Air pollution and risk of chronic obstructed pulmonary disease: The modifying effect of genetic susceptibility and lifestyle

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Summary

Background The effect of long-term exposure to air pollution on the development of chronic obstructive pulmonary disease (COPD) is still controversial, and the role of the interactions of air pollution with genetic risk and lifestyle in COPD risk is unclear.

Methods We included 452762 participants derived from the UK Biobank. Annual concentrations of air pollutions, including particle matter ($PM_{2.5}$, PM_{10}), nitrogen oxides (NO_x), and nitrogen dioxide (NO_2), were assessed using land-use regression model. We applied Cox proportional hazard model to evaluate the associations between air pollution and COPD risk. In addition, we constructed a polygenic risk score and a lifestyle score, and assessed whether genetic susceptibility and lifestyle modified the effect of air pollution on the COPD risk.

Findings Each interquartile range (IQR) increase in annual concentrations of $PM_{2.5}$, PM_{10}, NO_x, and NO_2 was associated with 1.17 (95% CI: 1.15,1.19), 1.05 (95% CI: 1.03,1.06), 1.13 (95% CI: 1.11,1.14), and 1.19 (95% CI: 1.16,1.21) times the risk of COPD, respectively. We observed an additive interaction between $PM_{2.5}$ and genetic risk (*P*-interact=0.095), and a negative interaction between $PM_{2.5}$ and lifestyle (*P*-interact=0.062). The HRs for each IQR increase in $PM_{2.5}$ were 1.21, (95% CI: 1.16-1.25) and 1.24, (95% CI: 1.21-1.26) in individuals with healthy and unfavourable lifestyle, respectively; and 1.16, (95% CI: 1.13-1.19) and 1.19, (95% CI: 1.16-1.22) in those with low genetic risk and high genetic risk, respectively. Participants with high air pollution exposure, high genetic risk and unfavourable lifestyle showed the highest risk of COPD.

Interpretation Long-term exposure to air pollution was associated with increased risk of COPD, especially in those with high genetic risk and unfavourable lifestyle.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, leading to over 3 million deaths every year.[1] COPD is characterized by persistent respiratory symptoms and progressive airflow obstruction, and environmental exposures to harmful gases and particles are important risk factors for development of COPD.[2] Because of the anatomic position

Research in Context

Evidence before this study

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Air pollution exposure is considered an important risk factor for COPD, and genetic susceptibility and lifestyle are also involved in development of COPD. We searched PubMed and Google Scholar for related studies until September 30, 2021. We used keywords: ("air pollution" OR "air pollutants" OR "particulate matter" OR "PM$_{2.5}$" OR "PM$_{10}$" OR "nitrogen oxides" OR "nitrogen dioxide" OR "NO$_x$" OR "NO$_2$") AND ("chronic obstructive pulmonary disease" OR "COPD") for studies that evaluated the associations between air pollution exposure and COPD risk. We additionally added keywords: ("genetic" OR "gene") OR ("lifestyle" OR "smoking" OR "smoke" OR "cigarette" OR "dinking" OR "drink" OR "alcohol" OR "diet" OR "physical activity") for studies on the modification effects of genetic risk and lifestyle on these associations. Although several studies have explored the association between long-term air pollution exposure and COPD risk, the existent evidence is still controversial. To date, whether genetic susceptibility and lifestyle could modify the impact of air pollution exposure on COPD risk is still unclear.

Added value of this study

To our knowledge, this is the first nationwide cohort study to evaluate the modification effects of genetic risk and overall lifestyle on the associations between air pollution and COPD risk. Our study showed that long-term exposures to particle matter with diameters ≤2.5 µm (PM$_{2.5}$), ≤10 µm (PM$_{10}$), and nitrogen oxides (NOx,) and nitrogen dioxide (NO$_2$) were positively associated with risk of COPD. We observed significant interactions of PM$_{2.5}$ exposure with genetic risk and lifestyle. The adverse effects of PM$_{2.5}$ were stronger in individuals with high genetic risk and unfavourable lifestyle. We also provided quantitative data about the effects of the interactions of high air pollution exposure with high genetic risk and healthy lifestyle. Participants with high air pollution exposure, high genetic risk, and unfavourable lifestyle showed the highest risk of COPD.

Implications of all the available evidence

Our study adds to the small but emerging evidence base indicating that long-term exposure to air pollution is associated with increased risk of COPD. In addition, we also provide evidence on the modification effects of genetic susceptibility and lifestyle on the association between air pollution exposure and COPD risk. Our findings indicated that the reduction in air pollution levels and improvement in lifestyle might be effective interventions in reducing the risk of COPD, especially in those with high genetic risk.

and the respiratory functions, the respiratory system is continuously in contact with harmful air pollution in the atmosphere, and is the main target of their toxic effect. Some previous studies have demonstrated the adverse effects of air pollution, especially particle matter (PM) and nitrogen oxides (NO$_x$), on COPD risk,[3,4] and the function of air pollution in the elicitation of inflammatory injury and oxidative damage played important roles in these associations.[5] However, the role of air pollution in the development of COPD based on results of extant studies is still controversial.[6,7]

