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# Associations between multiple ambient air pollutants, genetic risk, and incident mental disorders: An interaction study in the UK population

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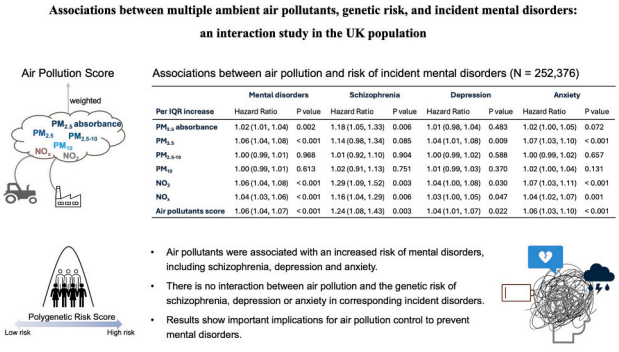
## HIGHLIGHTS

- Air pollutants were associated with a higher risk of incident mental disorders.
- Risk of incident schizophrenia, depression, and anxiety were assessed specifically.
- Genetic risks of schizophrenia, depression and anxiety did not alter the associations.
- Air pollution control is important for the prevention of mental disorders.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Mental disorders can be triggered by genetic and environmental risk factors. Limited studies have explored the effects of long-term exposure to air pollution on mental disorders, and most of the studies have focused on individual air pollutants. This study aimed to examine the relationship between long-term exposure to multiple air pollutants and incident mental disorders, including depression, anxiety, and schizophrenia, and whether the associations were affected by genetic susceptibility. Participants in the UK Biobank with no history of mental disorders were followed from baseline (2006 to 2010) to October 31st, 2022. Cox regression was applied to evaluate the correlation between $PM_{2.5}$ absorbance, $PM_{2.5}$, $PM_{2.5–10}$, $PM_{10}$, $NO_2$, and NOx and any or specific mental disorders. Additive and multiplicative scales were used to measure the interaction between air pollution and schizophrenia polygenic risk score (PRS), depression PRS, or anxiety PRS on specific mental diseases. After a median of 13.36 years of follow-up on 252,376 participants, we observed per interquartile increase of $PM_{2.5}$ absorbance (0.32 per meter), $PM_{2.5}$ (1.28 μg/m$^3$), $NO_2$ (10.08 μg/m$^3$), and $NO_x$ (16.78 μg/m$^3$) were related to a

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2–6 % higher risk of incident mental disorders. The HR (95 % CI) of incident mental disorder for the 2nd, 3rd, and 4th quartile of the air pollution score were 1.05 (1.01–1.18), 1.13 (1.09–1.18), and 1.14 (1.09–1.19), respectively, in comparison to the lowest level of the score. Per interquartile increase in the air pollution score was associated with a 6 %, 24 %, 4 %, and 6 % higher risk of incident mental disorders, schizophrenia, depression, and anxiety, respectively. No interaction between air pollution and genetic risk of schizophrenia, depression or anxiety on corresponding incident disorders was observed. These findings emphasize the importance of implementing air pollution control standards to decrease the burden of mental disorders.

## 1. Introduction

Systematic reviews have demonstrated that mental disorders introduce an increased risk of premature mortality (Plana-Ripoll et al., 2019). In terms of disability-adjusted life years (DALYs), the global number of DALYs due to mental disorders increased by 55 % between 1990 and 2019, moving from the 13th to the 7th leading cause (GBD, 2019). Mental disorders contribute to a significant burden of disease worldwide (Adorjan and Falkai, 2019). In 2019, depressive disorders, anxiety disorders, and schizophrenia were recognised as the top three specific mental disorders (GBD, 2019). Identifying risk factors for mental disorders and intervening effectively would, therefore, be an important public health priority to reduce their risks and burden on healthcare and economics.

Ambient air pollution is one of the most significant health threats (World Health Organization, 2023). Excess risks of cardiovascular disease, respiratory disease and cancers caused by ambient air pollution have been widely reported (Landrigan et al., 2018; Cohen et al., 2017; Figueres et al., 2018). In recent years, air pollutants' effects on the central nervous system have been increasingly recognised (Buoli et al., 2018). Mechanisms indicated that different air pollutants could induce neuroinflammation and oxidative stress, a plausible pathogenesis of mental disorders, through various pathways (Hurley and Tizabi, 2013; Szymkowicz et al., 2023; Lyons et al., 2024; Lundberg and Weitzberg, 2022; Adar et al., 2014). Distinct mental disorders may involve different biological pathways and exhibit varying susceptibility to air pollutants (Thomson, 2019; Dantzer et al., 2008; Hasler, 2010; Marsman et al., 2013; McCutcheon et al., 2023; Braithwaite et al., 2019). Recent studies have investigated the relationship between air pollution and mental well-being. Nevertheless, there was a lack of achieved consensus on associations between air pollution and certain mental disorders, such as depression, anxiety or schizophrenia, due to variations in outcome identification and study design (Braithwaite et al., 2019; Fan et al., 2020). Ambient air pollution is a complex mixture of particulate matter and gaseous pollutants. However, previous studies have primarily discussed the individual effects of single air pollutants, especially particulate matter (Braithwaite et al., 2019; Zeng et al., 2019; Nobile et al., 2023). Exploring the compound effects of this mixture on incident mental disorders will be crucial to gaining a more comprehensive understanding of how air pollution affects mental well-being.

Recent studies have suggested the existence of an interplay between genetic predisposition and environmental factors in the risk of chronic disease (Peters et al., 2021). It is well known that the occurrence and development of mental disorders are influenced by genetic and environmental risk factors (Assary et al., 2018). Genome-wide association studies (GWAS) have identified hundreds of potential genetic risk variants of several mental disorders, such as schizophrenia, depression, and anxiety (Howard et al., 2019; O'Donovan et al., 2008; Li et al., 2024). These genetic determinants would preliminarily identify at-risk individuals in the pre-disease stage. Nevertheless, it is unclear to what extent genetic predisposition affects the relationship between concurrent exposure to certain air contaminants and the development of specific mental disorders. Consequently, there is a need to explore the combined effects of genetic and environmental risk factors to improve the risk assessment for mental disorders.

The primary objective of this study is to investigate the association between long-term exposure to multiple air pollutants and any or specific mental disorders, including schizophrenia, depression and anxiety, with data from a national longitudinal cohort in the UK. Additionally, we aim to examine whether genetic predisposition interacts with air pollution and thus alters the associations between air pollution and specific mental disorders.

## 2. Methods

### 2.1. Study population and data source

The study's data was sourced from the UK Biobank, a nationwide prospective cohort of over 500,000 people in the UK who were initially recruited between 2006 and 2010 when they were aged 40 to 69. The UK Biobank collected comprehensive information about participants through questionnaires, physical assessments, and biological sampling, allowing for a thorough understanding of their phenotypic characteristics. Participants' genotypic information was collected, and longitudinal health outcomes were obtained through data linkage from various sources, including self-reports, primary care records, hospital admissions, cancer register, and death records.

We collected participants with information on air pollutants, excluded participants without complete information on covariates and excluded those who had any mental disorders at baseline. The flowchart for participant selection was shown in Fig. 1. We followed the eligible participants from the date of baseline assessment until the date of death, the earliest date of diagnosis of mental disorders, or 31st October 2022, whichever came first.

