

RESEARCH ARTICLE

Open Access



# Genetic susceptibility and lifestyle modify the association of long-term air pollution exposure on major depressive disorder: a prospective study in UK Biobank

Dankang Li<sup>1,2</sup>, Junqing Xie<sup>3</sup>, Lulin Wang<sup>1,2</sup>, Yu Sun<sup>4</sup>, Yonghua Hu<sup>5</sup> and Yaohua Tian<sup>1,2\*</sup>

## Abstract

**Background** Evidence linking air pollution to major depressive disorder (MDD) remains sparse and results are heterogeneous. In addition, the evidence about the interaction and joint associations of genetic risk and lifestyle with air pollution on incident MDD risk remains unclear. We aimed to examine the association of various air pollutants with the risk of incident MDD and assessed whether genetic susceptibility and lifestyle influence the associations.

**Methods** This population-based prospective cohort study analyzed data collected between March 2006 and October 2010 from 354,897 participants aged 37 to 73 years from the UK Biobank. Annual average concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, and NO<sub>x</sub> were estimated using a Land Use Regression model. A lifestyle score was determined based on a combination of smoking, alcohol drinking, physical activity, television viewing time, sleep duration, and diet. A polygenic risk score (PRS) was defined using 17 MDD-associated genetic loci.

**Results** During a median follow-up of 9.7 years (3,427,084 person-years), 14,710 incident MDD events were ascertained. PM<sub>2.5</sub> (HR: 1.16, 95% CI: 1.07–1.26; per 5 µg/m<sup>3</sup>) and NO<sub>x</sub> (HR: 1.02, 95% CI: 1.01–1.05; per 20 µg/m<sup>3</sup>) were associated with increased risk of MDD. There was a significant interaction between the genetic susceptibility and air pollution for MDD (*P*-interaction < 0.05). Compared with participants with low genetic risk and low air pollution, those with high genetic risk and high PM<sub>2.5</sub> exposure had the highest risk of incident MDD (PM<sub>2.5</sub>: HR: 1.34, 95% CI: 1.23–1.46). We also observed an interaction between PM<sub>2.5</sub> exposure and unhealthy lifestyle (*P*-interaction < 0.05). Participants with the least healthy lifestyle and high air pollution exposures had the highest MDD risk when compared to those with the most healthy lifestyle and low air pollution (PM<sub>2.5</sub>: HR: 2.22, 95% CI: 1.92–2.58; PM<sub>10</sub>: HR: 2.09, 95% CI: 1.78–2.45; NO<sub>2</sub>: HR: 2.11, 95% CI: 1.82–2.46; NO<sub>x</sub>: HR: 2.28, 95% CI: 1.97–2.64).

**Conclusions** Long-term exposure to air pollution is associated with MDD risk. Identifying individuals with high genetic risk and developing healthy lifestyle for reducing the harm of air pollution to public mental health.

**Keywords** Air pollution, Major depressive disorder, Genetic susceptibility, Healthy lifestyle, Interaction

\*Correspondence:

Yaohua Tian

yaohua\_tian@hust.edu.cn

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

## Background

Major depressive disorder (MDD) is among the most common mental illnesses, and it severely limits psychosocial functioning and negatively affects the quality of life [1]. MDD affects approximately 6% of the adult population worldwide each year [2], and patients with MDD are nearly 20-fold more likely to die by suicide than individuals without MDD [3]. According to the World Health Organization, MDD will be the leading disease burden worldwide by 2030 [4].

Evidence indicates that socioeconomic status, medical conditions, and family history play a major role in the development of mental health disorders and that environmental factors may also influence the development of such disorders through neuroinflammatory pathways and oxidative stress [5, 6]. Although air pollution is the most common environmental risk to human health, results on the correlation between air pollution and health are sparse and inconsistent. For example, a recent systematic review reported that long-term exposure to air pollution was associated with an increased risk of depression, but the association was not significant in more than half of the studies included in the review [7]. Furthermore, the size and quality of these studies varied considerably. Therefore, additional large population-based cohort studies are necessary to test the potential association between long-term exposure to air pollution and MDD.

Evidence suggests that genetic factors play a critical role in the development of MDD [8, 9]. A genome-wide association study (GWAS) identified some genetic variants associated with MDD risk [10]. Analyzing the cumulative genetic burden of these genetic variants by using polygenic risk scores (PRSs) could provide quantitative measures of genetic susceptibility and could help effectively identify individuals at high risk of MDD [11]. Recent studies have suggested that genetic susceptibility may influence the environment–disease relationship [12, 13]. However, the influence of genetic susceptibility on the association between exposure to air pollution and MDD risk is unclear. In addition, unhealthy lifestyle behaviors, such as smoking, excessive alcohol intake, and lack of physical activity, increase the risk of MDD [14–16]. Several studies have revealed that healthy lifestyle habits played a pivotal role in attenuating the effect of air pollution on the risk of various diseases [17–19]. However, whether a healthy lifestyle can mitigate the effect of air pollution on MDD risk is unclear.

To address the aforementioned questions, this study investigated the association between exposure to air pollution and the incidence of MDD in a large population-based cohort (UK Biobank). In addition, we examined the potential modifying effect of genetic susceptibility and lifestyle on this association.

## Methods

### Study population

In this prospective cohort study, we sourced data from the UK Biobank. Details of the design and survey methods of the UK Biobank have been described elsewhere [20]. Briefly, the baseline survey was done between March 13, 2006, and October 1, 2010, at 22 assessment centers in urban areas of England, Wales, and Scotland [20]. More than 0.5 million participants provided demographics, socioeconomics, lifestyle, and health information through touchscreen questionnaires and anthropometric measurements [21].

In the present study, we excluded participants who had experienced a MDD at baseline ( $N = 31,325$ ) and those with MDD identified by medical records at baseline from the current study ( $N = 9278$ ). Then, we excluded participants with missing information on genetic data ( $N = 72,717$ ) and air pollution ( $N = 34,263$ ). Finally, data from 354,897 individuals were available for the final analyses (Additional file 1: Fig. S1). All participants provided informed consent to participate.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the North West Multi-centre Research Ethics Committee (REC reference: 16/NW/0274).

### Air pollutants

Estimates of particulate matter with aerodynamic diameter  $\leq 2.5\mu\text{m}$  ( $\text{PM}_{2.5}$ ), particulate matter with aerodynamic diameter  $\leq 10\mu\text{m}$  ( $\text{PM}_{10}$ ), nitrogen dioxide ( $\text{NO}_2$ ), and nitrogen oxides ( $\text{NO}_x$ ) concentrations were available for the year 2010. Land Use Regression (LUR) techniques were employed to model the annual average concentrations of these air pollutants by using the predictor variables obtained from the Geographic Information System such as traffic, land use, and topography [22, 23]. Air pollution exposures for all participants in the UK Biobank were linked to the records through geocoded residential addresses given at the baseline visit. LUR techniques were developed by the ESCAPE project, which estimates for particulates are valid up to 400 km from the monitoring area and required a spatial resolution of at least 100 m. More details of the ESCAPE LUR model development and validation methodology have been published elsewhere. Briefly, leave-one-out cross-validation showed good model performance for  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$ ,  $\text{NO}_2$ , and  $\text{NO}_x$  (cross-validation  $R^2=77\%$ ,  $88\%$ ,  $87\%$ , and  $88\%$ , respectively) [23].

### Polygenic risk score

We used the imputed genetic data from UK Biobank. Details of genotyping, imputation, and quality control have been described previously [24]. In the present analysis, 17 single-nucleotide polymorphisms (SNPs) were selected based on their association with MDD in previous GWAS to create a weighted PRS for MDD (selected SNPs are provided in Additional file 1: Table S1) [10]. Details regarding PRS calculation have been described in a previous study [12]. We calculated PRS by summing the product of the weighted risk estimate (the SNP's  $\beta$  coefficient from reported MDD GWAS) and the number of risk alleles (0, 1, and 2) for each risk variant:  $PRS = \sum_{n=1}^M \beta_n \times SNP_n$ . In the present study, subjects were categorized as low, intermediate, and high genetic risk based on the tertile distribution of PRS.