In addition, individual factors including genetics and lifestyle were also deeply involved in the pathogenesis of COPD.[8,9] It is likely that COPD not only results from multiple genetic factors but also their interactions with a number of environmental agents.[10] The genome-wide association studies (GWASs) have successfully identified genetic loci associated with COPD,[11] and the interactions between genetics and tobacco use were also demonstrated in a few studies.[12] Moreover, a set of common, modifiable lifestyle factors, including smoking, drinking alcohol, unhealthy diet, and physical inactivity, were thought to underlie noncommunicable diseases, which were integrated in the operational policies, strategies or action plans in most countries.[9] Evidence from previous studies suggested that these four lifestyle behaviours were significantly associated with the risk of COPD.[13–15] However, no study has evaluated the interactions of air pollution exposure with genetic susceptibility and overall lifestyle on COPD risk, which may advance some reasonable proposals to the targeted intervention in development of COPD.

The present study was derived from UK Biobank, a nation-wide population-based prospective study. We aimed to assess the associations between air pollution exposure and risk of COPD. Moreover, we further explored whether genetic susceptibility and lifestyle could modify the impact of air pollution exposure on COPD risk.

Methods

Study population

This study was derived from the UK Biobank, which is an ongoing population-based prospective cohort study.[16] The UK Biobank enrolled approximately 0.5 million participants (aged from 37 to 73 years old) across the UK at baseline during 2006 to 2010, and collected extensive phenotype and genotypic details, including information obtained from questionnaire, physical measurements, sample assays, genome-wide genotyping, and longitudinal follow-up for a wide range of health-related outcomes.[16] More details of study protocol of UK Biobank have been described before.[16]

In the present study, we excluded participants without available data about air pollutants exposure (n=41303), and those had history of COPD (self-reported COPD diagnosed by doctor) or developed COPD before December 31 in 2010 (identified from hospital inpatient records based on ICD-10 codes) (n=9359). There were 452762 participants finally included in our analysis. To explore the joint effect of air pollution and genetic risk on COPD, 396593 participants with available data on genome-wide genotyping were included for gene-related analyses.

Air pollution

The annual concentrations of air pollutants were assessed using land use regression (LUR)-based model, including particle matter with diameter < 2.5μm (PM$_{2.5}$), particle matter with diameter < 10μm (PM$_{10}$), nitrogen oxides (NO$_x$), and nitrogen dioxide (NO$_2$). The LUR model was developed by the ESCAPE project,[17,18] and was conducted according to the geographic predictor variables obtained from the Geographical Information System such as traffic, land use, and topography. Leave-one-out cross-validations showed good model performance for the four air pollutants (cross-validation R^2 ranges from 77% to 88%). In the present study, we used the annual average levels of air pollutants in 2010 as individual exposures.

Ascertainment of chronic obstructive pulmonary disease and death

All participants were followed until the date of COPD events occurred or death, or end of follow-up on December 31, 2020, whichever came first. Incident COPD was ascertained in the national hospital registers using International Classification Disease (ICD-10) codes (J40-J44) via linkage with hospital admission data (https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UKBiobank-Protocol.pdf). In addition, the death was ascertained with death registry records.

Genetic risk score

The UK Biobank genetic data were assayed using two similar genotyping arrays, the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) study and UK BiLEVE Axiom. Genotyping was carried out by Affymetrix Research Services Laboratory in 106 sequential batches of approximately 4,700 samples. Affymetrix applied a custom genotype calling pipeline and quality filtering optimized for biobank-scale genotyping experiments and the novel genotyping arrays, which contain markers that had not been previously typed using Affymetrix technology. More details about genotyping process in the UK Biobank study are described elsewhere.[19] In the present study, we selected 22 independent single nucleotide polymorphisms (SNPs), which were considered

significantly associated with COPD in a genome-wide association study.[11] (see Supplemental Table 1) We calculated the weighted genetic risk score using the following formula: Weighted genetic risk $= (\sum_{i=1}^{n} \beta_i SNP_i) * n / \sum_{i=1}^{n} \beta_i$,[20,21] where the SNP was the number of risk allele (recorded as 0, 1, 2) and the β coefficient for each SNP was obtained from stage I analysis in a genome-wide association study.[11] We divided participants into two groups by median: low and high genetic risk groups.

Healthy lifestyle

The lifestyle score was determined according to four modifiable factors, namely smoking status, drinking status, diet, and physical activity. All information on these factors were obtained from a touchscreen questionnaire at baseline. Smoking/drinking status was defined as current or not current smoker/drinker. Regular physical activity was defined as having moderate activities $\geq$ 150 min/week or vigorous activities $\geq$ 75 min/week or combination.[22] A healthy diet was assessed based on the intake of 7 dietary components (fruit, vegetables, fish, processed meat, red meat, whole grain, and refined grain) following the recommended dietary priorities for cardiometabolic health.[23] Participants who met more than 4 of 7 dietary criteria were considered to have healthy diet. Details about definitions of the 4 modifiable factors are presented in Supplemental Table 2. Lifestyle score ranged from 0 to 4, with the higher score representing the healthier lifestyle. We then categorized lifestyle score as unfavourable lifestyle (<3 scores) and healthy lifestyle ($\geq$3 scores). Participants with unidentified status of lifestyle factors for missing values were treated as not having optimal status. For instance, participants with missing information on physical activity were considered as not having regular physical activity (see Supplemental Table 3).