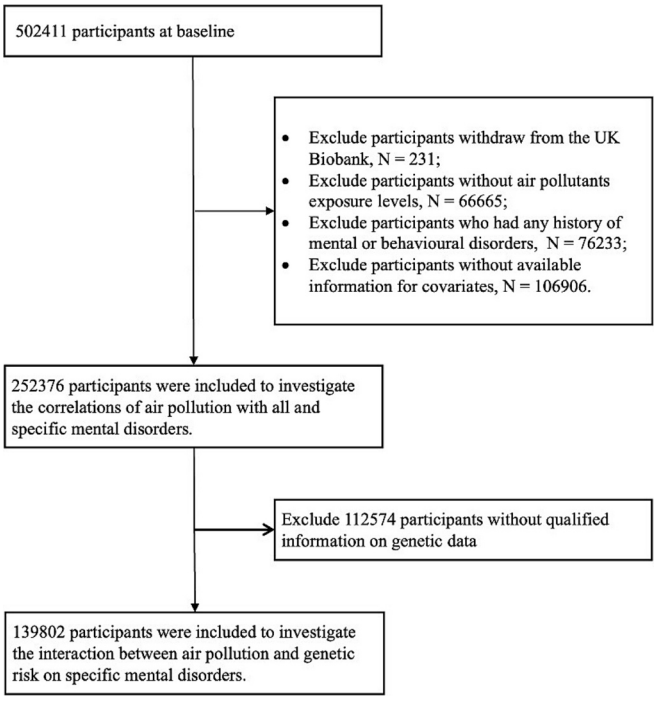


**Fig. 1.** Flowchart of study population selection.

### 2.2. Estimation of air pollutants and air pollution score

Estimates of ambient air pollutants for each residential baseline address with a 100 m*100 m resolution, including $PM_{2.5}$ absorbance (a proxy for elemental carbon) (Eeftens et al., 2012a), $PM_{2.5}$, $PM_{2.5–10}$, $PM_{10}$, $NO_2$, and NOx were assessed by the UK Biobank, using a Land Use Regression (LUR) model developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE, http://www.escapeproject.eu/) for the year 2010 (Eeftens et al., 2012b). The annual average concentrations of these six pollutants in 2010 were used to determine the air pollutant exposure levels for each individual. The LUR model was widely employed in high-impact research (Wolf et al., 2021; Cesaroni et al., 2014; Khomenko et al., 2021). We did not use air pollutant estimates provided by the UK Department for Environment, Food and Rural Affairs (DEFRA), because the LUR model was cost-effective and provided higher resolution data compared to the DEFRA's model (100 m*100 m vs 1 km*1 km) (Hoek et al., 2008; UK Air, 2022). In addition, the LUR model was able to generate exposure estimates for particulate matter components such as absorbance and ultrafine particulate matter, which were not available in DEFRA's data, and thus served the purpose of our research to better understand how these contaminants affect health (de Hoogh et al., 2013). Additionally, we constructed weighted air pollution scores to measure the combination effects of air pollutants. The score was calculated by adding the concentrations of each air pollutant and weighting them using the multivariable-adjusted risk estimates (β coefficients). These β coefficients originated from the adjusted associations between each air pollutant and any or specific mental disorders conducted in the primary analysis (detailed in Section 2.5). Previous research on UK Biobank data has made considerable use of this score to evaluate the link between concurrent exposure to cumulative air pollutants and the risk of diseases, e.g. chronic heart failure and rheumatoid arthritis (Zhang et al., 2023; Wang et al., 2021).

$$\begin{aligned}\text{Air pollution score} = &\left[\beta_{PM_{2.5\ absorbance}} \times PM_{2.5\ absorbance} + \beta_{PM_{2.5}} \times PM_{2.5}\right.\\ &+ \beta_{PM_{2.5-10}} \times PM_{2.5-10} + \beta_{PM_{10}} \times PM_{10} + \beta_{NO_2} \times NO_2\\ &\left.+ \beta_{NO_x} \times NO_x\right] \times \left[6 \Big/ \left(\beta_{PM_{2.5\ absorbance}} + \beta_{PM_{2.5}} + \beta_{PM_{2.5-10}}\right.\right.\\ &\left.\left.+ \beta_{PM_{10}} + \beta_{NO_2} + \beta_{NO_x}\right)\right]\end{aligned}$$

### 2.3. Outcome and covariate

The study identified the first instance of the incident mental disorders using the International Classification of Disease-10 (ICD-10), F00-F99, determined by self-reports, primary care records, hospital admissions, and death records (Liu et al., 2024; Gao et al., 2017). At the baseline assessment (and at follow-up assessments if they attended them), participants were asked to self-report all doctor-diagnosed health conditions. Their responses were further checked and verified by a nurse through a verbal interview. All self-reported diagnosed conditions and diagnoses from other sources were coded to the 3-character ICD-10 codes where appropriate (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=593). Given the high prevalence in the general population (GBD, 2019; Liu et al., 2024), we also examined three specific mental disorders, including schizophrenia (F20-F29) (Gao et al., 2017; Newbury et al., 2021), depression (F32) (Fu et al., 2022), and anxiety (F40-F41) (Liu et al., 2024), were also examined. The study used a directed acyclic graph (DAG, https://dagitty.net/dags.html#) to identify the minimal sufficient adjustments. Several potential covariates, including sex, ethnicity, age at the baseline, educational attainment, duration of residence at the current address, family income before taxes, employment status, Townsend deprivation index, level of physical activity, and percentage of green space coverage within a 300-m radius of the residence were considered (Supplementary Fig. 1). We used the Townsend deprivation index as the small area-level socioeconomic indicator. The deprivation index was calculated based on output areas from the most recent national census before participants were enrolled in the UK Biobank. These output areas have measures including households car ownership; households overcrowding; households owner occupation and persons unemployed. A higher deprivation score indicates greater socioeconomic deprivation (Foster et al., 2018; Blane et al., 1987).

### 2.4. Polygenetic risk score for schizophrenia, depression and anxiety

The UK Biobank offers a comprehensive repository of genetic data on research subjects. Genotyping was conducted using the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix, and Applied Biosystems UK Biobank Axiom Array covered 95 % of the gene sites (Bycroft et al., 2018). For the remaining 5 % of unique single-nucleotide polymorphisms (SNPs), imputation was performed using SHAPEIT3 and IMPUTE2 algorithms. The Haplotype Reference Consortium data was used as the main reference panel for imputation (Bycroft et al., 2018). We determined the polygenic risk scores (PRS) of schizophrenia, anxiety, and depression via the summary statistics from meta-analyses of GWAS excluding UK Biobank participants (Howard et al., 2019; Wray et al., 2018). This is to avoid sample overlap between base (i.e., the summary statistics) and target (UK Biobank) datasets. Summary statistics of these meta-analyses are available in the Psychiatric Genomics Consortium (schizophrenia: scz2022; anxiety: anx2016; depression: mdd2018_noUKBB) (Trubetskoy et al., 2022; Otowa et al., 2016; Adams, 2022). We excluded SNP with a low minor allele frequency of $<0.005$ and a low imputation accuracy of $<0.1$. We removed participants with non-European ancestry and those who are genetically correlated. We used all cases of specific mental disorders up until the end of follow-up to derive the PRS, with PRSice 2.0 program (Euesden et al., 2015). The clumping threshold was set as $P = 1$, linkage disequilibrium score $r^2 = 0.25$, and distance threshold = 250 kb (Shen et al., 2020). *P*-value cut-offs for thresholding SNPs in the summary statistics were set at 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, and 1. We used the PRS derived from the best-fit *p*-value cut-off threshold, which provided the highest R-squared value for prediction, in our genetic interaction analysis.

### 2.5. Statistical analysis

Continuous variables were reported as means with standard deviations (SD) or median with interquartile range (IQR). Categorical variables were reported as frequencies and percentages. We used the Cox regression model to evaluate the correlation of individual air pollutants and air pollution score with all or specific incident mental disorders, including schizophrenia, depression and anxiety, respectively. Based on the quartiles of the exposures, we sorted the individuals into four groups; the reference group was the group with the lowest exposure (the first quartile). Additionally, for each IQR increase in the exposures, the associated hazard ratio (HR) was computed. We conducted analyses using both crude HR and HR adjusted for potential covariates. The crude model was controlled for age (in a linear term) and sex. The adjusted model was controlled for ethnicity (White and non-White), annual family income before tax (< £18,000, £18,000 to £30,999, £31,000 to £51,999, £52,000 to £100,000, and £100,000 above), the highest educational qualification (University or college, A-level, GSCE and other), employment status (unemployed, employed and retired), duration of residence at the current address (in quintiles) and the Townsend deprivation index (in quintiles), physical activity level (light, medium, and heavy, categorised by the International Physical Activity Questionnaire) and percentage of green space coverage within 300 m buffer surrounding the participants' residential addresses. Furthermore, we applied Spearman's correlation coefficients to assess the correlations between different air pollutants. Additionally, we investigated whether the associations between air pollution and mental disorders varied by sex (female and male), age (≤55 years, 55 to 65 years and > 65 years), physical activity (low, medium and high-level activity), and small-area deprivation (low and high-level of Townsend deprivation index)

through interaction analyses. We also conducted stratified analyses by these factors.

To examine the possible interaction between air pollutants and PRS on the development of specific mental disorders, we created a categorical variable based on quartiles of the air pollution score and a dichotomised categorical variable for PRS (by the median). The reference group for comparison consisted of individuals with low PRS risk and exposure levels in the first quartile of the air pollution score. The Relative Excess Risk due to Interaction (RERI) was the indicator used to quantify additive interaction (Richardson and Kaufman, 2009). Zero on the RERI scale denotes the absence of additive interaction. A positive additive interaction is indicated by an RERI greater than zero. A negative additive interaction is indicated by an RERI less than zero. The significance of the interaction term in the regression model served as a proxy for the multiplicative scale of interactive effects (Yao et al., 2024). Age, sex, ethnicity, family income, educational attainment, employment status, duration of residence at the current address, Townsend deprivation index, physical activity level, percentage of green space coverage within 300 m buffer at the participants' addresses, and the leading 10 genetic principal components (PCs) were adjusted.

### 2.6. Sensitivity analysis

First, we restricted the diagnoses of any mental disorder to 3 years after the baseline survey to minimise the reverse causality effect on the observed associations. Second, we conducted a sensitivity analysis for participants who lived in the baseline address for at least five years to assess whether the relocation affected the main findings of air pollution and mental disorders. Third, we further adjusted for the average 24-h noise level (dB), which was modelled at the year 2009 with a version of the CNOSSOS-EU model (Kephalopoulos et al., 2014; Kephalopoulos et al., 2012). Fourth, we estimated the effects of the air pollution score on incident mental disorders with the participants whose PRSs for schizophrenia, depression and anxiety were available. Finally, to account for the influence of small-area climate factors (Thompson et al., 2023; Li et al., 2023), we controlled for the clustering effects of the 22 UK Biobank assessment centres as a sensitivity analysis. These centres are distributed across Scotland, England, and Wales, covering a majority of the cities in the UK. Participants took the baseline assessment at the assessment centre within 40 km of their residential address (Fry et al., 2017).