### Lifestyle score

Consistent with the previous study, the lifestyle score was constructed based on the following lifestyle variables: smoking status, alcohol intake, physical activity, television viewing time, sleep duration, fruit and vegetable intake, oily fish intake, red meat intake, and processed meat intake [25]. These factors comprise the score derived from touchscreen questionnaire responses at baseline (Additional file 1: Table S2). Participants scored 1 point for each unhealthy category defined on the basis of national guidelines (Additional file 1: Table S2). Unhealthy lifestyle was assessed as follows: current smoker, alcohol consumed daily or almost daily, <150 min per week of moderate-intensity physical activity or <75 min per week of vigorous-intensity physical activity,  $\geq 4$  h per day of television viewing time, <7 h or >9 h of sleep time per day, <400 g of fruits and vegetables per day, <1 portion of oily fish per week, >3 portions of red meat per week, and >1 portion of processed meat per week. An unweighted score was created by summing each component score with a range from 0 to 9, with higher scores indicating an unhealthier lifestyle. Then, participants were subsequently categorized into three categories: most healthy (scored 0, 1, or 2), moderately healthy (scored 3, 4, or 5), and least healthy (scored 6, 7, 8, or 9) [25].

### Assessment of MDD

Incident outcomes in the UK Biobank were linked to hospital admissions and death registries. Detailed information has been described elsewhere [26]. Incident MDD was diagnosed using the International Classification of Diseases, Tenth Revision (ICD-10) coding system and the ICD-10 codes of the categories of disorders are shown in Additional file 1: Table S3. Participants were followed

from January 1, 2011, to the first diagnosis of incident MDD, death, or until January 30, 2021, whichever came first (the timeline is shown in Additional file 1: Fig. S2).

In line with previous studies [27], individuals who experienced a prevalent MDD at baseline were defined as per UK Biobank's assessment protocol for lifetime experience of probable MDD. The structured and validated diagnostic criteria were used to assess the lifetime history of mood disorders in the UK Biobank [28, 29]. To briefly summarize, the assessment of MDD comprised a series of items from the Patient Health Questionnaire, items relating to lifetime experience of minor or major depression, and items on social support for mental health [28, 30]. The criteria for participants who had experienced a MDD included those who had experienced a single probable lifetime episode of major depression, probable recurrent major depression (moderate), or probable recurrent major depression (severe), or any combination thereof (panel).

### Covariates

We developed a directed acyclic graph (DAG) to identify potential covariates that need to be adjusted in our multivariate analyses, using the online DAGitty tool ([www.dagitty.net](http://www.dagitty.net)) [31]. Based on the priori knowledge and existing literature, we included a rich set of covariates in the DAG that should be considered in the analyses [27, 32, 33]. From the DAG (Additional file 1: Fig. S3), a minimally sufficient set of variables for adjustment were retained: age; gender (female or male); ethnicity (white; mixed; Asian; black; Chinese; or other); education level (college or university degree; A/AS levels or equivalent; O level/GCSE or equivalent; CSE or equivalent; NVQ or HND or HNC or equivalent; other professional qualification; or none of the above); employment status (employed; retired; or unemployed, home maker, or others); household income (less than £31,000 or £31,000 and above); and Townsend deprivation index (continuous). The proportions of missing data about covariates were as follows: 15% for household income, 2% for education level and employment status, and less than 1% for ethnicity and Townsend deprivation index. Multiple imputation by fully conditional specification (FCS) was performed to impute missing covariate data.

### Statistical analyses

Continuous and categorical variables were presented as mean  $\pm$  standard deviation (SD) and number (percentage), respectively. Cox proportional hazard regression models were used to estimate the associations between ambient air pollutants, genetic risk, and lifestyle score with incident MDD and to calculate the hazard ratio (HR) and 95% confidence interval (CI). Schoenfeld

residuals were used to test the assumptions of proportionality (Additional file 1: Fig. S4-S7). The Cox regression model was unadjusted in model 1. Model 2 was adjusted for age, gender, ethnicity, education, employment status, household income, and Townsend deprivation index. In addition, we then conducted several sensitivity analyses to assess the robustness of the findings. First, we excluded participants with MDD that occurred during the first 2 years of follow-up to minimize the influence of reverse causation. Second, we restricted all analyses among participants who resided in their current address for 5 or more years to consider the effects of reliable accumulated exposures. Third, to avoid misclassification bias and potential confounding, we excluded participants who were diagnosed with dementia (ICD-10 codes G30.x, G31.x, and F00.x–F03) or anxiety disorders (ICD-10 codes F40.x and F41.x) during the follow-up period. Fourth, we repeated the analyses by additional adjusting for BMI categories, cardiometabolic disease, diabetes, lifestyle, and MDD-PRS to reduce potential residual confounding. Fifth, we restricted the analysis to participants with complete covariate data for comparison with the results based on multiple imputation. Sixth, we examined the association between time-varying exposure to air pollution and MDD risk. Exposures to PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, and NO<sub>x</sub> during the follow-up were estimated at each participant's residential addresses using data from the UK's Department for Environment, Food and Rural Affairs based on a previous study [34]. Finally, to ensure comprehensive ascertainment, incident MDD was derived from linkage to both hospital inpatient and primary care records. In addition, to investigate the effects of pollutant mixtures and eliminate the problem of multicollinearity, principal component analysis (PCA) was applied [35].

We examined the dose–response association between air pollutants and MDD risk using restricted cubic spline regressions. We additionally examined the combination of air pollutants and genetic categories with incident MDD risk (12 categories with lowest genetic risk and lowest quartile of air pollution as reference) and the combination of air pollutants and lifestyle with incident MDD (12 categories with lowest lifestyle risk and lowest quartile of air pollution as reference). Moreover, the interactions between genetic risk and lifestyle with air pollutants were tested by stratifying genetic risk and lifestyle.

All data were analyzed using R (version 4.0.5) and the statistical significance was set to *P* value < 0.05 at two tails.

## Results

During a total of 3,427,084 person-years (median follow-up 9.7 years), 14,710 incident MDD events were recorded. Table 1 displays the baseline characteristics of

the study participants. Participants who developed MDD were more likely to have the least healthy lifestyle, high genetic risk, and higher air pollution exposure. The Pearson correlation coefficients and the summary statistics of air pollutants are shown in Additional file 1: Fig. S8 and Additional file 1: Table S4, respectively.

Table 2 presents the relations of each air pollutant with MDD risk. In the finally multivariate-adjusted model, PM<sub>2.5</sub> (HR: 1.16, 95% CI: 1.07–1.26; per 5 µg/m<sup>3</sup>) and NO<sub>x</sub> (HR: 1.02, 95% CI: 1.01–1.05; per 20 µg/m<sup>3</sup>) were significantly associated with MDD. However, we did not observe an association between PM<sub>10</sub> (HR: 1.00, 95% CI: 0.92–1.09; per 10 µg/m<sup>3</sup>) and NO<sub>2</sub> (HR: 1.00, 95% CI: 0.98–1.02; per 10 µg/m<sup>3</sup>) with MDD. Moreover, compared with the lowest quartile, the HRs (95% CIs) of MDD were 1.12 (1.06, 1.17) and 1.07 (1.02, 1.13) for subjects with the highest quartile of exposure to PM<sub>2.5</sub> and NO<sub>x</sub>, respectively. These results did not alter appreciably in the sensitivity analyses (Additional file 1: Table S5-S12). We then examined the association between principal components (PCs) and MDD risk (Additional file 1: Table S13). We found that the first PC (PC1) predominated by PM<sub>2.5</sub>, NO<sub>2</sub>, and NO<sub>x</sub> was associated with an increased risk of MDD (HR = 1.02, 95% CI: 1.01, 1.04). However, no significant association was observed for PC2 which predominated by PM<sub>10</sub> (HR = 1.00, 95% CI: 0.98, 1.01). We also used the restricted cubic spline to assess the potential dose-response relationship of air pollutants with MDD in Fig. 1. We found nonlinear relationships between PM<sub>2.5</sub>, NO<sub>2</sub>, and NO<sub>x</sub> with the risk of incident MDD (*P*-nonlinearity for PM<sub>2.5</sub>: 0.006; NO<sub>2</sub>: 0.003; NO<sub>x</sub>: 0.003). Additional file 1: Table S14 shows results about the association between air pollution and MDD stratified by age and sex group. No significant interaction was found between air pollution and age on the risk of incident MDD, whereas significant interactions were observed between PM<sub>2.5</sub> with gender on the risk of incident MDD (*P*-interactions were 0.049 for PM<sub>2.5</sub>). The association of air pollution exposure with MDD risk was stronger in men than in women (Additional file 1: Table S14).