Covariates

Information about other covariates were also collected through a touch screen questionnaire, including age, sex, race, educational level, household income, and employment status. Race was categorized as white or non-white race. The employment status was considered as paid employment and unpaid employment. Educational level was categorized as college or University degree, A level/AS levels or equivalent, O levels/GCSEs or CSEs or equivalent, NVQ or HND or HNC or equivalent or other professional qualifications, and none of the above. Household income was divided into four grades: less than £18,000, £18,000 to £30,999, £31,000 to £51,999, and greater than £52,000. Body mass index value is constructed from height and weight.

Statistical analysis

The characteristics of included participants were described using median (IQR) for abnormally distributed variables, mean (standard deviation) for normally distributed variables, and number (proportion) for categorical variables. We applied Cox proportional hazard model to assess the associations of air pollution (continuous and categorized by quartiles) exposure with risk of COPD. Model 1 showed crude associations. In model 2, we adjusted for age, sex, and race to control potential confounding from individual factors. In model 3, we additionally adjusted for body mass index, employment status, household income, educational levels, smoking status, drinking status, diet, and physical activity based on model 2 to rule out the influence of sociodemographic characteristics and health behaviours. All covariates included in our analyses were identified based on current literature. The results were presented as per interquartile range (IQR) increase in air pollution levels.

To explore the modification effects of genetic susceptibility and lifestyle, we fitted separated models for participants with low genetic risk and those with high genetic risk, and for those with unfavourable lifestyle and those with healthy lifestyle. The associations between air pollution exposure and risk of COPD in 4 separate groups according to genetic risk (low and high) and lifestyle (unfavourable and healthy) were also evaluated. The modification effect was tested by including interaction terms between air pollution exposure and modifiable factors (genetic susceptibility and lifestyle). We applied the Wald test[24] to assess the difference in associations of air pollution with risk of COPD between subgroups, and $P<0.1$ was considered as statistically significant. Analyses about associations of long-term exposure to air pollutants and risk of COPD according to lifestyle score (0~4) and quartiles of genetic risk were also performed. In addition, we also applied a SAS Program developed by Lundberg et al.[25] to calculate the relative excess risk (RERI) and the attributable proportion (AP) due to interaction and their 95% confidence interval, which have been proposed as measures of interaction in epidemiologic studies.[26] In these calculations, we defined high $PM_{2.5}$ (≥ 10 $\mu g/m^3$), PM_{10} (≥ 20 $\mu g/m^3$), and NO_2 (≥ 40 $\mu g/m^3$) according to the WHO air quality guidelines, and high NO_x was defined as ≥ 42.21 $\mu g/m^3$ (the median level of NO_x). The low air pollution exposure, low genetic risk, and unfavourable lifestyle were considered as references. Moreover, we also assessed the risk of COPD in 8 separate groups based on the air pollution exposure (low and high), genetic risk (low and high), and lifestyle (unfavourable and healthy). Individuals with high air pollution exposure, high genetic risk and unfavourable lifestyle were treated as reference. Missing values of categorical variables were coded as a missing indicator category.

To test the robustness of our results, we conducted a series of sensitivity analyses: (1) excluding participants with missing covariates; (2) excluding participants with COPD occurred within 1 year of follow up; (3) excluding participants staying at the current address less than 1 or 5 years; (4) assuming participants with unidentifiable lifestyle status as having optimal status, or excluding them. All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc.). Two-sided $P<0.05$ was considered statistically significant.

Ethics

Summary data was used and as such ethical approval was not required.

Role of Funders

This study was not funded.

Results

There were 452762 participants with median age of 58.00 (IQR: 50.00-63.00) years old included in our study. Characteristics of included participants are presented in Table 1. The mean body mass index was 27.42 (4.78) kg/m². Among them, 205833 (45.46%) were males, and white race accounted for 93.77% (424575). During 9.63±1.46 years of follow up, 15652 cases of COPD were identified. Compared with participants with COPD, those without COPD tended to be younger (median: 57.00 vs 62.00 years old) and had lower body mass index (mean: 27.39 vs 28.41 kg/m²), and be in paid employment (58.45% vs 31.94%), had higher household income (greater than £52,000, 22.31% vs 6.75%) and college or university degree (32.33% vs 14.11%). There were 41.00% (179200) having healthy lifestyle in participants without COPD, which was similar to that in all participants (40.43%, 183039), while only 24.53% (3839) participants had healthy lifestyle among those with COPD. Table 2 shows the distribution of air pollutants. The median (IQR) concentrations of $PM_{2.5}$, PM_{10}, NO_x, and NO_2 were 9.93 (9.29-10.56), 16.03 (15.25-17.01), 42.21 (34.18-50.71), and 26.12 (21.36-31.22) $\mu g/m^3$, respectively. Characteristics of 396593 participants included for analysis of genetic risk are presented in Supplemental Table 4, and those of 41303 participants excluded for missing estimates of air pollution are presented in Supplemental Table 5.