We used R software (version 4.3.1) for statistical analyses, with the *"survival"* package employed to analyse the Cox regression and the *"interactionR"* package used to calculate the interaction effects.

## 3. Results

We included 252,376 participants in the current study to assess the association between residential air pollution and incident mental disorders. Characteristics of participants with and without complete covariate information were shown in Supplementary Table 1. It indicated that there was no significant difference between the participants before and after the exclusion (Cohen, 1988; Austin, 2009). The characteristics of the analytic population were described (Table 1). The participants have lived at their current addresses for 17.21 ± 11.71 (mean ± SD) years. The participants' average age was 56.19 ± 8.14 years, with 90.9 % being White. The average percentage of green space coverage within a 300-m buffer surrounding the residential address was 35.52 ± 23.58. The distribution of air pollutants was shown in Fig. 2. Air pollutants' concentrations were correlated, with high correlations ($r > 0.8$) observed between $PM_{2.5}$ absorbance and $NO_2$ ($r = 0.84$), $PM_{2.5}$ and $NO_2$ ($r = 0.85$), $PM_{2.5}$ and $NO_x$ ($r = 0.88$), and $NO_2$ and $NO_x$ ($r = 0.92$).

After a median of 13.36 (IQR: 12.51–14.10) years follow-up, we observed 35,819 incidents of mental disorders, with 358 incidents of schizophrenia, 9586 incidents of depression and 10,227 incidents of anxiety. The adjusted and crude associations between air pollution and incident mental disorders were shown in Table 2 and Supplementary Table 2. Table 2 shows that per IQR increases in exposure to $PM_{2.5}$ absorbance (0.32 per meter), $PM_{2.5}$ (1.28 μg/m$^3$), $NO_2$ (10.08 μg/m$^3$), and $NO_x$ (16.78 μg/m$^3$) were associated with a higher risk of incident overall mental disorders ($PM_{2.5}$ absorbance: HR = 1.02, 95 % CI: 1.01–1.04; $PM_{2.5}$: HR = 1.06, 95 % CI: 1.04–1.08; $NO_2$: HR = 1.06, 95 % CI: 1.04–1.08; and $NO_x$: HR = 1.04, 95 % CI: 1.03–1.06). Specifically, $PM_{2.5}$ absorbance, $NO_2$, and $NO_x$ were associated with a higher risk of schizophrenia ($PM_{2.5}$ absorbance: HR = 1.18, 95 % CI: 1.05–1.33; $NO_2$: HR = 1.29, 95 % CI: 1.09–1.52; and $NO_x$: HR = 1.16, 95 % CI: 1.04–1.29). Per IQR increase in $PM_{2.5}$, $NO_2$ and $NO_x$ were correlated with an increased risk of depression ($PM_{2.5}$: HR = 1.04, 95 % CI:1.01–1.08; $NO_2$: HR = 1.04, 95 % CI:1.00–1.08; and $NO_x$: HR = 1.03, 95 % CI:1.00–1.05) and anxiety ($PM_{2.5}$: HR = 1.07, 95 % CI:1.03–1.10; $NO_2$: HR = 1.07, 95 % CI:1.03–1.11; and $NO_x$: HR = 1.04, 95 % CI:1.02–1.07). $PM_{2.5-10}$ and $PM_{10}$ were not associated with overall or specific mental disorders.

The associations between air pollution scores and incident mental disorders were described in Table 3. In comparison to the first quartile of air pollution score, the second (HR = 1.05, 95 % CI: 1.01–1.18), third (HR = 1.13, 95 % CI: 1.09–1.18) and fourth (HR = 1.14, 95 % CI: 1.09–1.19) quartile of the score were related to a larger risk of incident mental disorders. Similar associations were observed between the air pollution score and incident anxiety. Participants with exposure in the 3rd and 4th quartile of air pollution score were associated with an increased risk of depression (3rd quartile: HR = 1.12, 95 % CI: 1.04–1.20; 4th quartile: HR = 1.10, 95 % CI: 1.02–1.19), compared to the 1st quartile. No associations were observed for the quartile groups of air pollution score and schizophrenia. In addition, an interquartile increase in the air pollution score was associated with 6 % (HR = 1.06, 95

**Table 1**
Characteristics of the study population at baseline (2006–2010).

| | N (%) |
|---|---|
| | 252,376 |
| Age, years, Mean (SD) | 56.19 (8.14) |
| Sex | |
| Female | 125,671 (49.8) |
| Male | 126,705 (50.2) |
| Ethnicity | |
| White | 229,533 (90.9) |
| Non-white | 22,843 (9.1) |
| Length of living in current address, Mean (SD) | 17.21 (11.71) |
| Qualification | |
| University or college | 93,915 (37.2) |
| A-levels or equivalent | 30,255 (12.0) |
| GCSEs or equivalent | 67,373 (26.7) |
| Other | 60,833 (24.1) |
| Household income | |
| Less than £18,000 | 48,719 (19.3) |
| £18,000 to £30,999 | 62,563 (24.8) |
| £31,000 to £51,999 | 67,737 (26.8) |
| £52,000 to 100,000 | 57,069 (22.6) |
| >100,000 | 16,288 (6.5) |
| Employment status | |
| Employed | 164,604 (65.2) |
| Retired | 77,494 (30.7) |
| Unemployed | 10,278 (4.1) |
| Townsend Deprivation Index | |
| Qn1 (least deprived) | 50,490 (20.0) |
| Qn2 | 50,462 (20.0) |
| Qn3 | 50,475 (20.0) |
| Qn4 | 50,475 (20.0) |
| Qn5 (most deprived) | 50,474 (20.0) |
| Physical activity | |
| Low | 45,851 (18.2) |
| Medium | 103,493 (41.0) |
| High | 103,032 (40.8) |
| Green space coverage, Mean (SD) | 35.52 (23.58) |

SD: standard deviation; Qn: Quantile.

| Air Pollutants | Minimum | 1st quartile | Mean | 3rd quartile | Maximum | $PM_{2.5}$ absorbance | $PM_{2.5}$ | $PM_{2.5-10}$ | $PM_{10}$ | $NO_2$ | NOx |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $PM_{2.5}$ absorbance | 0.83 | 0.99 | 1.19 | 1.31 | 4.60 | 1.00 | | | | | |
| $PM_{2.5}$ | 8.17 | 9.26 | 9.96 | 10.54 | 21.31 | 0.63 | 1.00 | | | | |
| $PM_{2.5-10}$ | 5.57 | 5.84 | 6.42 | 6.62 | 12.82 | 0.45 | 0.28 | 1.00 | | | |
| $PM_{10}$ | 11.78 | 15.22 | 16.20 | 16.99 | 31.39 | 0.57 | 0.58 | 0.77 | 1.00 | | |
| $NO_2$ | 12.93 | 21.18 | 26.55 | 31.26 | 108.49 | 0.84 | 0.85 | 0.30 | 0.55 | 1.00 | |
| NOx | 19.74 | 33.82 | 43.67 | 50.60 | 265.94 | 0.73 | 0.88 | 0.30 | 0.56 | 0.92 | 1.00 |

**Fig. 2.** Air pollutant concentrations and their correlations
Footnotes: The units for $PM_{2.5}$, $PM_{2.5–10}$, $PM_{10}$, $NO_2$, and $NO_x$ are μg/m$^3$. The unit for $PM_{2.5}$ absorbance is per metre.