Additional file 1: Table S15 presents the associations of PRS with the risk of MDD. We found a significant association of PRS with MDD in the multivariable-adjusted model (HR: 1.10, 95% CI: 1.07–1.12). Figure 2 shows the risk of incident MDD for combined air pollutants and genetic risk. Compared with participants with low genetic risk and low air pollution exposure, those with high genetic risk and high PM<sub>2.5</sub> exposures had the highest risk of incident MDD (PM<sub>2.5</sub>: HR: 1.34, 95% CI: 1.23–1.46). The interaction effects between PRS with PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub> on the risk of incident MDD were

**Table 1** Descriptive characteristics of the study participants and stratified by major depressive disorder (MDD) status at follow-up

Variables	Total (n=354,897)	Individuals without MDD (n=340,187)	Individuals with MDD (n=14,710)
Age, years (mean ± SD)	56.71 ± 8.07	56.71 ± 8.07	56.87 ± 8.08
Gender, n (%)			
Female	189,358 (53.4)	179,981 (52.9)	9377 (63.7)
Male	165,539 (46.6)	160,206 (47.1)	5333 (36.3)
Ethnicity, n (%)			
White ethnicity	340,408 (96.3)	326,236 (96.3)	14,172 (96.9)
Mixed ethnicity	1600 (0.5)	1519 (0.4)	81 (0.6)
Asian ethnicity	5131 (1.5)	4966 (1.5)	165 (1.1)
Black ethnicity	3105 (0.9)	3014 (0.9)	91 (0.6)
Chinese ethnicity	783 (0.2)	775 (0.2)	8 (0.1)
Other ethnicities	2322 (0.7)	2214 (0.7)	108 (0.7)
Missing data	1548 (0.4)	1463 (0.4)	85 (0.6)
Education level, n (%)			
College or university degree	111,478 (31.8)	108,187 (32.2)	3291 (22.8)
A/AS levels or equivalent	39,041 (11.1)	37,616 (11.2)	1425 (9.9)
O level/GCSE or equivalent	77,115 (22.0)	73,973 (22.0)	3142 (21.8)
CSE or equivalent	20,170 (5.8)	19,148 (5.7)	1022 (7.1)
NVQ or HND or HNC or equivalent	23,484 (6.7)	22,381 (6.7)	1103 (7.6)
Other professional qualifications	18,141 (5.2)	17,385 (5.2)	756 (5.2)
None of the above	60,991 (17.4)	57,287 (17.1)	3704 (25.6)
Missing data	4477 (1.3)	4210 (1.2)	267 (1.8)
Employment status, n (%)			
Employed	203,737 (58.0)	197,160 (58.5)	6577 (45.3)
Retired	120,405 (34.3)	115,095 (34.2)	5310 (36.6)
Unemployed, home maker, or others	27,126 (7.7)	24,506 (7.3)	2620 (18.1)
Missing data	3629 (1.0)	3426 (1.0)	203 (1.4)
Household income, n (%)			
Less than £31,000	143,987 (47.7)	136,113 (46.9)	7874 (65.3)
£31,000 and above	157,996 (52.3)	153,806 (53.1)	4190 (34.7)
Missing data	52,914 (14.9)	50,268 (14.8)	2646 (18.0)
Townsend deprivation index, (mean ± SD)	−1.46 ± 2.98	−1.50 ± 2.96	−0.65 ± 3.35
Missing data	369 (0.1)	360 (0.11)	9 (0.06)
Healthy lifestyle factors, n (%)			
Smoking	34,974 (9.9)	32,459 (9.6)	2515 (17.2)
Alcohol intake	74,074 (20.9)	71,391 (21.0)	2683 (18.3)
Physical activity	55,686 (19.5)	52,823 (19.2)	2863 (26.1)
TV viewing	102,308 (28.9)	96,759 (28.5)	5549 (37.8)
Sleep time	93,612 (26.4)	88,292 (26.0)	5320 (36.2)
Fruit and vegetable intake	63,882 (18.5)	60,721 (18.4)	3161 (22.5)
Oily fish intake	156,756 (44.2)	149,735 (44.1)	7021 (47.8)
Red meat intake	174,118 (49.7)	167,380 (49.8)	6738 (46.8)
Processed meat intake	112,094 (31.6)	107,355 (31.6)	4739 (32.3)
Lifestyle category, n (%)			
More healthy	152,734 (54.7)	147,875 (55.1)	4859 (46.2)
Moderately healthy	117,865 (42.2)	112,779 (42.0)	5086 (48.3)
Least healthy	8489 (3.0)	7907 (2.9)	582 (5.5)
Genetic risk category, n (%)			
Low	118,478 (33.4)	113,888 (33.5)	4590 (31.2)
Intermediate	118,295 (33.3)	113,420 (33.3)	4875 (33.1)

**Table 1** (continued)

Variables	Total (n=354,897)	Individuals without MDD (n=340,187)	Individuals with MDD (n=14,710)
High	118,124 (33.3)	112,879 (33.2)	5245 (35.7)
Air pollution, µg/m <sup>3</sup> (mean ± SD)			
PM <sub>2.5</sub>	9.98 ± 1.06	9.97 ± 1.06	10.13 ± 1.09
PM <sub>10</sub>	16.20 ± 1.90	16.20 ± 1.91	16.30 ± 1.88
NO <sub>2</sub>	26.41 ± 7.59	26.37 ± 7.58	27.22 ± 7.65
NO <sub>x</sub>	43.68 ± 15.55	43.60 ± 15.52	45.53 ± 16.05

Continues variables are displayed as means ± SD, and categorical variables are displayed as numbers (percentages)

Abbreviations: SD standard deviation, A/AS advanced, CSE Certificate of Secondary Education, GCSE General Certificate of Secondary Education, HNC Higher National Certificate, HND Higher National Diploma, NVQ National Vocational Qualification, BMI body mass index, MDD major depressive disorder, PM<sub>2.5</sub> fine particulate matter with diameter ≤2.5µm, PM<sub>10</sub> particulate matter with diameter ≤10µm, NO<sub>2</sub> nitrogen dioxide, NO<sub>x</sub> nitrogen oxides

**Table 2** Association between long-term exposure to air pollutants and major depressive disorder (MDD)

Air pollution	No. MDD cases/person-years	MDD HR (95% CI)	
		Model 1	Model 2
PM <sub>2.5</sub> , per 5-µg/m <sup>3</sup> increase	--	1.92 (1.79, 2.07)	1.16 (1.07, 1.26)
Q1	3075/880,978	1.00 (Ref.)	1.00 (Ref.)
Q2	3452/849,441	1.16 (1.11, 1.22)	1.08 (1.03, 1.13)
Q3	3885/858,381	1.30 (1.24, 1.36)	1.12 (1.06, 1.17)
Q4	4398/838,285	1.47 (1.40, 1.54)	1.11 (1.06, 1.17)
P for trend		<0.001	<0.001
PM <sub>10</sub> , per 10-µg/m <sup>3</sup> increase	--	1.30 (1.20, 1.41)	1.00 (0.92, 1.09)
Q1	3420/879,257	1.00 (Ref.)	1.00 (Ref.)
Q2	3741/868,525	1.11 (1.06, 1.16)	1.03 (0.98, 1.07)
Q3	3838/838,579	1.18 (1.12, 1.23)	1.05 (1.00, 1.10)
Q4	3711/840,723	1.14 (1.08, 1.19)	0.98 (0.94, 1.03)
P for trend		<0.001	0.610
NO <sub>2</sub> , per 10-µg/m <sup>3</sup> increase	--	1.15 (1.13, 1.17)	1.00 (0.98, 1.02)
Q1	3365/914,056	1.00 (Ref.)	1.00 (Ref.)
Q2	3688/879,294	1.14 (1.09, 1.19)	1.02 (0.98, 1.07)
Q3	3739/828,930	1.23 (1.17, 1.28)	1.02 (0.98, 1.07)
Q4	3918/804,805	1.32 (1.26, 1.39)	0.99 (0.94, 1.04)
P for trend		<0.001	0.695
NO <sub>x</sub> , per 20-µg/m <sup>3</sup> increase	--	1.15 (1.13, 1.17)	1.02 (1.01, 1.05)
Q1	3254/911,938	1.00 (Ref.)	1.00 (Ref.)
Q2	3620/970,880	1.17 (1.11, 1.22)	1.06 (1.01, 1.12)
Q3	3634/819,160	1.24 (1.19, 1.30)	1.05 (1.00, 1.11)
Q4	4202/825,106	1.43 (1.36, 1.50)	1.07 (1.02, 1.13)
P for trend		<0.001	0.017