Table 3 presents association between air pollution and risk of COPD. Each interquartile range (IQR) increase in annual concentrations of $PM_{2.5}$, PM_{10}, NO_x, and NO_2 was associated with 1.17 (95% CI: 1.15,1.19), 1.05 (95% CI: 1.03,1.06), 1.13 (95% CI: 1.11,1.14), and 1.19 (95% CI: 1.16,1.21) times the risk of COPD, respectively, after adjusting for potential confounders. Similar associations were observed when the concentrations of

Characteristics	Total participants (n=452762)	Participants without COPD (n=437110)	Participants with COPD (n=15652)
Age, year	58.00 (50.00-63.00)	57.00 (50.00-63.00)	62.00 (57.00-66.00)
Body mass index, kg/m^2	27.42 (4.78)	27.39 (4.75)	28.41 (5.57)
Male, %	205833 (45.46)	197495 (45.18)	8338 (53.27)
White race, %	424575 (93.77)	409530 (93.69)	15045 (96.12)
Employment, %			
Paid employment	260482 (57.53)	255483 (58.45)	4999 (31.94)
Not paid employment	186993 (41.30)	176552 (40.39)	10441 (66.71)
Missing data	5287 (1.17)	5075 (1.16)	212 (1.35)
Household income, %			
Less than £18,000	86137 (19.02)	80193 (18.35)	5944 (37.98)
£18,000 to £30,999	97840 (21.61)	94427 (21.60)	3413 (21.81)
£31,000 to £51,999	100174 (22.13)	98310 (22.49)	1864 (11.91)
Greater than £52,000	98569 (21.77)	97513 (22.31)	1056 (6.75)
Missing data	70042 (15.47)	66667 (15.25)	3375 (21.56)
Educational level, %			
College or University degree	143547 (31.70)	141339 (32.33)	2208 (14.11)
A level/AS levels or equivalent	49791 (11.00)	48731 (11.15)	1060 (6.77)
O levels/GCSEs or CSEs or equivalent	122926 (27.15)	119442 (27.33)	3484 (22.26)
NVQ or HND or HNC or equivalent or other professional qualifications	52561 (11.61)	50276 (11.50)	2285 (14.60)
None of the above	74597 (16.48)	68500 (15.67)	6097 (38.95)
Missing data	9340 (2.06)	8822 (2.02)	518 (3.31)
Healthy lifestyle, %	183039 (40.43)	179200 (41.00)	3839 (24.53)
Not current smoker, %	404577 (89.36)	394446 (90.24)	10131 (64.73)
Not current drinker, %	35960 (7.94)	34158 (7.81)	1802 (11.51)
Healthy diet, %	339187 (74.92)	329659 (75.42)	9528 (60.87)
Regular physical activity, %	229764 (50.75)	223107 (51.04)	6657 (42.53)

Table 1: Characteristics of participants included (*n*=452762).
Abbreviations: COPD, chronic obstructive pulmonary disease.
The distributions of age and body mass index were described using median (interquartile range) and mean (standard deviation), respectively.

air pollutions were included as categorical variables (quartiles) (see Supplemental Table 6). The exclusion of participants with missing covariates, participants with events of COPD occurred within 1 year of follow-up, or participants staying at current address less than 1 or 5 years did not alter these associations (see Supplemental Tables 7−9).

The associations of genetic risk score and lifestyle score with risk of COPD are presented in Supplemental Tables 10, 11. Higher genetic risk score was associated

with increased risk of COPD, while the negative association between lifestyle score and COPD risk was not significant after adjustment for potential confounders. When stratified by lifestyle or genetic risk, the magnitude of effect of air pollution exposure on COPD risk was smaller among participants with healthy lifestyle or low genetic risk than those with unfavourable lifestyle or high genetic risk, respectively. However, only interactions of $PM_{2.5}$ exposure with lifestyle (*P*-interact=0.075) were statistically significant (see Table 4). The HRs per

Air pollutants	Mean (SD)	5th	25th	50th (median)	75th	95th
$PM_{2.5}$, μg/m^3	9.99 (1.06)	8.29	9.29	9.93	10.56	11.86
PM_{10}, μg/m^3	16.24 (1.90)	13.21	15.25	16.03	17.01	20.24
NO_x, μg/m^3	43.97 (15.63)	22.97	34.18	42.21	50.71	71.16
NO_2, μg/m^3	26.64 (7.63)	15.00	21.36	26.12	31.22	39.56

Table 2: Distribution of air pollutants.