**Table 2**
Associations between individual air pollutants and the risk of incident mental disorders.

| Air pollutants | | Mental disorders Cases = 35,819 | | Schizophrenia Cases = 358 | | Depression Cases = 9568 | | Anxiety Cases = 10,227 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Hazard ratio | *P* value | Hazard ratio | *P* value | Hazard ratio | *P* value | Hazard ratio | *P* value |
| $PM_{2.5}$ Absorbance | 1st quartile | Reference | | Reference | | Reference | | Reference | |
| | 2nd quartile | 1.06 (1.02, 1.09) | 0.001 | 1.03 (0.74, 1.43) | 0.864 | 1.08 (1.01, 1.14) | 0.017 | 1.10 (1.03, 1.16) | 0.002 |
| | 3rd quartile | 1.10 (1.06, 1.14) | < 0.001 | 1.16 (0.82, 1.64) | 0.393 | 1.08 (1.02, 1.16) | 0.014 | 1.17 (1.10, 1.25) | < 0.001 |
| | 4th quartile | 1.08 (1.04, 1.12) | < 0.001 | 1.39 (0.98, 1.98) | 0.064 | 1.05 (0.98, 1.12) | 0.203 | 1.09 (1.02, 1.16) | 0.012 |
| | P for trend | | < 0.001 | | 0.032 | | 0.498 | | 0.035 |
| | Per IQR increase | 1.02 (1.01, 1.04) | 0.002 | 1.18 (1.05, 1.33) | 0.006 | 1.01 (0.98, 1.04) | 0.483 | 1.02 (1.00, 1.05) | 0.072 |
| $PM_{2.5}$ | 1st quartile | Reference | | Reference | | Reference | | Reference | |
| | 2nd quartile | 1.06 (1.03, 1.10) | 0.001 | 1.44 (0.99, 2.10) | 0.057 | 1.07 (1.00, 1.14) | 0.068 | 1.13 (1.06, 1.21) | < 0.001 |
| | 3rd quartile | 1.10 (1.06, 1.14) | < 0.001 | 1.51 (1.00, 2.28) | 0.047 | 1.11 (1.03, 1.19) | 0.008 | 1.15 (1.07, 1.24) | < 0.001 |
| | 4th quartile | 1.13 (1.09, 1.18) | < 0.001 | 1.85 (1.21, 2.84) | 0.005 | 1.13 (1.04, 1.22) | 0.003 | 1.21 (1.12, 1.31) | < 0.001 |
| | P for trend | | < 0.001 | | 0.007 | | 0.003 | | < 0.001 |
| | Per IQR increase | 1.06 (1.04, 1.08) | < 0.001 | 1.14 (0.98, 1.34) | 0.085 | 1.04 (1.01, 1.08) | 0.009 | 1.07 (1.03, 1.10) | < 0.001 |
| $PM_{2.5–10}$ | 1st quartile | Reference | | Reference | | Reference | | Reference | |
| | 2nd quartile | 1.01 (0.98, 1.04) | 0.344 | 0.84 (0.62, 1.14) | 0.266 | 0.95 (0.89, 1.00) | 0.058 | 1.03 (0.97, 1.08) | 0.360 |
| | 3rd quartile | 1.02 (0.99, 1.05) | 0.144 | 0.97 (0.72, 1.31) | 0.844 | 0.96 (0.90, 1.01) | 0.143 | 1.02 (0.97, 1.08) | 0.441 |
| | 4th quartile | 1.00 (0.97, 1.03) | 0.888 | 1.06 (0.79, 1.41) | 0.711 | 0.96 (0.90, 1.01) | 0.115 | 1.00 (0.95, 1.06) | 0.868 |
| | P for trend | | 0.779 | | 0.350 | | 0.324 | | 0.838 |
| | Per IQR increase | 1.00 (0.99, 1.01) | 0.968 | 1.01 (0.92, 1.10) | 0.904 | 1.00 (0.99, 1.02) | 0.588 | 1.00 (0.99, 1.02) | 0.657 |
| $PM_{10}$ | 1st quartile | Reference | | Reference | | Reference | | Reference | |
| | 2nd quartile | 1.01 (0.98, 1.05) | 0.392 | 1.19 (0.85, 1.67) | 0.307 | 1.00 (0.94, 1.07) | 0.987 | 1.07 (1.01, 1.14) | 0.034 |
| | 3rd quartile | 1.05 (1.01, 1.09) | 0.006 | 1.11 (0.78, 1.58) | 0.573 | 1.04 (0.97, 1.11) | 0.241 | 1.11 (1.04, 1.18) | 0.002 |
| | 4th quartile | 1.00 (0.97, 1.04) | 0.896 | 1.15 (0.82, 1.61) | 0.430 | 0.98 (0.92, 1.05) | 0.598 | 1.05 (0.98, 1.12) | 0.141 |
| | P for trend | | 0.883 | | 0.597 | | 0.540 | | 0.321 |
| | Per IQR increase | 1.00 (0.99, 1.01) | 0.613 | 1.02 (0.91, 1.13) | 0.751 | 1.01 (0.99, 1.03) | 0.370 | 1.02 (1.00, 1.04) | 0.131 |
| $NO_2$ | 1st quartile | Reference | | Reference | | Reference | | Reference | |
| | 2nd quartile | 1.07 (1.04, 1.11) | < 0.001 | 1.07 (0.74, 1.55) | 0.717 | 1.10 (1.03, 1.18) | 0.004 | 1.09 (1.02, 1.16) | 0.008 |
| | 3rd quartile | 1.13 (1.09, 1.18) | < 0.001 | 1.26 (0.85, 1.87) | 0.243 | 1.14 (1.06, 1.23) | < 0.001 | 1.19 (1.11, 1.27) | < 0.001 |
| | 4th quartile | 1.16 (1.11, 1.21) | < 0.001 | 1.62 (1.06, 2.48) | 0.027 | 1.11 (1.03, 1.21) | 0.009 | 1.19 (1.10, 1.29) | < 0.001 |
| | P for trend | | < 0.001 | | 0.010 | | 0.024 | | < 0.001 |
| | Per IQR increase | 1.06 (1.04, 1.08) | < 0.001 | 1.29 (1.09, 1.52) | 0.003 | 1.04 (1.00, 1.08) | 0.030 | 1.07 (1.03, 1.11) | < 0.001 |
| $NO_x$ | 1st quartile | Reference | | Reference | | Reference | | Reference | |
| | 2nd quartile | 1.06 (1.02, 1.09) | 0.002 | 1.10 (0.76, 1.59) | 0.604 | 1.06 (0.99, 1.13) | 0.107 | 1.11 (1.04, 1.18) | 0.002 |
| | 3rd quartile | 1.11 (1.07, 1.16) | < 0.001 | 1.18 (0.80, 1.75) | 0.399 | 1.08 (1.00, 1.16) | 0.043 | 1.20 (1.12, 1.28) | < 0.001 |
| | 4th quartile | 1.15 (1.11, 1.20) | < 0.001 | 1.63 (1.09, 2.45) | 0.017 | 1.10 (1.02, 1.19) | 0.011 | 1.22 (1.14, 1.32) | < 0.001 |
| | P for trend | | < 0.001 | | 0.005 | | 0.015 | | < 0.001 |
| | Per IQR increase | 1.04 (1.03, 1.06) | < 0.001 | 1.16 (1.04, 1.29) | 0.006 | 1.03 (1.00, 1.05) | 0.047 | 1.04 (1.02, 1.07) | 0.001 |

Adjusted for sex, gender, ethnicity, duration of residence at the current address, income level, education qualifications, employment status, activity group, Townsend deprivation index, and green space coverage in a 300 m buffer of residential addresses. The units for $PM_{2.5}$, $PM_{2.5–10}$, $PM_{10}$, $NO_2$ and $NO_x$ are μg/m$^3$, and the unit for $PM_{2.5}$ absorbance is per meter.

% CI: 1.04–1.07), 24 % (HR = 1.24, 95 % CI: 1.08–1.43), 4 % (HR = 1.04, 95 % CI: 1.01–1.07) and 6 % (HR = 1.06, 95 % CI: 1.03–1.10) larger risk of incident mental disorder, schizophrenia, depression and anxiety, respectively. Age and deprivation levels varied the associations between air pollution scores and mental disorders, depression and anxiety (Fig. 3).

The distributions of PRS between participants with and without schizophrenia, depression and anxiety were shown in Supplementary Fig. 2. The associations between PRS decile and the presence of schizophrenia, depression and anxiety until the end of follow-up were

**Table 3**
Associations between air pollution score and risk of incident mental disorders.

| | Mental disorders | | Schizophrenia | | Depression | | Anxiety | |
|---|---|---|---|---|---|---|---|---|
| | Hazard Ratio | *P* value | Hazard Ratio | *P* value | Hazard Ratio | *P* value | Hazard Ratio | *P* value |
| 1st quartile | Reference | | Reference | | Reference | | Reference | |
| 2nd quartile | 1.05 (1.01, 1.08) | 0.010 | 1.10 (0.77, 1.59) | 0.597 | 1.04 (0.97, 1.11) | 0.305 | 1.13 (1.06, 1.21) | < 0.001 |
| 3rd quartile | 1.13 (1.09, 1.18) | < 0.001 | 1.18 (0.80, 1.74) | 0.410 | 1.12 (1.04, 1.2) | 0.003 | 1.25 (1.16, 1.34) | < 0.001 |
| 4th quartile | 1.14 (1.09, 1.19) | < 0.001 | 1.42 (0.94, 2.15) | 0.094 | 1.10 (1.02, 1.19) | 0.018 | 1.21 (1.12, 1.31) | < 0.001 |
| P for trend | | < 0.001 | | 0.064 | | 0.013 | | < 0.001 |
| Per IQR increase | 1.06 (1.04, 1.07) | < 0.001 | 1.24 (1.08, 1.43) | 0.003 | 1.04 (1.01, 1.07) | 0.022 | 1.06 (1.03, 1.10) | < 0.001 |

Adjusted for sex, gender, ethnicity, duration of residence at the current address, income level, education qualifications, employment status, activity group, Townsend deprivation index, and green space coverage in a 300 m buffer of residential addresses.