Model 1: Unadjusted

Model 2: Adjusted for age, gender, ethnicity, education level, employment status, household income, and Townsend deprivation index

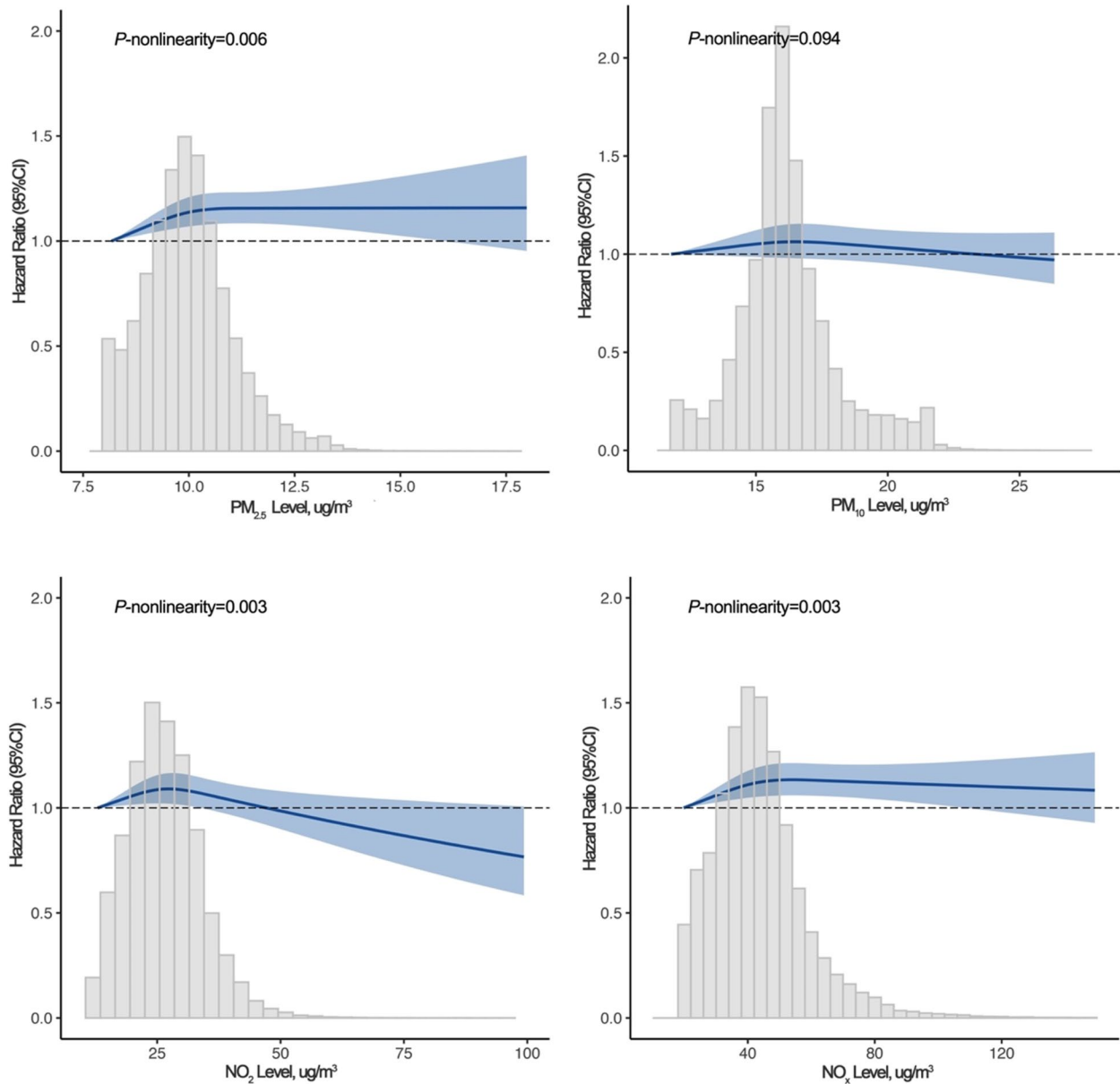
Abbreviations: MDD major depressive disorder, HR hazards ratio, CI confidence interval, PM<sub>2.5</sub> fine particulate matter with diameter ≤2.5µm, PM<sub>10</sub> particulate matter with diameter ≤10µm, NO<sub>2</sub> nitrogen dioxide, NO<sub>x</sub> nitrogen oxides, Ref reference

P value for trend calculated treating the air pollution concentrations (quartile) as a continuous variable

significant (P-interaction for PM<sub>2.5</sub>: 0.036; PM<sub>10</sub>: 0.025; NO<sub>2</sub>: 0.030; NO<sub>x</sub>: 0.080).

The risks of incident MDD according to lifestyle categories and lifestyle score are provided in Additional

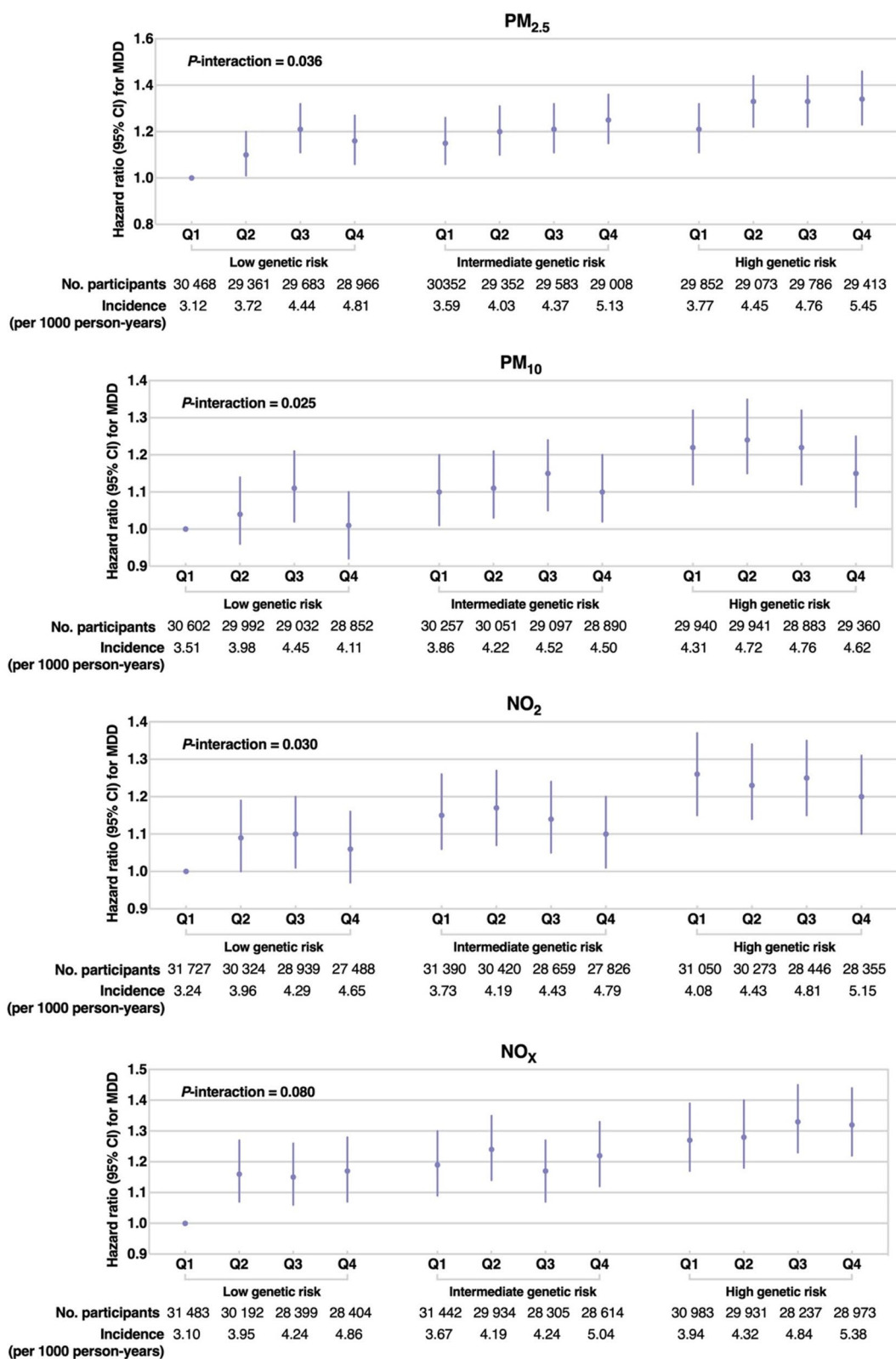
file 1: Table S16-S17. MDD risk increased monotonically across lifestyle categories and scores. The risk of incident MDD was 98% higher among those who have the least healthy lifestyle compared with those



