interplay between environmental and host factor involved in the onset and progression of COVID-19-related outcomes. For instance, variations in *TMPRSS2*, *ACE2*, and *IFNAR2* genes have been linked to inflammation (55, 56), whereas SNPs in *JAK1* and *MUC5B* have been associated with oxidative stress (57, 58). Both are proven pathological pathways underlying air pollution–induced respiratory diseases (59, 60). Our findings also have important practical implications, including mask-wearing and limiting outdoor activities during periods of high pollution.

One major strength of this study is that it conducts an analysis specifically among the infected cohort to uncover the role of

Table 4. Additive and multiplicative interactions between air pollutants and polygenic risk score on the risk of COVID-19 death in the COVID-19 naive cohort

	RERIs (95% CIs)	APs (95% CIs)	*P* for interaction
$PM_{2.5}$			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
$PM_{2.5}$-Q1	Ref.	Ref.	
$PM_{2.5}$-Q2	−0.07 (−0.61, 0.46)	−0.06 (−0.57, 0.44)	
$PM_{2.5}$-Q3	0.11 (−0.44, 0.66)	0.07 (−0.29, 0.44)	
$PM_{2.5}$-Q4	0.15 (−0.41, 0.70)	0.11 (−0.30, 0.51)	**0.006**
High genetic risk			
$PM_{2.5}$-Q1	Ref.	Ref.	
$PM_{2.5}$-Q2	**0.82 (0.36, 1.30)**	**0.49 (0.22, 0.75)**	
$PM_{2.5}$-Q3	**0.90 (0.40, 1.39)**	**0.44 (0.20, 0.68)**	
$PM_{2.5}$-Q4	**1.31 (0.77, 1.87)**	**0.57 (0.37, 0.77)**	

Table 4. (Continued)

	RERIs (95% CIs)	APs (95% CIs)	*P* for interaction
PM_{10}			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
PM_{10}-Q1	Ref.	Ref.	
PM_{10}-Q2	0.01 (−0.51, 0.52)	0.01 (−0.48, 0.50)	
PM_{10}-Q3	0.17 (−0.33, 0.68)	0.13 (−0.25, 0.52)	
PM_{10}-Q4	0.16 (−0.38, 0.69)	0.12 (−0.28, 0.51)	**0.003**
High genetic risk			
$PM_{2.5}$-Q1	Ref.	Ref.	
PM_{10}-Q2	**0.84 (0.37, 1.31)**	**0.53 (0.24, 0.80)**	
PM_{10}-Q3	**1.17 (0.70, 1.64)**	**0.57 (0.36, 0.79)**	
PM_{10}-Q4	**1.11 (0.60, 1.59)**	**0.55 (0.32, 0.76)**	
NO_2			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
NO_2-Q1	Ref.	Ref.	
NO_2-Q2	0.09 (−0.44, 0.63)	0.08 (−0.38, 0.56)	0.434
NO_2-Q3	−0.05 (−0.65, 0.54)	−0.04 (−0.48, 0.40)	
NO_2-Q4	0.28 (−0.30, 0.86)	0.16 (−0.16, 0.49)	
High genetic risk			
NO_2-Q1	Ref.	Ref.	
NO_2-Q2	**0.59 (0.07, 1.12)**	**0.35 (0.04, 0.66)**	
NO_2-Q3	**0.58 (0.01, 1.15)**	**0.29 (0.01, 0.57)**	
NO_2-Q4	**0.88 (0.28, 1.47)**	**0.36 (0.13, 0.60)**	
NO_x			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
NO_x-Q1	Ref.	Ref.	
NO_x-Q2	0.12 (−0.40, 0.67)	0.10 (−0.34, 0.57)	
NO_x-Q3	−0.06 (−0.66, 0.52)	−0.05 (−0.50, 0.40)	
NO_x-Q4	0.27 (−0.32, 0.85)	0.15 (−0.17, 0.48)	0.431
High genetic risk			
NO_x-Q1	Ref.	Ref.	
NO_x-Q2	**0.60 (0.07, 1.13)**	**0.35 (0.05, 0.66)**	
NO_x-Q3	**0.60 (0.03, 1.17)**	**0.30 (0.02, 0.58)**	
NO_x-Q4	**0.86 (0.26, 1.47)**	**0.36 (0.12, 0.59)**	

P values, RERIs, Aps, and 95% CIs in bold represent significance at $P < 0.05$. If the CIs of RERI and AP include 0, it suggests that there is no additive interaction. The low air pollutants exposure (Q1, Ref.) and the low genetic risk groups (Ref.) were used to calculate the interaction results for other categories. Cox regression models adjusted for age, sex, ethnicity, income, education, employment, alcohol consumption status, tobacco consumption status, physical activity, BMI, hypertension, other CVDs, diabetes, dyslipidemia, COPD, asthma, lung cancer, genotyping batch, and the first 10 genetic principal components. Abbreviations: $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; BMI, body mass index; CVDs, cardiovascular diseases; COPD, chronic obstructive pulmonary disease; PRS, polygenic risk score.

exposure to air pollution in relation to COVID-19 progression and susceptibility. This is an important clinical question that is unclear and understudied in previous research. Additionally, this study explores the relationship between air pollution exposure and the risk of COVID-19-related events in the context of gene–environment interactions. Unlike previous studies (19, 61), we accounted for changes in participants' residential addresses in the modeling, thereby reducing potential misclassification bias in exposure estimation. However, there are limitations: First, this study is observational in nature, and findings should be not necessarily interpreted as causal. Second, despite considering various covariates, residual confounding remains a potential issue in this study. Future studies should leverage natural experiments or quasiexperimental designs, which allow for a clearer isolation of air pollution changes from other socioeconomic variables. Also, the UK Biobank is limited to the representation of ethnic minority populations, as most participants are of Caucasian descent.