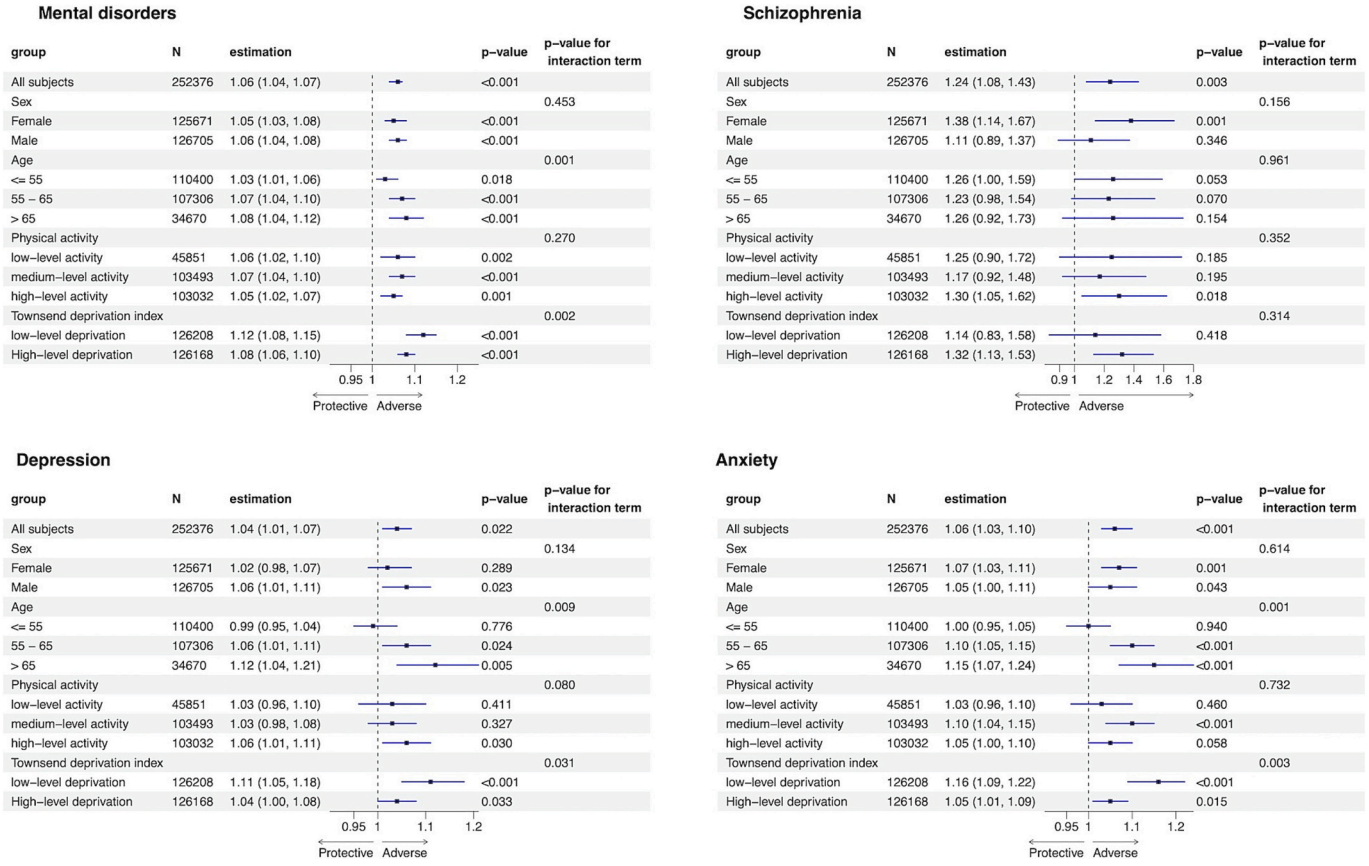


**Fig. 3.** Stratification analyses for the association of an interquartile range increase in air pollution score and risk of incident mental disorders.

demonstrated in Supplementary Fig. 3, with the first decile as the reference group and adjustment of age, sex, and the primary ten genetic PCs. People in the highest PRS decile had 414 % higher risk of schizophrenia (odds ratio = 5.14, 95 % CI: 3.88, 6.83), 79 % higher risk of depression (odds ratio = 1.79, 95 % CI: 1.70, 1.89), and 20 % higher risk of anxiety (odds ratio = 1.20, 95 % CI: 1.13, 1.28) than those in the lowest decile, respectively. Participants with a high genetic risk were associated with a higher risk of incident mental disorders regardless of air pollution exposure (Fig. 4). Neither additive nor multiplicative interaction effects between air pollutant exposure and PRS was found on incident schizophrenia, depression, or anxiety.

A series of sensitivity analyses showed consistent results with our main analyses. The associations between air pollution score and incident mental disorders remained similar after excluding participants who were diagnosed with mental disorders within three years of recruitment (Supplementary Table 3) or excluding those who have stayed at their current address for <5 years (Supplementary Table 4). The associations between air pollution score and incident mental disorders remained comparable to the main analysis when we additionally adjusted for 24-h average noise (Supplementary Table 5), or when we limited to participants whose PRS was available (Supplementary Table 6), or when we additionally adjusted for small-area climate factors (Supplementary Table 7).

## 4. Discussion

Based on a large-scale and long-term prospective cohort, we investigated the relationship between exposure to air pollutants and the incident mental disorders, including schizophrenia, depression, and anxiety. Our findings revealed that $PM_{2.5}$, $NO_2$, and NOx were risk factors for incident mental disorders, depression, and anxiety. By constructing an innovative composite score of air pollutants, we demonstrated a robust positive relationship between multiple air pollutants and the risk of mental disorders. Additionally, we explored the interaction between air pollution and genetic susceptibility. To the best of our knowledge, this is the first study to provide evidence on whether

| Air pollutantion score | Genetic risk | Hazard Ratio | Additive effect RERI | Multiplicative effect P value |
|---|---|---|---|---|
| Schizophrenia | | | | |
| Q1 | Low | reference | - | - |
| | High | 2.46 (1.26, 4.83) | | |
| Q2 | Low | 1.37 (0.63, 3.00) | -0.27 (-1.91, 1.37) | 0.551 |
| | High | 2.56 (1.26, 5.19) | | |
| Q3 | Low | 1.26 (0.55, 2.90) | -0.14 (-1.78, 1.49) | 0.693 |
| | High | 2.58 (1.23, 5.40) | | |
| Q4 | Low | 2.12 (0.95, 4.72) | -0.98 (-2.91, 0.96) | 0.117 |
| | High | 2.61 (1.20, 5.64) | | |
| Depression | | | | |
| Q1 | Low | reference | | |
| | High | 1.25 (1.11, 1.40) | | |
| Q2 | Low | 1.00 (0.88, 1.13) | 0.08 (-0.10, 0.25) | 0.451 |
| | High | 1.32 (1.17, 1.49) | | |
| Q3 | Low | 1.16 (1.02, 1.32) | -0.03 (-0.21, 0.16) | 0.548 |
| | High | 1.38 (1.22, 1.56) | | |
| Q4 | Low | 1.12 (0.97, 1.28) | 0.04 (-0.14, 0.23) | 0.914 |
| | High | 1.40 (1.23, 1.60) | | |
| Anxiety | | | | |
| Q1 | Low | reference | | |
| | High | 1.04 (0.94, 1.16) | | |
| Q2 | Low | 1.17 (1.05, 1.32) | 0.01 (-0.15, 0.18) | 0.957 |
| | High | 1.23 (1.10, 1.38) | | |
| Q3 | Low | 1.25 (1.11, 1.41) | -0.01 (-0.18, 0.16) | 0.825 |
| | High | 1.29 (1.14, 1.45) | | |
| Q4 | Low | 1.27 (1.12, 1.45) | 0.00 (-0.17, 0.18) | 0.938 |
| | High | 1.32 (1.16, 1.50) | | |

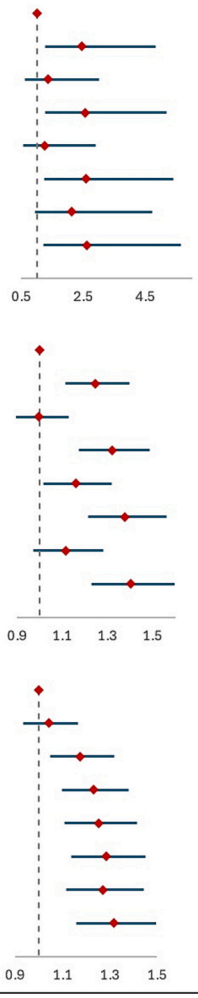


**Fig. 4.** Interaction of air pollution and genetic risk on specific mental disorders ($N$ = 139,802).
Footnotes: Adjusted for sex, gender, ethnicity, length of living at the current address, income level, education qualifications, employment status, activity group, Townsend deprivation index, green space coverage at a 300 m buffer of residential addresses, polygenetic risk scores (PRS) of specific mental disorders (including schizophrenia, depressions, and anxiety, respectively) and the first 10 genetic principal components.
Genetic risk was categorised into two levels by median of PRS. Air pollution score was categorised into four levels by quartile. We used the first quartile of the air pollution score and the low PRS as the reference group to calculate additive and multiplicative effects for the other seven groups.
The *p*-values of the interaction of air pollution score (as a linear term) and genetic risk (as a linear term) on specific mental disorders were 0.946, 0.439 and 0.742 for schizophrenia, depression and anxiety, respectively.

genetic susceptibility modifies the relationship between concurrent exposure to various air pollutants and incident mental disorders. We observed that although no additive or multiplicative interaction of PRS and air pollution scores on incident schizophrenia, depression or anxiety was found, the associations between air pollution and schizophrenia, depression and anxiety consistently showed a trend of enhancement in the group with a high genetic predisposition.