**Fig. 1** Dose–response relationship of long-term exposure to air pollution and incident major depressive disorder (MDD). Multiple-adjusted hazard ratio (HR) for continuous air pollution is modeled using restricted cubic splines. Models are adjusted for age, gender, ethnicity, education level, employment status, household income, and Townsend deprivation index. The reference group is considered the minimum exposure level of air pollution in the entire population. Gray bars represent the distribution of the exposure levels in the entire population. The blue solid line indicates HR and the shaded area indicates a 95% confidence interval

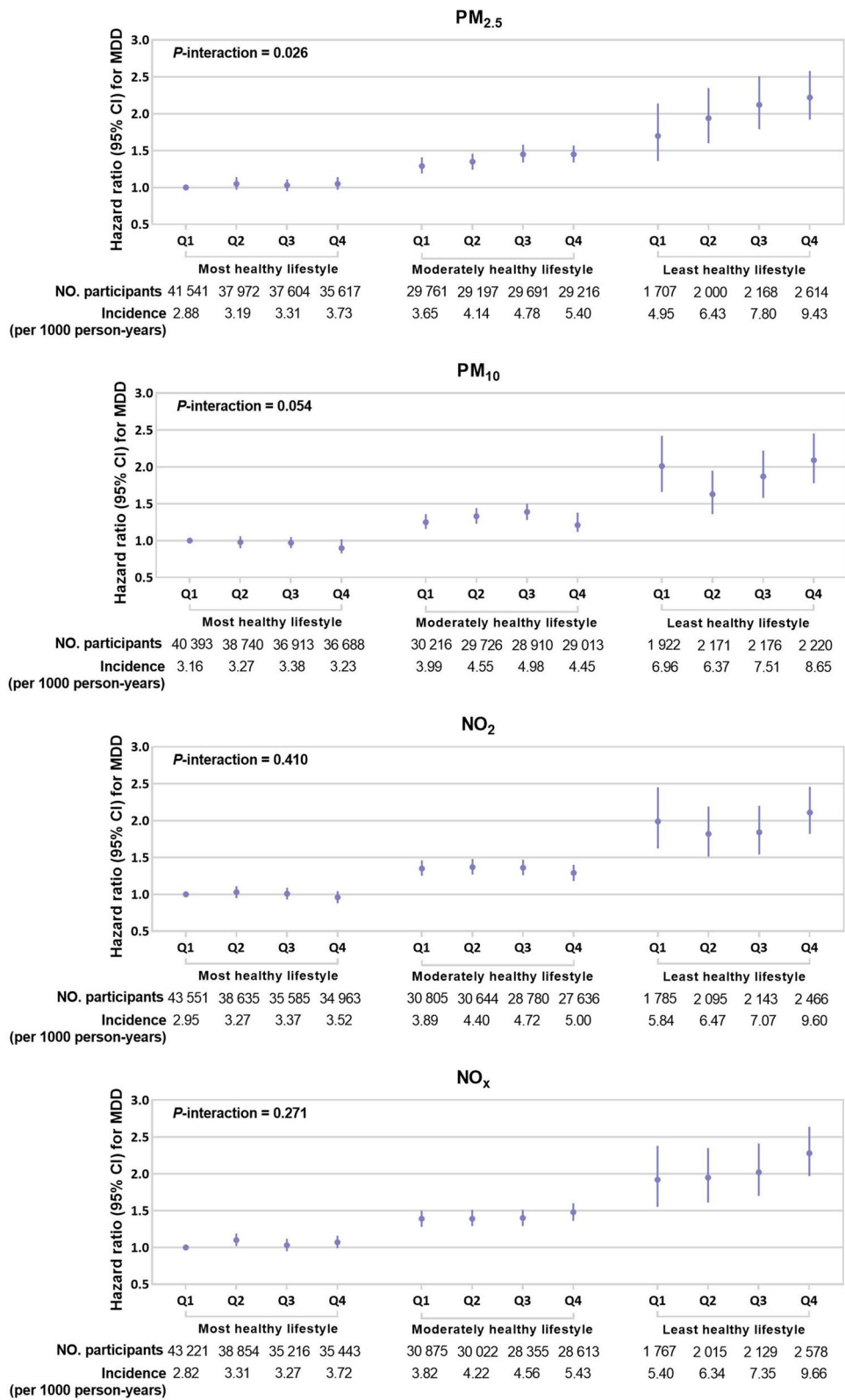
who have the most healthy lifestyle (HR: 1.98, 95% CI: 1.81–2.16). Figure 3 shows the risk of incident MDD for combined air pollutants and lifestyle. The highest MDD risk was observed in participants with the least healthy lifestyle and high PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, and NO<sub>x</sub> exposures (PM<sub>2.5</sub>: HR: 2.22, 95% CI: 1.92–2.58; PM<sub>10</sub>: HR: 2.09, 95% CI: 1.78–2.45; NO<sub>2</sub>: HR: 2.11, 95% CI:

1.82–2.46; NO<sub>x</sub>: HR: 2.28, 95% CI: 1.97–2.64). The interaction effects between lifestyle with PM<sub>2.5</sub> in relation to incident MDD risk were significant (*P*-interaction for PM<sub>2.5</sub>: 0.026; PM<sub>10</sub>: 0.054; NO<sub>2</sub>: 0.410; NO<sub>x</sub>: 0.271). The potential effect modifications of individual lifestyle factors on MDD risk are presented in Additional file 1: Table S18. We observed a significant



**Fig. 2** Joint associations of genetic risk score with incident major depressive disorder (MDD). Hazard ratios were adjusted for age, gender, ethnicity, education level, employment status, household income, and Townsend deprivation index. The interaction between genetic risk with air pollutants was tested by stratifying genetic risk





**Fig. 3** Joint associations of healthy lifestyle score with incident major depressive disorder (MDD). Hazard ratios were adjusted for age, gender, ethnicity, education level, employment status, household income, and Townsend deprivation index. The interaction between lifestyle with air pollutants was tested by stratifying lifestyle categories

interaction between  $PM_{2.5}$  and processed meat intake to MDD risk ( $P$ -interaction = 0.022).

## Discussion

In this large-scaled population-based longitudinal study, we found that long-term exposures to  $PM_{2.5}$  and  $NO_x$  were significantly associated with the incident MDD risk. The risk of incident MDD was higher among those with high genetic risk or unhealthy lifestyle compared with those with low genetic risk or healthy lifestyle. We also found significant interactions of genetic susceptibility and lifestyles with exposure to air pollution. Increased genetic susceptibility and unhealthy lifestyles may intensify the impact of long-term exposure to air pollution on the risk of MDD.