Air pollutants	Cases/N	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
$PM_{2.5}$	15652/452762	1.27 (1.25, 1.29)	<.001	1.34 (1.32, 1.37)	<.001	1.17 (1.15, 1.19)	<.001
PM_{10}	15652/452762	1.08 (1.07, 1.10)	<.001	1.11 (1.09, 1.12)	<.001	1.05 (1.03, 1.06)	<.001
NO_x	15652/452762	1.18 (1.16, 1.19)	<.001	1.22 (1.21, 1.24)	<.001	1.13 (1.11, 1.14)	<.001
NO_2	15652/452762	1.25 (1.22, 1.27)	<.001	1.34 (1.31, 1.36)	<.001	1.18 (1.16, 1.21)	<.001

Table 3: Associations between long-term exposure to air pollutants (per IQR increase) and risk of chronic obstructive pulmonary disease (*n*=452762).
Model 1: crude.
Model 2: Adjusted for age, sex, and race.
Model 3: Adjusted for age, sex, race, body mass index, employment status, household income, educational level, smoking status, drinking status, diet, and physical activity.

IQR increase in $PM_{2.5}$ were higher in individuals with unfavourable lifestyle (1.24, 95% CI: 1.21-1.26) than in those with healthy lifestyle (1.20, 95% CI: 1.15-1.24). In addition, we also performed analyses after stratification according to lifestyle score and quartiles of genetic risk score, and the results also showed that adverse effect of air pollution was more evident among participants with higher genetic risk and lifestyle score (see Supplemental Tables 12, 13).

Measures for interaction of air pollution (low and high) with lifestyle and genetic risk are presented in Table 5. RERI and AP for interaction between high $PM_{2.5}$ and high genetic risk was 0.154 (0.083, 0.226) and 0.114 (0.062, 0.166), respectively, which indicated that the interaction was responsible for 0.154 relative excess risk and accounted for 11.8% of the risk of COPD. Similarly, 0.156 (95% CI: 0.085−0.226) relative excess risk was attributed to the interaction between high NO_x and high genetic risk, accounting for 11.7% (95% CI: 6.5%−16.9%) risk of COPD. However, we did not observe any significant interactions between air pollution exposure (low and high) and lifestyle.

The joint effects of air pollution, lifestyle, and genetic risk on risk of COPD behaved in a dose-response manner. (see Figure 1) Risk of COPD was reduced with decreased air pollution and genetic risk, as well as the improvement in lifestyle. Participants with low air pollution exposure, healthy lifestyle and low genetic risk showed the lowest risk of COPD ($PM_{2.5}$, HR: 0.33, 95% CI: 0.31−0.36; PM_{10}, HR: 0.41, 95% CI: 0.36-0.46; NO_x, HR: 0.35, 95% CI: 0.32-0.37; and NO_2, HR: 0.27, 95% CI: 0.24-0.30). In addition, the effect of air pollution on risk of COPD also showed smallest magnitude in participants with healthy lifestyle and low genetic risk (see Supplemental Table 14).

All analyses related with lifestyle were repeated under assumption of participants with unidentified status of lifestyle having optimal status or after excluding them for missing information, which came to similar results to those in the main analysis (see Supplemental Tables 15−24).

Subgroups	Cases/N	HR (95% CI)	*P*-value	Cases/N	HR (95% CI)	*P*-value	*P*-interact
Lifestyle		Unfavorable lifestyle			Healthy lifestyle		
$PM_{2.5}$	11813/269723	1.24 (1.21, 1.26)	<.001	3839/183039	1.20 (1.15, 1.24)	<.001	0.075
PM_{10}	11813/269723	1.07 (1.05, 1.09)	<.001	3839/183039	1.06 (1.03, 1.09)	<.001	0.607
NO_x	11813/269723	1.17 (1.15, 1.19)	<.001	3839/183039	1.16 (1.12, 1.19)	<.001	0.540
NO_2	11813/269723	1.27 (1.24, 1.30)	<.001	3839/183039	1.23 (1.18, 1.28)	<.001	0.245
Genetic risk		Low genetic risk			High genetic risk		
$PM_{2.5}$	6410/198433	1.16 (1.12, 1.19)	<.001	7367/198160	1.19 (1.16, 1.22)	<.001	0.101
PM_{10}	6410/198433	1.04 (1.02, 1.07)	<.001	7367/198160	1.05 (1.02, 1.07)	<.001	0.753
NO_x	6410/198433	1.12 (1.10, 1.15)	<.001	7367/198160	1.14 (1.11, 1.16)	<.001	0.258
NO_2	6410/198433	1.17 (1.14, 1.21)	<.001	7367/198160	1.20 (1.17, 1.24)	<.001	0.123

Table 4: Association of long-term exposure to air pollutants (per IQR increase) and risk of chronic obstructive pulmonary disease according to the lifestyle (*n*=452762) and genetic risk (*n*=396593).
Models for subgroups by lifestyle were adjusted for age, body mass index, sex, race, employment status, household income, and educational level.
Models for subgroups by genetic risk were adjusted for age, body mass index, sex, race, employment status, household income, educational level, smoking status, drinking status, diet, and physical activity.