Studies investigating the impact of a single air pollutant on mental well-being have been widely reported. However, because of inconsistencies in outcome identification and study design, there's no consensus on the link between air pollution and specific mental illnesses such as depression, anxiety or schizophrenia (Braithwaite et al., 2019; Fan et al., 2020; Antonsen et al., 2020; Zhang et al., 2024). Our study demonstrated that long-term exposure to $PM_{2.5}$ was associated with a higher risk of mental disorders, consistent with previous studies (Braithwaite et al., 2019; Zhang et al., 2024; Borroni et al., 2022). $NO_2$, NOx and $PM_{2.5}$ absorbance, a surrogate indicator of elemental carbon, are principally released from road transport in the UK (Lyons et al., 2024; Zeng et al., 2019; Eeftens et al., 2012b). Our findings support the findings seen in other studies that exposure to a certain higher level of traffic-related air pollutants could result in a higher risk of mental disorders (Nobile et al., 2023; Yang et al., 2023; Zare Sakhvidi et al., 2022). The association was evident after further adjustment of traffic-related noise (Supplementary Table 5). Different from previous studies using the same cohort, our studies did not observe adverse associations between $PM_{10}$ and incident depression, anxiety or schizophrenia (Zhang et al., 2024; Gao et al., 2023). One possible explanation for this discrepancy is that we only used the 2010 air pollutant measurements, not the average concentrations for 2007 and 2010. As different regression models for air pollutant estimation were used for each of these two years (air pollution estimates for the year 2007 were derived using the EU-wide air pollution maps instead of the LUR), UK Biobank did not

consider it appropriate to average concentrations for these two years (https://biobank.ctsu.ox.ac.uk/ukb/label.cgi?id=114). Furthermore, the aforementioned study employed the depression screening questionnaire (9-item Patient Health Questionnaire) to determine the outcome of depression rather than using the ICD-10 for clinical diagnosis. This might lead to an overestimation of the associations (Thombs et al., 2018). Nevertheless, our findings were consistent with those of previous research conducted in Europe that indicated long-term exposure to $PM_{10}$ had no significant associations with depression, anxiety or schizophrenia (Zeng et al., 2019; Antonsen et al., 2020; Petrowski et al., 2021). We also observed similar findings to this study in previous research on the health effects of $PM_{2.5–10}$, with no significant adverse effects on depression. This suggests that the mental health implications of $PM_{2.5–10}$ may be less threatening than those for $PM_{2.5}$, which were similar to those findings observed in other health outcomes (Adar et al., 2014; Zhang et al., 2023). In agreement with earlier investigations using air pollution scores, our study, which had a longer follow-up period, covered more types of air pollutants and defined study outcomes based on clinician-diagnosed episodes of mental disorders, supporting the hypothesis that concurrent air pollutants exposure could lead to a higher risk of mental disorders (Zhang et al., 2024; Yang et al., 2023; Gao et al., 2023).

Previous research has explored the underlying mechanisms that could elucidate the associations between exposure to air pollutants and the occurrence of mental disorders. Neuroinflammation and oxidative stress are well-recognised as common mechanisms of air pollution that contribute to mental disorders (Antonsen et al., 2020; Block and Calderón-Garcidueñas, 2009; Power et al., 2015; van den Bosch and Meyer-Lindenberg, 2019; Sawa and Sedlak, 2016; Vogelzangs et al., 2013). The particulate matter, especially small particles, would reach the brain and induce inflammation and oxidative stress in the central nervous system, and nitrogen oxides would initiate an oxidative signalling cascade that further induces neuroinflammation (Lundberg and Weitzberg, 2022; Adar et al., 2014). However, distinct psychiatric diseases may involve different biological pathways and exhibit varying susceptibility to air pollutants. For instance, inhaling air pollutants can activate the hypothalamic-pituitary-adrenal (HPA) axis, increasing stress hormone levels and leading to dopaminergic neurotoxicity, which raises the risk of depression and anxiety (Thomson, 2019; Dantzer et al., 2008; Hasler, 2010; Braithwaite et al., 2019; Thomson et al., 2013; Li et al., 2017; Lim et al., 2012). As a neurodevelopmental disorder (Antonsen et al., 2020), schizophrenia may exhibit greater susceptibility to air pollution compared to depression or anxiety. Previous studies have indicated that air pollution can induce neurotoxicity, disrupt neurodevelopment, and lead to neurological dysfunction, thereby increasing the risk of schizophrenia. Specifically, inflammation caused by air pollution can interfere with glutamate-mediated neurotransmission and induce neurotoxic effects, further contributing to the pathogenesis of schizophrenia (Marsman et al., 2013; Moghaddam and Javitt, 2012). Long-term exposure to air pollutants during early life can disrupt normal brain development, thereby elevating the likelihood of developing schizophrenia in later stages (Antonsen et al., 2020). Additionally, evidence suggests that prolonged exposure to air pollution is associated with cognitive decline and other neurological impairments, which may exacerbate the severity of schizophrenia (McCutcheon et al., 2023; Schikowski and Altuğ, 2020). Our findings showed that air pollution's adverse effects were more health-threatening among older adults. Older adults are more susceptible to inflammation triggered by substances such as air pollutants due to increased vulnerability of the immune system and nervous system (Qiu et al., 2023; Shumake et al., 2013). Associations between air pollution and mental disorders (e.g. depression and anxiety) possibly varied by area deprivation (Brunt et al., 2016).

Studying the interaction between genetic susceptibility and the environment may help explain disease development (Peters et al., 2021; Jin et al., 2020). Gene-environment interaction studies using a longitudinal study design are not sufficient. Our study provides research evidence on the interaction of genetic predisposition and multiple air pollutants on incident schizophrenia, anxiety and depression. The results implied that mental disorders might be affected by genes and air pollutants in separate pathways. In one previous research investigating the interaction between genetic predisposition and joint effects of multiple air pollutants on mental disorders (depression and anxiety), no evidence was found for either additive or multiplicative gene-environment interactions (Gao et al., 2023). Another gene-environment interaction study observed an additive joint interaction between individual air pollutants and genetic factors on the risk of depression (Fu et al., 2022). In another interaction effects study investigating the genetic effects of schizophrenia and four specific air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, $NO_x$ and joint effect) on late-onset incident schizophrenia, additive effects were observed among the highest level of genetic risk (categorised by tertile) and the high level of air pollutant scores (categorised by median) (Zhang et al., 2024). Our study found no multiplicative nor additive gene-environment interactions on mental disorders, including schizophrenia, depression and anxiety. In this study, we considered the combined effects of various air pollutants instead of a single pollutant and covered wider composites of air pollution. In addition, we assessed the PRS based on summary statistics from meta-analyses excluding UK Biobank participants. This minimises the overfitting concern in PRS calculation introduced by sample overlap between base and target data. We also considered a broader range of SNPs from the White ethnic samples, which better reflects the genetic basis of the mental disorders (Wray et al., 2013; Collister et al., 2022). Nevertheless, despite the absence of interaction between PRS and air pollution scores on incident mental disorders in our study, the positive correlations between air pollution and these specific mental disorders are on the rise in people with high genetic susceptibility.

This study used a large-scale cohort with a median of 13.36 years follow-up that enabled sufficient statistical power for observations of incident mental disorders. To date, limited research has examined the combined effects of particulate matter and gaseous air pollutants on the incidence of mental disorders. Given that ambient air pollution is a combination of gaseous pollutants and particulate matter, examining their combined impacts on mental illnesses is essential to illuminating the comprehensive influence of air pollution on mental health in real-world situations. We added to the previous literature by assessing the combined impacts of exposures to $PM_{2.5}$ absorbance, $PM_{2.5}$, $PM_{2.5–10}$, $PM_{10}$, $NO_2$, and $NO_x$ with a novel air pollution score, and found a positive correlation with the onset of mental disorders. We also carefully addressed methodological limitations in PRS calculation in previous studies and yielded the most predictive information on an individual's genetic risk for mental disorders.

However, several limitations exist in this study. Firstly, participants in the UK Biobank were recruited voluntarily. Selection bias might exist and have an impact on the representativeness and generalisability (Fry et al., 2017). Secondly, we used annual average air pollution exposure levels at the baseline and did not take into account dynamic changes in air pollution because dynamic monitoring data were limited. However, according to the follow-up surveys in the UK Biobank, participants who relocated was at a low rate of about 2 %. Since 2010, the annual emissions of particulate matter ($PM_{10}$ and $PM_{2.5}$) in the UK have been relatively stable, while the emissions of nitrogen oxides have shown a downward trend (Department for Environment, Food and Rural Affairs, The UK Government, 2024). Accordingly, the baseline airborne particulate matter levels could be a suitable surrogate representing long-term exposure, and we may have underestimated the association between nitrogen oxides and mental disorders. Thirdly, the average age of the participants is 56.19 years, so conclusions drawn from our study would not be generalised to younger adults. Future studies on air pollution and mental health among younger adults are suggested. Fourthly, the possibility of residual confounding, such as the climate factors (Thompson et al., 2023; Li et al., 2023), cannot be ruled out, though we have taken into account a range of important confounding variables, e.g.,

demographic features, individual and area-level socioeconomic level, duration of residence at the current address, physical activity, green space coverage, noise, and the clustering effects of assessment centres. Fifthly, the incident schizophrenia in this study should be interpreted with caution, which might be more related to late-onset schizophrenia (Shen et al., 2024). Finally, the majority of participants in this study were of European descent, and PRS was calculated based on GWAS in European descent. Therefore, caution should be exercised to generalise the findings of gene-environment interactions to different populations.