Research on the role of air pollution exposure in the development of MDD is limited. We comprehensively examined the association between long-term exposure to various air pollutants and the risk of incident MDD. We used air pollution data from 2010 to capture long-term air pollution exposure, consistent with previous research [12, 36–38]. Air pollution levels in England have been relatively stable over these years [39, 40]. As the fluctuation of the temporal trend of most air pollution was generally stable during the study period, the average values of air pollution could be used as a surrogate measure of long-term exposure [41]. The use of the average air pollution levels as the mean estimates in our sensitivity analysis further demonstrated the robustness of this approach. Our findings are consistent with those of previous studies. For example, in a prospective study of 27,270 participants in Korea, the researchers observed a 44% increase in the risk of MDD for each  $10\text{-}\mu\text{g}/\text{m}^3$  increase in  $PM_{2.5}$  levels [42]. Similarly, a nationwide prospective cohort study in the USA found an association between exposure to  $PM_{2.5}$  and the onset of depression [32]. Meanwhile, there are some other studies that are not consistent with our findings. For example, Zhang et al. discovered that long-term exposure to outdoor  $PM_{10}$  was associated with the development of depression; nevertheless, they did not find this association for  $PM_{2.5}$  [43]. Notably, previous studies lacked large-scale cohort settings and primarily examined particulate matter exposure (e.g.,  $PM_{2.5}$ ), excluding other gaseous pollutants (e.g.,  $NO_x$ ), which led to inconsistent results regarding the role of long-term exposure to air pollution in the development of MDD. Our study provides new evidence for epidemiological studies on the association between air pollutants and MDD. Our findings may have implications for policy regulation and clinical trials because changes in policies and individual behavior may help reduce air pollution and thus help mitigate symptoms of MDD.

There are some underlying mechanisms that could shed light on the associations of air pollution with MDD. One of the underlying mechanisms is that oxidative stress and neuroinflammation pathways induced by air pollutants could stimulate the onset and progression of MDD [44]. Air pollutants can penetrate the lung tissue compartments, enter the circulatory system, and reach the brain, causing oxidative stress and inflammation of the central nervous system [45]. In addition, experimental and animal studies have observed that inhalation of particulate matter could stimulate increased expression of redox/glucocorticoid-sensitive genes in rats, suggesting the involvement of the hormonal pathway in mental health disorders associated with particulate matter [46]. However, determining which pathway offers the most critical link is difficult because of the existing scarcity of particle-specific translocation kinetics and exposure levels [47]. In addition, vascular disease is an essential intermediate factor in the association between air pollution exposure and an increased risk of subsequent MDD. Increasing bodies of evidence demonstrate that exposure to air pollution leads to cerebrovascular disease, which may affect the central nervous system and the brain, contributing to an increased risk of depression and other related conditions [48]. Previous studies have also indicated that vascular disease is associated with inflammatory pathway activation, leading to MDD or dysthymia [49]. Additional studies are necessary to determine the precise mechanisms underlying the air pollution-induced pathogenesis of MDD.

Previous research demonstrated that the etiology of MDD is multifactorial and that its heritability is approximately 35% [9]. Research also demonstrated that PRS may serve as an early indicator of clinically significant levels of depression and be associated with the risk of depression [50]. Our results are consistent with these findings. Additionally, we investigated the contribution of genetic susceptibility to the association between air pollution and MDD and found that air pollution may increase the risk of MDD, particularly among individuals with high genetic susceptibility. Li et al. explored how  $PM_{2.5}$  exposure interacts with polygenic risk in the development of MDD across multiple levels of brain network function [51]. They observed that a combination of exposure to high levels of air pollution and a relatively high polygenic risk for MDD disproportionately augmented stress-related effects on the brain circuitry. Working memory and stress-related information transfer across cortical and subcortical brain networks were influenced by  $PM_{2.5}$  exposures to differing extents depending on the polygenic risk for MDD in gene-by-environment interactions [51]. However, other explanations for these mechanisms can be applied when they are separated into particular variants. Previous studies have

revealed that patients with psychiatric disorders had a higher mRNA expression level of vaccinia-related kinase 2 (*VRK2*) than did healthy individuals [52, 53]. In addition, a randomized crossover study suggested that higher  $PM_{2.5}$  exposure was positively associated with the mRNA expression of cytokine [54]. Therefore, air pollution may interact with rs1518395 located in *VRK2* to jointly affect the onset of MDD. In addition, some SNPs from an MDD GWAS, such as rs10514299, could be enriched in genes expressed in the central nervous system and function in transcriptional regulation related to neurodevelopment [10]. Because of their toxicity to the central nervous system, air pollutants may also contribute to the development of mental diseases [55]. Therefore, by affecting the central nervous system, SNPs and air pollution may contribute to the onset of depression. Accordingly, elucidating the pathophysiology of MDD is imperative.

In addition, we also confirmed that unhealthy lifestyles were associated with higher risks of MDD. Considering the complexity of health behaviors and that most health behaviors are interconnected, a comprehensive analysis of healthy lifestyles may better capture the impact of lifestyle than an analysis based on a single factor. Our findings are in concert with the previous studies. Adjibade and colleagues formulated a healthy lifestyle index that incorporates multiple lifestyle factors and discovered that combined healthy lifestyles were associated with a lower risk of depressive symptoms [56]. We also observed that the deleterious associations between  $PM_{2.5}$  and MDD were stronger among individuals who led unhealthy lifestyles. Indeed, besides long-term air pollution exposure may reach the brain through the lung–brain axis and induce systemic inflammation [57], unhealthy lifestyle factors have also been associated with elevated inflammation levels [58, 59]. Conversely, higher levels of systemic inflammation marker may contribute to the development of different neuropsychiatric disorders including depression [60]. Therefore, when air pollution and unhealthy lifestyle are employed together for MDD, it is reasonable to appear enhanced effect. These findings emphasize the importance of lifestyle changes. The benefit of air pollution exposure reduction in lowering the risk of MDD is expected to be greatest among individuals with healthy lifestyles; this finding can inform the establishment of personalized preventive strategies for reducing the risk of MDD.

To the best of our knowledge, our study is the first to evaluate the modifying effect of genetic susceptibility and lifestyles on the association between air pollution exposure and the risk of MDD. The main strengths of our study are its inclusion of a large sample size, prospective design, and consistent results in several sensitivity analyses. Nevertheless, we also acknowledge several limitations of our study. First, an exposure assessment based on a

single address does not eliminate the possibility of exposure misclassification caused by outside activities. Further studies with more accurate estimates are needed to confirm the present findings. In addition, we had to admit that the effect of the collinearity cannot be ruled out, single-pollutant associations may be not independent, and the results should be interpreted with caution. Second, common to most previous environmental epidemiology studies [12, 36–38], we used the annual average air pollution concentration in 2010 as a proxy for the long-term air pollution exposure, which might induce the exposure misclassification. However, previous studies have suggested that the fluctuation of the temporal trend of most air pollution was generally stable during the study period in UK Biobank [12, 61, 62]. Furthermore, of note, similar results were found when a time-varying air pollution exposure was used in the sensitivity analysis, supporting the validity of using the baseline concentration. In addition, the UK Biobank lacks data on air pollution composition; therefore, there is still uncertainty as to which components are the most harmful. Third, incident MDD cases are not always well captured through hospital inpatient records and death registries. Although diagnosis by a doctor is a more common and precise way, some mildly depressed people may do not go to the hospital, resulting in MDD cases that were likely to be underreported. Fourth, a sample of 500,000 was recruited in UK Biobank with remarkable speed and efficiency, but this efficiency was achieved at the expense of a response rate (5.5%) and was subject to selection bias. Nevertheless, the absolute difference in these estimates was low and lead to the practical importance of such risk underestimation is likely to be small [63]. Fifth, additional MDD-related variants may be identified in future GWAS, the inclusion of additional SNPs in further study may help to further refine the estimation of genetic risk. Sixth, although we have adjusted for a series of potential confounders in our analysis, potential residual confounding from unmeasured or unknown variables might still be present. Finally, because the majority of our study's participants were of European descent, the generalization of our findings regarding the associations of air pollution exposure and genetic susceptibility with MDD to other populations should be interpreted with caution.