Air pollution	High genetic risk		Healthy lifestyle	
	RERI	AP	RERI	AP
High $PM_{2.5}$	0.154 (0.083, 0.226)	0.114 (0.062, 0.166)	0.025 (-0.059, 0.110)	0.019 (-0.043, 0.081)
High PM_{10}	0.059 (-0.092, 0.211)	0.050 (-0.075, 0.174)	-0.065 (-0.233, 0.102)	-0.057 (-0.205, 0.091)
High NO_x	0.156 (0.085, 0.226)	0.117 (0.065, 0.169)	-0.045 (-0.133, 0.043)	-0.032 (-0.096, 0.031)
High NO_2	0.047 (-0.152, 0.246)	0.030 (-0.096, 0.156)	-0.172 (-0.402, 0.057)	-0.118 (-0.278, 0.043)

Table 5: The interaction of air pollution with genetic risk and healthy lifestyle.
Abbreviations: AP, Attributable proportion due to interaction; RERI, relative excess risk due to interaction;
References were low air pollution exposure, low genetic risk, and unfavorable lifestyle.
Models for genetic risk were adjusted for age, sex, race, body mass index, employment status, household income, and educational level.
Models for lifestyle were adjusted for age, sex, race, body mass index, employment status, household income, educational level, smoking status, drinking status, diet, and physical activity.
$PM_{2.5}$ level was categorized as low $PM_{2.5} < 10 \ \mu g/m^3$ and high $PM_{2.5} \geq 10 \ \mu g/m^3$ according to the WHO air quality guidelines.
PM_{10} level was categorized as low $PM_{10} < 20 \ \mu g/m^3$ and high $PM_{10} \geq 20 \ \mu g/m^3$ according to the WHO air quality guidelines.
NO_x level was categorized as low $NO_x < 42.21 \ \mu g/m^3$ and high $NO_x \geq 42.21 \ \mu g/m^3$ by to median level of NO_x.
NO_2 level was categorized as low $NO_2 < 40 \ \mu g/m^3$ and high $NO_2 \geq 40 \ \mu g/m^3$ according to the WHO air quality guidelines.
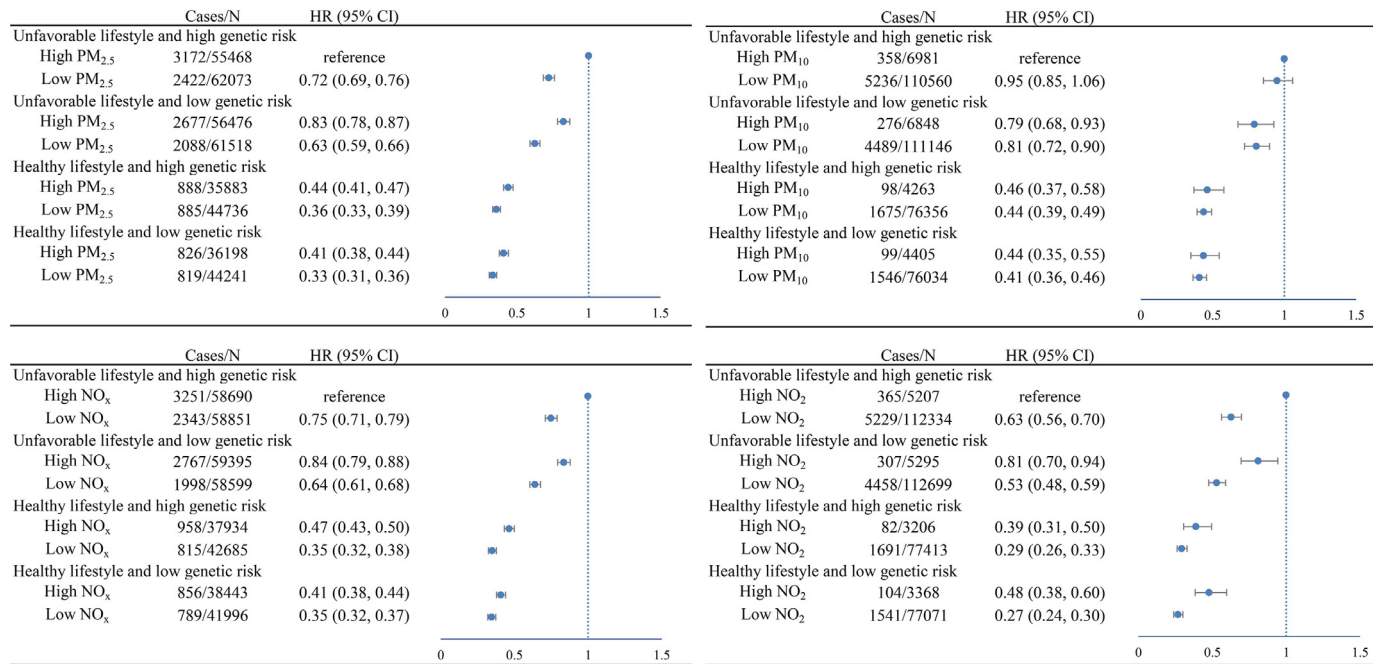
Discussion

Results from our study suggested that long-term exposures to air pollution, including $PM_{2.5}$, PM_{10}, NO_x, and NO_2, were positively associated with risk of COPD. High genetic risk and unfavourable lifestyle were associated with increased COPD risk. The adverse effects of $PM_{2.5}$ were stronger in individuals with high genetic risk and unfavourable lifestyle. We also provided quantitative data about the effects of the interactions of high air pollution exposure with high genetic risk and healthy lifestyle. When examining the joint effects of air pollution, genetic risk, and lifestyle, participants with high air pollution exposure, high genetic risk, and unfavourable lifestyle showed the highest risk of COPD.