## 5. Conclusions

This study offered compelling evidence that long-term exposure to a variety of air pollutants was correlated to an increased risk of incident mental disorders, including schizophrenia, depression, and anxiety. Notably, we assessed the combined effects of air pollutants by constructing an innovative air pollution index, revealing the potential dose-response to air pollution exposure and incident mental disorders. Regardless of the genetic risk of schizophrenia, depression and anxiety in this population, air pollution increased the likelihood of all and specific mental disorders. These results highlighted the importance of implementing strict air pollution control standards to reduce the disease burden of mental disorders, even in areas with milder levels of air pollution.

## CRediT authorship contribution statement

**Xiaoxin I. Yao:** Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Writing – original draft. **Shengzhi Sun:** Methodology, Writing – review & editing. **Qian Yang:** Methodology, Writing – review & editing. **Xinning Tong:** Supervision, Software, Methodology, Investigation, Formal analysis, Writing – original draft. **Chen Shen:** Validation, Supervision, Software, Resources, Investigation, Data curation, Writing – review & editing.

## Ethics approval

All participants in this study provided written informed consent. UK Biobank was approved by the North West Multi-centre Research Ethics Committee (MREC) (Reference 16/NW/0274).

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2025.179137.

## Data availability

UK Biobank data were used under license and thus not publicly available. Access to the UK Biobank data can be requested through a standard protocol (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

## References

Adams, Mark James, 2022. Consortium, Major Depressive Disorder Working Group of the Psychiatric Genomics. MDD2 (MDD2018) GWAS sumstats w/o UKBB. figshare. Dataset.
Adar, S.D., Filigrana, P.A., Clements, N., Peel, J.L., 2014. Ambient coarse particulate matter and human health: a systematic review and Meta-analysis. Curr. Environ. Health Reports 1 (3), 258–274.
Adorjan, K., Falkai, P., 2019. Premature mortality, causes of death, and mental disorders. Lancet 394 (10211), 1784–1786.
Antonsen, S., Mok, P.L.H., Webb, R.T., et al., 2020. Exposure to air pollution during childhood and risk of developing schizophrenia: a national cohort study. Lancet Planet. Health 4 (2), e64–e73.
Assary, E., Vincent, J.P., Keers, R., Pluess, M., 2018. Gene-environment interaction and psychiatric disorders: review and future directions. Semin. Cell. Dev. Biol 77, 133–143.
Austin, P.C., 2009. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat. Med. 28 (25), 3083–3107.
Blane, D., Townsend, P., Phillimore, P., Beattie, A., 1987. Health and deprivation: inequality and the north. Br. J. Sociol. 40, 344.
Block, M.L., Calderón-Garcidueñas, L., 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 32 (9), 506–516.
Borroni, E., Pesatori, A.C., Bollati, V., Buoli, M., Carugno, M., 2022. Air pollution exposure and depression: a comprehensive updated systematic review and meta-analysis. Environ. Pollut. 292, 118245.
Braithwaite, I., Zhang, S., Kirkbride, J.B., Osborn, D.P.J., Hayes, J.F., 2019. Air pollution (particulate matter) exposure and associations with depression, anxiety, bipolar, psychosis and suicide risk: a systematic review and Meta-analysis. Environ. Health Perspect. 127 (12), 126002.
Brunt, H., Barnes, J., Jones, S.J., Longhurst, J.W.S., Scally, G., Hayes, E., 2016. Air pollution, deprivation and health: understanding relationships to add value to local air quality management policy and practice in Wales. UK. J. Public Health 39 (3), 485–497.
Buoli, M., Grassi, S., Caldiroli, A., et al., 2018. Is there a link between air pollution and mental disorders? Environ. Int. 118, 154–168.
Bycroft, C., Freeman, C., Petkova, D., et al., 2018. The UK biobank resource with deep phenotyping and genomic data. Nature 562 (7726), 203–209.
Cesaroni, G., Forastiere, F., Stafoggia, M., et al., 2014. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project. BMJ : Brit. Med. J. 348, f7412.
Cohen, A.J., Brauer, M., Burnett, R., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the global burden of diseases study 2015. Lancet 389 (10082), 1907–1918.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Routledge.
Collister, J.A., Liu, X., Clifton, L., 2022. Calculating polygenic risk scores (PRS) in UK biobank: a practical guide for epidemiologists. Front. Genet. 13.
Dantzer, R., O'connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9 (1), 46–56.
de Hoogh, K., Wang, M., Adam, M., et al., 2013. Development of land use regression models for particle composition in twenty study areas in Europe. Environ. Sci. Technol. 47 (11), 5778–5786.
Department for Environment, Food and Rural Affairs, The UK Government, 2024. https://www.gov.uk/government/statistics/emissions-of-air-pollutants/emissions-of-air-pollutants-in-the-uk-summary (accessed June 24 2024).