## Conclusions

In summary, based on this large prospective cohort study, we found that long-term exposure to ambient air pollution was associated with a higher risk of MDD. High genetic risk and unhealthy lifestyle may intensify the impact of air pollution on MDD risk, highlighting the importance of identifying individuals with high genetic risk and developing healthy lifestyles for reducing the harm of air pollution to public mental health.

## Abbreviations

CI	Confidence interval
DAG	Directed acyclic graph
FCS	Fully conditional specification
GWAS	Genome-wide association study
HR	Hazards ratio
ICD-10	International Classification of Diseases, Tenth Revision
LUR	Land Use Regression
MDD	Major depressive disorder
NO <sub>2</sub>	Nitrogen dioxide
NO <sub>x</sub>	Nitrogen oxides
PCA	Principal component analysis
PM <sub>10</sub>	Particulate matter with aerodynamic diameter ≤ 10µm
PM <sub>2.5</sub>	Particulate matter with aerodynamic diameter ≤ 2.5µm
PRSs	Polygenic risk scores
SD	Standard deviation
SNPs	Single-nucleotide polymorphisms
VRK2	Vaccinia-related kinase 2

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-023-02783-0>.

**Additional file 1: Table S1.** Summary results of SNPs. **Table S2.** Variables used to create lifestyle score. **Table S3.** ICD-10 codes to assist in identifying MDD. **Table S4.** Summary statistics of air pollution data. **Table S5.** Sensitivity analysis by excluding MDD occurred in the first 2 years of follow-up. **Table S6.** Sensitivity analysis by excluding participants who live in the current address for less than 5 years. **Table S7.** Sensitivity analysis by excluding anxiety cases. **Table S8.** Sensitivity analysis by excluding dementia cases. **Table S9.** Sensitivity analysis after additional adjustment for other covariates. **Table S10.** Sensitivity analysis restricted to participants with complete covariates. **Table S11.** Sensitivity analysis was further linked primary care records. **Table S12.** Time-varying air pollution exposure and MDD. **Table S13.** Major principal components and MDD. **Table S14.** Stratified analysis by age and gender. **Table S15.** Genetic risk and MDD. **Table S16.** Lifestyle category and MDD. **Table S17.** MDD risk according to lifestyle score. **Table S18.** Stratified analysis by lifestyle factors. **Figure S1.** Flow chat. **Figure S2.** The description of time line. **Figure S3.** Directed Acyclic Graph. **Figure S4.** Schoenfeld residuals test for PM<sub>2.5</sub>. **Figure S5.** Schoenfeld residuals test for PM<sub>10</sub>. **Figure S6.** Schoenfeld residuals test for NO<sub>2</sub>. **Figure S7.** Schoenfeld residuals test for NO<sub>x</sub>. **Figure S8.** Pearson correlations between air pollution. **Figure S9.** Distribution of MDD genetic risk score.

## Acknowledgements

We thank the investigators of all the cohort studies included in this analysis for their hard work and dedication in collecting the underlying data. We also thank the study participants, whose time and commitment have transformed our understanding of health and disease.

## Authors' contributions

DKL and YHT designed the study. DKL, JQX, LLW, and YHT conducted the data analysis. DKL drafted the manuscript. YS, YHH, and YHT critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. All authors read and approved the final manuscript. The corresponding author attests that all the listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## Funding

None.

## Availability of data and materials

The data used in this current study are available from the UK Biobank data resources. Permissions are required in order to gain access to the UK Biobank data resources, subject to successful registration and application process. Further information can be found on the UK Biobank website (<https://www.ukbiobank.ac.uk/>).

## Declarations

### Ethics approval and consent to participate

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.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>Ministry of Education Key Laboratory of Environment and Health, and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, No.13 Hangkong Road, Wuhan 430030, China. <sup>2</sup>Department of Maternal and Child Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, No.13 Hangkong Road, Wuhan 430030, China. <sup>3</sup>Center for Statistics in Medicine, NDORMS, University of Oxford, The Botnar Research Centre, Oxford, UK. <sup>4</sup>Department of Otorhinolaryngology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China. <sup>5</sup>Department of Epidemiology and Biostatistics, School of Public Health, Peking University, No.38 Xueyuan Road, Beijing 100191, China.

Received: 17 March 2022 Accepted: 13 February 2023

Published online: 21 February 2023

## References

- Malhi GS, Mann JJ. Depression. *Lancet*. 2018;392(10161):2299–312.
- Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med*. 2011;9:90.
- Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry*. 2014;13(2):153–60.
- WHO: World Health Organization. The Global Burden of Disease: 2004 Update. 2008.
- Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int J Neuropsychopharmacol*. 2008;11(6):851–76.
- Vogelzangs N, Beekman AT, de Jonge P, Penninx BW. Anxiety disorders and inflammation in a large adult cohort. *Transl Psychiatry*. 2013;3:e249.
- Borrioni E, Pesatori AC, Bollati V, Buoli M, Carugno M. Air pollution exposure and depression: a comprehensive updated systematic review and meta-analysis. *Environ Pollut*. 2022;292(Pt A):118245.
- Ye J, Wen Y, Sun X, Chu X, Li P, Cheng B, et al. Socioeconomic deprivation index is associated with psychiatric disorders: an observational and genome-wide gene-by-environment interaction analysis in the UK Biobank cohort. *Biol Psychiatry*. 2021;89(9):888–95.
- Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. *Nat Rev Dis Primers*. 2016;2:16065.
- Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nat Genet*. 2016;48(9):1031–6.
- Fang Y, Scott L, Song P, Burmeister M, Sen S. Genomic prediction of depression risk and resilience under stress. *Nat Hum Behav*. 2020;4(1):111–8.
- Huang Y, Zhu M, Ji M, Fan J, Xie J, Wei X, et al. Air pollution, genetic factors, and the risk of lung cancer: a prospective study in the UK Biobank. *Am J Respir Crit Care Med*. 2021;204(7):817–25.
- Eid A, Mhatre I, Richardson JR. Gene-environment interactions in Alzheimer's disease: a potential path to precision medicine. *Pharmacol Ther*. 2019;199:173–87.
- Choi KW, Chen CY, Stein MB, Klimentidis YC, Wang MJ, Koenen KC, et al. Major Depressive Disorder Working Group of the Psychiatric Genomics C:

- Assessment of bidirectional relationships between physical activity and depression among adults: a 2-sample Mendelian randomization study. *JAMA Psychiatry*. 2019;76(4):399–408.
15. Boden JM, Fergusson DM. Alcohol and depression. *Addiction*. 2011;106(5):906–14.
  16. Wootton RE, Richmond RC, Stuijzand BG, Lawn RB, Sallis HM, Taylor GMJ, et al. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychol Med*. 2020;50(14):2435–43.
  17. Kim SR, Choi S, Keum N, Park SM. Combined effects of physical activity and air pollution on cardiovascular disease: a population-based study. *J Am Heart Assoc*. 2020;9(11):e013611.
  18. Lim CC, Hayes RB, Ahn J, Shao Y, Silverman DT, Jones RR, et al. Mediterranean diet and the association between air pollution and cardiovascular disease mortality risk. *Circulation*. 2019;139(15):1766–75.
  19. Baccarelli A, Kaufman JD. Ambient particulate air pollution, environmental tobacco smoking, and childhood asthma: interactions and biological mechanisms. *Am J Respir Crit Care Med*. 2011;184(12):1325–7.
  20. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
  21. Collins R. What makes UK Biobank special? *Lancet*. 2012;379(9822):1173–4.
  22. Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. Development of NO<sub>2</sub> and NO<sub>x</sub> land use regression models for estimating air pollution exposure in 36 study areas in Europe - the ESCAPE project. *Atmospher Environ*. 2013;72:10–23.
  23. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. Development of land use regression models for PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance, PM<sub>10</sub> and PM<sub>coarse</sub> in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol*. 2012;46(20):11195–205.
  24. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. Genome-wide genetic data on ~500,000 UK Biobank participants; 2017. p. 166298.
  25. Foster HME, Celis-Morales CA, Nicholl BI, Petermann-Rocha F, Pell JP, Gill JMR, et al. The effect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. *Lancet Public Health*. 2018;3(12):e576–85.
  26. Dregan A, Rayner L, Davis KAS, Bakolis I, de la Torre JA, Das-Munshi J, et al. Associations between depression, arterial stiffness, and metabolic syndrome among adults in the UK Biobank population study: a mediation analysis. *JAMA Psychiatry*. 2020;77(6):598–606.
  27. Sarkar C, Webster C, Gallacher J. Residential greenness and prevalence of major depressive disorders: a cross-sectional, observational, associational study of 94 879 adult UK Biobank participants. *Lancet Planet Health*. 2018;2(4):e162–73.
  28. Smith DJ, Nicholl BI, Cullen B, Martin D, Ul-Haq Z, Evans J, et al. Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PLoS One*. 2013;8(11):e75362.
  29. Nicholl BI, Mackay D, Cullen B, Martin DJ, Ul-Haq Z, Mair FS, et al. Chronic multisite pain in major depression and bipolar disorder: cross-sectional study of 149,611 participants in UK Biobank. *BMC Psychiatry*. 2014;14:350.
  30. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire*. *JAMA*. 1999;282(18):1737–44.
  31. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37–48.
  32. Kioumourtzoglou MA, Power MC, Hart JE, Okereke OI, Coull BA, Laden F, et al. The association between air pollution and onset of depression among middle-aged and older women. *Am J Epidemiol*. 2017;185(9):801–9.
  33. Wei F, Yu Z, Zhang X, Wu M, Wang J, Shui L, et al. Long-term exposure to ambient air pollution and incidence of depression: a population-based cohort study in China. *Soc Total Environ*. 2022;804:149986.
  34. Wu Y, Zhang S, Qian SE, Cai M, Li H, Wang C, et al. Ambient air pollution associated with incidence and dynamic progression of type 2 diabetes: a trajectory analysis of a population-based cohort. *BMC Med*. 2022;20(1):375.
  35. Wang Y, Wang K, Han T, Zhang P, Chen X, Wu W, et al. Exposure to multiple metals and prevalence for preeclampsia in Taiyuan, China. *Environ Int*. 2020;145:106098.
  36. Liu S, Jorgensen JT, Ljungman P, Pershagen G, Bellander T, Leander K, et al. Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. *Eur Respir J*. 2021;57(6):106267.
  37. Strak M, Weinmayr G, Rodopoulou S, Chen J, de Hoogh K, Andersen ZJ, et al. Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. *BMJ*. 2021;374:n1904.
  38. Liu S, Lim YH, Chen J, Strak M, Wolf K, Weinmayr G, et al. Long-term air pollution exposure and pneumonia-related mortality in a large pooled European cohort. *Am J Respir Crit Care Med*. 2022;205(12):1429–39.
  39. Department for Environment Food and Rural Affairs: Emissions of air pollutants in the UK, 1970 to 2017., Emissions of Air Pollutants in the UK, 1970 to 2017, 2019.
  40. Sheridan C, Klompaker J, Cummins S, James P, Fecht D, Roscoe C. Associations of air pollution with COVID-19 positivity, hospitalisations, and mortality: observational evidence from UK Biobank. *Environ Pollut*. 2022;308:119686.
  41. Li FR, Zhu B, Liao J, Cheng Z, Jin C, Mo C, et al. Ambient air pollutants and incident microvascular disease: a cohort study. *Environ Sci Technol*. 2022;56(12):8485–95.
  42. Kim KN, Lim YH, Bae HJ, Kim M, Jung K, Hong YC. Long-term fine particulate matter exposure and major depressive disorder in a community-based urban cohort. *Environ Health Perspect*. 2016;124(10):1547–53.
  43. Zhang Z, Zhao D, Hong YS, Chang Y, Ryu S, Kang D, et al. Long-term particulate matter exposure and onset of depression in middle-aged men and women. *Environ Health Perspect*. 2019;127(7):77001.
  44. Brites D, Fernandes A. Neuroinflammation and depression: microglia activation, extracellular microvesicles and microRNA dysregulation. *Front Cell Neurosci*. 2015;9:476.
  45. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci*. 2009;32(9):506–16.
  46. Thomson EM, Vladislavjevic D, Mohottalage S, Kumarathasan P, Vincent R. Mapping acute systemic effects of inhaled particulate matter and ozone: multiorgan gene expression and glucocorticoid activity. *Toxicol Sci*. 2013;135(1):169–81.
  47. Heusinkveld HJ, Wahle T, Campbell A, Westerink RHS, Tran L, Johnston H, et al. Neurodegenerative and neurological disorders by small inhaled particles. *Neurotoxicology*. 2016;56:94–106.
  48. Hahad O, Lelieveld J, Birklein F, Lieb K, Daiber A, Munzel T. Ambient air pollution increases the risk of cerebrovascular and neuropsychiatric disorders through induction of inflammation and oxidative stress. *Int J Mol Sci*. 2020;21(12):4306.
  49. Ziegelstein RC. Association of depression and cardiovascular disease: which comes first? *JAMA Cardiol*. 2017;2(6):702.
  50. Halldorsdottir T, Piechaczek C, Soares de Matos AP, Czamara D, Pehl V, Wagenbuechler P, et al. Polygenic risk: predicting depression outcomes in clinical and epidemiological cohorts of youths. *Am J Psychiatry*. 2019;176(8):615–25.
  51. Li Z, Yan H, Zhang X, Shah S, Yang G, Chen Q, et al. Air pollution interacts with genetic risk to influence cortical networks implicated in depression. *Proc Natl Acad Sci U S A*. 2021;118(46):e2109310118.
  52. Edwards SL, Beesley J, French JD, Dunning AM. Beyond GWAS: illuminating the dark road from association to function. *Am J Hum Genet*. 2013;93(5):779–97.
  53. Li M, Yue W. VRK2, a candidate gene for psychiatric and neurological disorders. *Mol Neuropsychiatry*. 2018;4(3):119–33.
  54. Chen R, Li H, Cai J, Wang C, Lin Z, Liu C, et al. Fine particulate air pollution and the expression of microRNAs and circulating cytokines relevant to inflammation, coagulation, and vasoconstriction. *Environ Health Perspect*. 2018;126(1):017007.
  55. Buoli M, Grassi S, Caldiroli A, Carnevali GS, Mucci F, Iodice S, et al. Is there a link between air pollution and mental disorders? *Environ Int*. 2018;118:154–68.
  56. Adijbade M, Lemogne C, Julia C, Hercberg S, Galan P, Assmann KE, et al. Prospective association between combined healthy lifestyles and risk

- of depressive symptoms in the French NutriNet-Sante cohort. *J Affect Disord.* 2018;238:554–62.
57. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol.* 2008;36(2):289–310.
  58. Shiels MS, Katki HA, Freedman ND, Purdue MP, Wentzensen N, Trabert B, et al. Cigarette smoking and variations in systemic immune and inflammation markers. *J Natl Cancer Inst.* 2014;106(11):dju294. <https://doi.org/10.1093/jnci/dju294>.
  59. Dias JA, Wirfalt E, Drake J, Gullberg B, Hedblad B, Persson M, et al. A high quality diet is associated with reduced systemic inflammation in middle-aged individuals. *Atherosclerosis.* 2015;238(1):38–44.
  60. Pasco JA, Nicholson GC, Williams LJ, Jacka FN, Henry MJ, Kotowicz MA, et al. Association of high-sensitivity C-reactive protein with de novo major depression. *Br J Psychiatry.* 2010;197(5):372–7.
  61. Furlong MA, Klimentidis YC. Associations of air pollution with obesity and body fat percentage, and modification by polygenic risk score for BMI in the UK Biobank. *Environ Res.* 2020;185:109364.
  62. Li X, Wang M, Song Y, Ma H, Zhou T, Liang Z, et al. Obesity and the relation between joint exposure to ambient air pollutants and incident type 2 diabetes: a cohort study in UK Biobank. *PLoS Med.* 2021;18(8):e1003767.
  63. Stamatakis E, Owen KB, Shepherd L, Drayton B, Hamer M, Bauman AE. Is cohort representativeness passe? Poststratified associations of lifestyle risk factors with mortality in the UK Biobank. *Epidemiology.* 2021;32(2):179–88.

### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