Conclusion

Long-term exposure to air pollutants is significantly associated with an increased risk of COVID-19 incidence or severity. Importantly, genetic susceptibility may interact with air pollution exposure, playing a crucial role in the progression and exacerbation of COVID-19.

Table 5. Additive and multiplicative interactions between air pollutants and polygenic risk score on the risk of COVID-19 death in the COVID-19 infection cohort

	RERIs (95% CIs)	APs (95% CIs)	*P* for interaction
$PM_{2.5}$			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
$PM_{2.5}$-Q1	Ref.	Ref.	
$PM_{2.5}$-Q2	0.08 (−0.40, 0.51)	0.08 (−0.38, 0.50)	
$PM_{2.5}$-Q3	0.05 (−0.51, 0.54)	0.04 (−0.39, 0.42)	
$PM_{2.5}$-Q4	0.17 (−0.36, 0.62)	0.13 (−0.28, 0.48)	**0.014**
High genetic risk			
$PM_{2.5}$-Q1	Ref.	Ref.	
$PM_{2.5}$-Q2	**0.84 (0.35, 1.32)**	**0.51 (0.23, 0.77)**	
$PM_{2.5}$-Q3	**0.80 (0.29, 1.29)**	**0.43 (0.16, 0.66)**	
$PM_{2.5}$-Q4	**1.06 (0.57, 1.56)**	**0.52 (0.29, 0.73)**	
PM_{10}			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
PM_{10}-Q1	Ref.	Ref.	
PM_{10}-Q2	0.15 (−0.35, 0.60)	0.14 (−0.32, 0.56)	
PM_{10}-Q3	0.10 (−0.43, 0.57)	0.08 (−0.33, 0.45)	
PM_{10}-Q4	0.16 (−0.37, 0.62)	0.13 (−0.29, 0.49)	**0.010**
High genetic risk			
PM_{10}-Q1	Ref.	Ref.	
PM_{10}-Q2	**0.93 (0.46, 1.40)**	**0.55 (0.28, 0.79)**	
PM_{10}-Q3	**0.95 (0.42, 1.44)**	**0.49 (0.23, 0.71)**	
PM_{10}-Q4	**0.96 (0.46, 1.46)**	**0.50 (0.25, 0.73)**	
NO_2			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
NO_2-Q1	Ref.	Ref.	
NO_2-Q2	0.16 (−0.34, 0.63)	0.16 (−0.34, 0.64)	0.533
NO_2-Q3	−0.03 (−0.57, 0.46)	−0.02 (−0.47, 0.38)	
NO_2-Q4	0.17 (−0.39, 0.68)	0.11 (−0.26, 0.45)	
High genetic risk			
NO_2-Q1	Ref.	Ref.	
NO_2-Q2	0.47 (−0.03, 0.94)	0.32 (−0.02, 0.64)	
NO_2-Q3	0.48 (−0.08, 1.01)	0.26 (−0.03, 0.53)	
NO_2-Q4	**0.59 (0.03, 1.11)**	**0.28 (0.02, 0.52)**	
NO_x			
Low genetic risk	Ref.	Ref.	–
Intermediate genetic risk			
NO_x-Q1	Ref.	Ref.	
NO_x-Q2	0.14 (−0.37, 0.62)	0.14 (−0.37, 0.61)	
NO_x-Q3	−0.03 (−0.58, 0.46)	−0.03 (−0.48, 0.38)	
NO_x-Q4	0.22 (−0.34, 0.74)	0.14 (−0.21, 0.46)	0.541
High genetic risk			
NO_x-Q1	Ref.	Ref.	
NO_x-Q2	0.45 (−0.06, 0.93)	0.31 (−0.04, 0.63)	
NO_x-Q3	0.54 (−0.03, 1.08)	0.28 (−0.01, 0.54)	
NO_x-Q4	**0.62 (0.05, 1.15)**	**0.29 (0.03, 0.53)**	

P values, RERIs, Aps, and 95% CIs in bold represent significance at $P < 0.05$. If the CIs of RERI and AP include 0, it suggests that there is no additive interaction. The low air pollutants exposure (Q1, Ref.) and the low genetic risk groups (Ref.) were used to calculate the interaction results for other categories. Cox regression models adjusted for age, sex, ethnicity, income, education, employment, alcohol consumption status, tobacco consumption status, physical activity, BMI, hypertension, other CVDs, diabetes, dyslipidemia, COPD, asthma, lung cancer, genotyping batch, and the first 10 genetic principal components. Abbreviations: $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; BMI, body mass index; CVDs, cardiovascular diseases; COPD, chronic obstructive pulmonary disease; PRS, polygenic risk score.

These findings are expected to provide important evidence for future research on the interplay of genetics and air pollution on the onset and progression of acute respiratory infections.

Ethical Approval. UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 16/NW/0274). All participants provided informed consent to participate. The present analyses were conducted under UK Biobank application number 69741.

Data, Materials, and Software Availability. Open access data have been deposited in UK Biobank (22).

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