Eeftens, M., Tsai, M.-Y., Ampe, C., et al., 2012a. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2 – results of the ESCAPE project. Atmos. Environ. 62, 303–317.
Eeftens, M., Beelen, R., de Hoogh, K., et al., 2012b. Development of land use regression models for PM2.5, PM2.5 absorbance, PM10 and PMcoarse in 20 European study areas; results of the ESCAPE project. Environ. Sci. Technol. 46 (20), 11195–11205.
Euesden, J., Lewis, C.M., O'Reilly, P.F., 2015. PRSice: polygenic risk score software. Bioinformatics 31 (9), 1466–1468.
Fan, S.-J., Heinrich, J., Bloom, M.S., et al., 2020. Ambient air pollution and depression: a systematic review with meta-analysis up to 2019. Sci. Total Environ. 701, 134721.
Figueres, C., Landrigan, P.J., Fuller, R., 2018. Tackling air pollution, climate change, and NCDs: time to pull together. Lancet 392 (10157), 1502–1503.
Foster, H.M.E., Celis-Morales, C.A., Nicholl, B.I., et al., 2018. 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 3 (12) e576-e85.
Fry, A., Littlejohns, T.J., Sudlow, C., et al., 2017. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am. J. Epidemiol. 186 (9), 1026–1034.
Fu, Z., Liu, Q., Liang, J., et al., 2022. Air pollution, genetic factors and the risk of depression. Sci. Total Environ. 850, 158001.
Gao, Q., Xu, Q., Guo, X., Fan, H., Zhu, H., 2017. Particulate matter air pollution associated with hospital admissions for mental disorders: a time-series study in Beijing. China. Eur. Psychiatry 44, 68–75.
Gao, X., Jiang, M., Huang, N., Guo, X., Huang, T., 2023. Long-term Air pollution, genetic susceptibility, and the risk of depression and anxiety: a prospective study in the UK biobank cohort. Environ. Health Perspect. 131 (1), 017002.
GBD, 2019. Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry 2022 9 (2), 137–150.
Hasler, G., 2010. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry 9 (3), 155.
Hoek, G., Beelen, R., de Hoogh, K., et al., 2008. A review of land-use regression models to assess spatial variation of outdoor air pollution. Atmos. Environ. 42 (33), 7561–7578.
Howard, D.M., Adams, M.J., Clarke, T.-K., et al., 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat. Neurosci. 22 (3), 343–352.
Hurley, L.L., Tizabi, Y., 2013. Neuroinflammation, neurodegeneration, and depression. Neurotox. Res. 23, 131–144.
Jin, G., Lv, J., Yang, M., et al., 2020. Genetic risk, incident gastric cancer, and healthy lifestyle: a meta-analysis of genome-wide association studies and prospective cohort study. Lancet Oncol. 21 (10), 1378–1386.
Kephalopoulos, S., Paviotti, M., Anfosso-Lédée, F., 2012. Common noise assessment methods in Europe (CNOSSOS-EU). In: EUR 25379 EN, JRC72550. Publications Office of the European Union, Luxembourg (Luxembourg).
Kephalopoulos, S., Paviotti, M., Anfosso-Lédée, F., Van Maercke, D., Shilton, S., Jones, N., 2014. Advances in the development of common noise assessment methods in Europe: the CNOSSOS-EU framework for strategic environmental noise mapping. Sci. Total Environ. 482-483, 400–410.
Khomenko, S., Cirach, M., Pereira-Barboza, E., et al., 2021. Premature mortality due to air pollution in European cities: a health impact assessment. Lancet Planet. Health 5 (3) e121-e34.
Landrigan, P.J., Fuller, R., Acosta, N.J., et al., 2018. The lancet commission on pollution and health. Lancet 391 (10119), 462–512.
Li, D., Zhang, Y., Li, X., Zhang, K., Lu, Y., Brown, R.D., 2023. Climatic and meteorological exposure and mental and behavioral health: a systematic review and meta-analysis. Sci. Total Environ. 892, 164435.
Li, H., Cai, J., Chen, R., et al., 2017. Particulate matter exposure and stress hormone levels: a randomized, double-blind. Crossover Trial of Air Purification. Circulation 136 (7), 618–627.
Li, W., Chen, R., Feng, L., et al., 2024. Genome-wide meta-analysis, functional genomics and integrative analyses implicate new risk genes and therapeutic targets for anxiety disorders. Nat. Hum. Behav. 8 (2), 361–379.
Lim, Y.-H., Kim, H., Kim, J.H., Bae, S., Park, H.Y., Hong, Y.-C., 2012. Air pollution and symptoms of depression in elderly adults. Environ. Health Perspect. 120 (7), 1023–1028.
Liu, B.-P., Huxley, R.R., Schikowski, T., Hu, K.-J., Zhao, Q., Jia, C.-X., 2024. Exposure to residential green and blue space and the natural environment is associated with a lower incidence of psychiatric disorders in middle-aged and older adults: findings from the UK biobank. BMC Med. 22 (1), 15.
Lundberg, J.O., Weitzberg, E., 2022. Nitric oxide signaling in health and disease. Cell 185 (16), 2853–2878.
Lyons, S., Nolan, A., Carthy, P., Griffin, M., O'Connell, B., 2024. Long-term exposure to PM2.5 air pollution and mental health: a retrospective cohort study in Ireland. Environ. Health 23 (1), 54.
Marsman, A., van den Heuvel, M.P., Klomp, D.W., Kahn, R.S., Luijten, P.R., Hulshoff Pol, H.E., 2013. Glutamate in schizophrenia: a focused review and meta-analysis of $^{1}$H-MRS studies. Schizophr. Bull. 39 (1), 120–129.
McCutcheon, R.A., Keefe, R.S.E., McGuire, P.K., 2023. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol. Psychiatry 28 (5), 1902–1918.
Moghaddam, B., Javitt, D., 2012. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology 37 (1), 4–15.
Newbury, J.B., Stewart, R., Fisher, H.L., et al., 2021. Association between air pollution exposure and mental health service use among individuals with first presentations of psychotic and mood disorders: retrospective cohort study. Br. J. Psychiatry 219 (6), 678–685.
Nobile, F., Forastiere, A., Michelozzi, P., Forastiere, F., Stafoggia, M., 2023. Long-term exposure to air pollution and incidence of mental disorders. A large longitudinal cohort study of adults within an urban area. Environ. Int. 181, 108302.
O'Donovan, M.C., Craddock, N., Norton, N., et al., 2008. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat. Genet. 40 (9), 1053–1055.
Otowa, T., Hek, K., Lee, M., et al., 2016. Meta-analysis of genome-wide association studies of anxiety disorders. Mol. Psychiatry 21 (10), 1391–1399.
Peters, A., Nawrot, T.S., Baccarelli, A.A., 2021. Hallmarks of environmental insults. Cell 184 (6), 1455–1468.
Petrowski, K., Bührer, S., Strauß, B., Decker, O., Brähler, E., 2021. Examining air pollution (PM10), mental health and well-being in a representative German sample. Sci. Rep. 11 (1), 18436.
Plana-Ripoll, O., Pedersen, C.B., Agerbo, E., et al., 2019. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. Lancet 394 (10211), 1827–1835.
Power, M.C., Kioumourtzoglou, M.-A., Hart, J.E., Okereke, O.I., Laden, F., Weisskopf, M. G., 2015. The relation between past exposure to fine particulate air pollution and prevalent anxiety: observational cohort study. BMJ : Brit. Med. J. 350, h1111.
Qiu, X., Shi, L., Kubzansky, L.D., et al., 2023. Association of Long-term Exposure to Air pollution with late-life depression in older adults in the US. JAMA Netw. Open 6 (2) e2253668-e.
Richardson, D.B., Kaufman, J.S., 2009. Estimation of the relative excess risk due to interaction and associated confidence bounds. Am. J. Epidemiol. 169 (6), 756–760.
Sawa, A., Sedlak, T.W., 2016. Oxidative stress and inflammation in schizophrenia. Schizophr. Res. 176 (1), 1–2.
Schikowski, T., Altuğ, H., 2020. The role of air pollution in cognitive impairment and decline. Neurochem. Int. 136, 104708.
Shen, C., Tong, X., Ran, J., et al., 2024. Associations between residential environments and late-onset schizophrenia in UK biobank: interaction with genetic risk factor. Schizophr. Res. 270, 85–93.
Shen, X., Howard, D.M., Adams, M.J., et al., 2020. A phenome-wide association and Mendelian randomisation study of polygenic risk for depression in UK biobank. Nat. Commun. 11 (1), 2301.
Shumake, K.L., Sacks, J.D., Lee, J.S., Johns, D.O., 2013. Susceptibility of older adults to health effects induced by ambient air pollutants regulated by the European Union and the United States. Aging Clin. Exp. Res. 25 (1), 3–8.
Szymkowicz, S.M., Gerlach, A.R., Homiack, D., Taylor, W.D., 2023. Biological factors influencing depression in later life: role of aging processes and treatment implications. Transl. Psychiatry 13 (1), 160.
Thombs, B.D., Kwakkenbos, L., Levis, A.W., Benedetti, A., 2018. Addressing overestimation of the prevalence of depression based on self-report screening questionnaires. CMAJ 190 (2). E44-E9.
Thompson, R., Lawrance, E.L., Roberts, L.F., et al., 2023. Ambient temperature and mental health: a systematic review and meta-analysis. Lancet Planet. Health 7 (7) e580-e9.
Thomson, E.M., 2019. Air pollution, stress, and allostatic load: linking systemic and central nervous system impacts. J. Alzheimers Dis. 69 (3), 597–614.
Thomson, E.M., Vladisavljevic, D., Mohottalage, S., Kumarathasan, P., Vincent, R., 2013. Mapping acute systemic effects of inhaled particulate matter and ozone: multiorgan gene expression and glucocorticoid activity. Toxicol. Sci. 135 (1), 169–181.
Trubetskoy, V., Pardiñas, A.F., Qi, T., et al., 2022. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604 (7906), 502–508.
UK Air, 2022. Modelled Background Pollution Data. Department for Environment, Food and Rural Affairs, London. https://uk-air.defra.gov.uk/data/pcm-data (accessed February 5 2025).
van den Bosch, M., Meyer-Lindenberg, A., 2019. Environmental exposures and depression: biological mechanisms and epidemiological evidence. Annu. Rev. Public Health 40, 239–259.
Vogelzangs, N., Beekman, A.T.F., de Jonge, P., Penninx, B.W.J.H., 2013. Anxiety disorders and inflammation in a large adult cohort. Transl. Psychiatry 3 (4) e249-e.
Wang, M., Zhou, T., Song, Y., et al., 2021. Joint exposure to various ambient air pollutants and incident heart failure: a prospective analysis in UK biobank. Eur. Heart J. 42 (16), 1582–1591.
Wolf, K., Hoffmann, B., Andersen, Z.J., et al., 2021. Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project. Lancet Planet. Health 5 (9) e620-e32.
World Health Organization, 2023. Air Pollution: The Invisible Health Threat. https://www.who.int/news-room/feature-stories/detail/air-pollution–the-invisible-health-threat (accessed April 22 2024).

Wray, N.R., Yang, J., Hayes, B.J., Price, A.L., Goddard, M.E., Visscher, P.M., 2013. Pitfalls of predicting complex traits from SNPs. Nat. Rev. Genet. 14 (7), 507–515.
Wray, N.R., Ripke, S., Mattheisen, M., et al., 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat. Genet. 50 (5), 668–681.
Yang, T., Wang, J., Huang, J., Kelly, F.J., Li, G., 2023. Long-term exposure to multiple ambient Air pollutants and association with incident depression and anxiety. JAMA Psychiatry 80 (4), 305–313.
Yao, X.I., Tong, X., Shen, C., et al., 2024. Green space, genetic susceptibility, and risk of osteoporosis:a cohort study from the UK biobank. Chemosphere 353, 141632.
Zare Sakhvidi, M.J., Lafontaine, A., Lequy, E., et al., 2022. Ambient air pollution exposure and depressive symptoms: findings from the French CONSTANCES cohort. Environ. Int. 170, 107622.
Zeng, Y., Lin, R., Liu, L., Liu, Y., Li, Y., 2019. Ambient air pollution exposure and risk of depression: a systematic review and meta-analysis of observational studies. Psychiatry Res. 276, 69–78.
Zhang, J., Fang, X.-Y., Wu, J., et al., 2023. Association of Combined Exposure to ambient Air pollutants, genetic risk, and incident rheumatoid arthritis: a prospective cohort study in the UK biobank. Environ. Health Perspect. 131 (3), 037008.
Zhang, Q., Meng, X., Luo, H., et al., 2024. Air pollutants, genetic susceptibility, and incident schizophrenia in later life: a prospective study in the UK biobank. Sci. Total Environ. 934, 173009.