Previous studies have assessed the effect of long-term exposure to air pollution on risk of COPD, but did not arrive at the same conclusion. A population-based cohort study of Ontarians reported a positive association of 3-year moving average of $PM_{2.5}$ exposure with COPD risk.[3] A study from Taiwan demonstrated that long-term exposure to $PM_{2.5}$ was not only related to an increased risk of the incidence of COPD, but also related to reduced and faster declines in lung function.[27] Significant associations between long-term exposures to $PM_{2.5}$, NO_2 and COPD risk were also observed in a pooled analysis of three cohort studies within the "Effects of Low-Level Air Pollution: A Study in Europe" (ELAPSE) study,[28] in a retrospective cohort study in Korea,[29] and among 1.1 million adults from Toronto, Canada.[30] As for the NO_x, Zorana et al. assessed the long-term traffic-related air pollution (NO_2 and NO_x), and demonstrated that the 35-year mean concentrations of NO_2 and NO_x were related to high risk of COPD, while those over 25-year or 15-year periods did not show significant associations with COPD risk.[4] Nevertheless, some other studies reported negative results. For example, Atkinson et al. conducted a prospective cohort study of 812063 patients aged 40−89 years. However, the hazards ratios for COPD and $PM_{2.5}$, PM_{10} and NO_2 were close to unity, and the associations were not statistically significant.[31] A meta-analysis integrated four cohort studies participating in ESCAPE (European Study on Chronic Air Pollution Effect), and reported that none of air pollutants ($PM_{2.5}$, PM_{10}, NO_x, NO_2, PM_{coarse} (particle matter with diameter from $2.5 \mu m$ to $10 \mu m$)) were significantly associated with incidence of COPD.[7] In the present study, our results indicated that exposures of four air pollutions of $PM_{2.5}$, PM_{10}, NO_x, and NO_2 significantly increased the risk of COPD. The discrepancy across studies might be caused by the differences in sociodemographic characteristics, air pollution levels, and chemical profiles of pollution.

It is widely recognized that the pathogenesis of COPD involves a complex interplay between genetic background and exposure to environmental factors.[32] Although the effects are seen in the population, there is clearly interindividual variability in the respiratory effect of air pollutants. Evidence from some genetic linkage studies of air pollution exposure in animals and human demonstrated that gene polymorphisms influenced the lung function response to PM and NO_2 exposures.[33] To the best of our knowledge, this is the first study to assess the interaction between genetic susceptibility and air pollution exposure in the development of COPD. Results from our study suggested that participants with higher genetic risk were more vulnerable to adverse effect of $PM_{2.5}$ exposure.

Moreover, we also evaluated the potential effect of modifiable lifestyle on association between air pollution and COPD risk. Although the modifiable lifestyle factors have been recognized as cost-effective interventions in preventing and controlling non-communicable disease,[9] the evidence about interaction between air pollution and lifestyle in COPD risk is still scarce. Fisher et al. assessed the associations between PM exposure and COPD risk in subgroups of current smokers, former smokers, and never smokers, but did not observe significant associations in any subgroups.[34] A study

	Cases/N	HR (95% CI)
Unfavorable lifestyle and high genetic risk		
High PM$_{2.5}$	3172/55468	reference
Low PM$_{2.5}$	2422/62073	0.72 (0.69, 0.76)
Unfavorable lifestyle and low genetic risk		
High PM$_{2.5}$	2677/56476	0.83 (0.78, 0.87)
Low PM$_{2.5}$	2088/61518	0.63 (0.59, 0.66)
Healthy lifestyle and high genetic risk		
High PM$_{2.5}$	888/35883	0.44 (0.41, 0.47)
Low PM$_{2.5}$	885/44736	0.36 (0.33, 0.39)
Healthy lifestyle and low genetic risk		
High PM$_{2.5}$	826/36198	0.41 (0.38, 0.44)
Low PM$_{2.5}$	819/44241	0.33 (0.31, 0.36)

	Cases/N	HR (95% CI)
Unfavorable lifestyle and high genetic risk		
High PM$_{10}$	358/6981	reference
Low PM$_{10}$	5236/110560	0.95 (0.85, 1.06)
Unfavorable lifestyle and low genetic risk		
High PM$_{10}$	276/6848	0.79 (0.68, 0.93)
Low PM$_{10}$	4489/111146	0.81 (0.72, 0.90)
Healthy lifestyle and high genetic risk		
High PM$_{10}$	98/4263	0.46 (0.37, 0.58)
Low PM$_{10}$	1675/76356	0.44 (0.39, 0.49)
Healthy lifestyle and low genetic risk		
High PM$_{10}$	99/4405	0.44 (0.35, 0.55)
Low PM$_{10}$	1546/76034	0.41 (0.36, 0.46)

	Cases/N	HR (95% CI)
Unfavorable lifestyle and high genetic risk		
High NO$_x$	3251/58690	reference
Low NO$_x$	2343/58851	0.75 (0.71, 0.79)
Unfavorable lifestyle and low genetic risk		
High NO$_x$	2767/59395	0.84 (0.79, 0.88)
Low NO$_x$	1998/58599	0.64 (0.61, 0.68)
Healthy lifestyle and high genetic risk		
High NO$_x$	958/37934	0.47 (0.43, 0.50)
Low NO$_x$	815/42685	0.35 (0.32, 0.38)
Healthy lifestyle and low genetic risk		
High NO$_x$	856/38443	0.41 (0.38, 0.44)
Low NO$_x$	789/41996	0.35 (0.32, 0.37)

	Cases/N	HR (95% CI)
Unfavorable lifestyle and high genetic risk		
High NO$_2$	365/5207	reference
Low NO$_2$	5229/112334	0.63 (0.56, 0.70)
Unfavorable lifestyle and low genetic risk		
High NO$_2$	307/5295	0.81 (0.70, 0.94)
Low NO$_2$	4458/112699	0.53 (0.48, 0.59)
Healthy lifestyle and high genetic risk		
High NO$_2$	82/3206	0.39 (0.31, 0.50)
Low NO$_2$	1691/77413	0.29 (0.26, 0.33)
Healthy lifestyle and low genetic risk		
High NO$_2$	104/3368	0.48 (0.38, 0.60)
Low NO$_2$	1541/77071	0.27 (0.24, 0.30)

Figure 1. Risk of incident chronic obstructive pulmonary disease according to air pollution, genetic susceptibility, and lifestyle. Abbreviations: CI, confidence interval; HR, hazards ratio; PM$_{2.5}$, particle matter with diameter $<2.5\mu$m; PM$_{10}$, particle matter with diameter $<10\mu$m; NO$_x$, nitrogen oxides; NO$_2$, nitrogen dioxide. HRs were obtained from Cox proportional hazards models, and all models were adjusted for age, sex, race, body mass index, employment status, household income, and educational level.

from the Danish Diet, Cancer, and Health study also performed stratified analyses to assess the modifying effect of smoking status and fruit consumption, but the interactions of them with NO_2 exposure were not statistically significant in COPD risk.[4] Results from the same cohort also demonstrated the protective effect of physical activities and the negative effect of NO_2 exposure on the development of COPD, but the interactions between them did not show any significance.[35] In addition, a review from Whyand et al. suggested that some nutrients, such as carotenoids, vitamin D and vitamin E, helped protect against pollution damage which could trigger COPD and lung cancer initiation, but there was no evidence about Mediterranean diet protecting against air pollution.[36] In the present study, results from stratified analysis showed that the adverse effect of exposure to $PM_{2.5}$ could be partly compensated by healthy lifestyle, however, which could not be deduced from measures of RERI and AP. These discrepancies might be attributable to loss of information, since air pollution levels had to be treated as categorical variables in these calculations. This study observed the modification by overall lifestyle on risk of COPD induced by air pollution exposure, which suggested that targeted intervention on modifiable lifestyle might offset the adverse effect of $PM_{2.5}$ exposure on COPD risk.

Our study was conducted based on a nation-wide population study. Besides evaluation of associations of long-term exposures to various air pollutants with COPD risk, we also conducted investigations into the modification effects of genetic risk and lifestyle on these associations and the interactions of air pollution with genetic risk and lifestyle. However, there were also some limitations in our study. First, air pollutions, especially PM, are heterogeneous mixtures of solid and liquid particles that varies in size and chemical compositions. We could not evaluate the effect of specific components of air pollutions because of the limited data. Second, exposure of air pollution was evaluated based on the address collected at baseline, which might be influenced by the length of time at this address. However, we performed sensitivity analyses after excluding participants staying less than 1 or 5 years at current address, and we did not observe substantial alteration of our main results. Third, data we used to identify the status of lifestyle were self-reported, which might lead to misclassification. Fourth, our study was conducted on UK Biobank data, and most participants were of European descent. This might limit the generalizability of our results. However, the UK biobank recruited about 0.5 million participants living within reasonable distance of a total of 22 assessment centres across the UK,[37] which made it nationally representative. The results can be well represented in European countries. Fifth, in this study, demographic and lifestyle information for some participants were missing, which might bias our results. However, such incompleteness

is unlikely related to air pollutant levels. Moreover, a series of sensitivity analyses were conducted after excluding participants with missing information, and the results did not change.

In conclusion, findings from our study indicated the great influence of air pollution exposure on development of COPD, and highlighted the important role of improvement in lifestyle in the intervention for COPD. As for individuals with high genetic risk of COPD, they should be paid extra attention in prevention of adverse effect of air pollutions.

Contributors
L.W. and Y.T. conceived the study. Y.T., L.W., Y.H., and J.X. contributed to the study design. L.W. and Y.T. prepared and conducted the data analysis. L.W. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. Y.T. acts as guarantor.

Data sharing statement
All data are available on the aforementioned public repository and are accessible with permission from the corresponding data committee. No restrictions on data availability other than those imposed by the corresponding data committee.

Declaration of interests
None.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.103994.

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