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Original Article

Air pollutants, genetic susceptibility and the risk of schizophrenia: large prospective study

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Background

Evidence linking air pollutants and the risk of schizophrenia remains limited and inconsistent, and no studies have investigated the joint effect of air pollutant exposure and genetic factors on schizophrenia risk.

Aims

To investigate how exposure to air pollution affects schizophrenia risk and the potential effect modification of genetic susceptibility.

Method

Our study was conducted using data on 485 288 participants from the UK Biobank. Cox proportional hazards models were used to estimate the schizophrenia risk as a function of long-term air pollution exposure presented as a time-varying variable. We also derived the schizophrenia polygenic risk score (PRS) utilising data provided by the UK Biobank, and investigated the modification effect of genetic susceptibility.

Results

During a median follow-up period of 11.9 years, 417 individuals developed schizophrenia (mean age 55.57 years, s.d. = 8.68; 45.6% female). Significant correlations were observed between long-term exposure to four air pollutants ($PM_{2.5}$; PM_{10}; nitrogen oxides, NO_x; nitrogen dioxide, NO_2) and the schizophrenia risk in each genetic risk group. Interactions between genetic factors and the pollutants NO_2 and NO_x had an effect on schizophrenia events. Compared with those with low PRS and low air pollution, participants with high PRS and high air pollution had the highest risk of incident schizophrenia ($PM_{2.5}$: hazard ratio = 6.25 (95% CI 5.03–7.76); PM_{10}: hazard ratio = 7.38 (95% CI 5.86–9.29); NO_2: hazard ratio = 6.31 (95% CI 5.02–7.93); NO_x: hazard ratio = 6.62 (95% CI 5.24–8.37)).

Conclusions

Long-term exposure to air pollutants was positively related to the schizophrenia risk. Furthermore, high genetic susceptibility could increase the effect of NO_2 and NO_x on schizophrenia risk.

Keywords

Air pollution; schizophrenia; genetic susceptibility; interaction; cohort study.

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Schizophrenia is considered to be one of the most severe mental disorders. It is a complicated and clinically heterogeneous behavioural and cognitive syndrome, with an estimated lifetime risk of approximately 1%.[1] Individuals affected by this disease often struggle to achieve complete recovery, and even those with a good prognosis may experience negative effects on their lives, such as poor social and occupational functioning.[2,3] Moreover, the annual economic burden of schizophrenia is huge, ranging from an estimated US$94 million in Puerto Rico to US$102 billion in the USA.[4]

Environmental risk factors

Evidence indicates that the environment and genes are both risk factors for schizophrenia. As an important environmental factor, air pollution, has been proven to strongly affect respiratory diseases[5] and other health problems. In recent years, an increasing amount of research has focused on the influence of air pollution on mental health. Population studies have indicated that air pollution may raise schizophrenia risk through cytokine mediation.[6] Experimental studies have reported that exposure to air pollution induces neuro-inflammation, endothelial dysfunction and microglia activation, all of which contribute to the pathogenesis of schizophrenia.[7] However, epidemiological research on this association is quite scarce and still ambiguous. For instance, some studies showed that short-term exposure to air pollution with fine particulate matter (particle diameter <2.5 μm, $PM_{2.5}$) was positively related to schizophrenia,[6,8] whereas others on short-term exposure reported no significant relationship between $PM_{2.5}$ pollution and schizophrenia.[9,10] It should be noted that all these studies have focused on the impact of short-term exposure to air pollution. Furthermore, because of limitations in the design of time-series studies, these studies cannot be used to infer causal relationships well. To our knowledge, one study has explored the relationship between long-term air pollution exposure during childhood and schizophrenia risk,[11] but the effects on schizophrenia of long-term exposure to air pollutants during adulthood remain unknown. Therefore, cohort studies involving large populations are essential to investigate the possible link between long-term exposure to air pollution and schizophrenia risk in adults.

Genetic risk factors

Evidence indicates that the risk of schizophrenia can also be influenced by genetic factors. Comprehensive genome-wide association studies (GWAS) have pinpointed certain genetic variants associated with the risk of schizophrenia.[12] Through these susceptible regions, researchers can calculate polygenic risk scores (PRS) to assess genetic susceptibility and identify high-risk populations.[13] Emerging evidence has indicated that the interplay between genetic factors and the environment might play a crucial role in the aetiology of the disease.[14] Gene–environment interaction is currently explored as a facet of schizophrenia aetiology. A previous study suggested that the *YWHA* gene family and the *TPH1* gene potentially exert a cumulative effect in schizophrenia.[15] Lei et al discovered that $PM_{2.5}$ and the *YWHAB* gene polymorphism locus rs6031849 together affected the relapse of schizophrenia.[16] The *YWHAB* gene is associated with schizophrenia through inflammatory pathways, aligning with a pathway linked to air pollution.[17] Therefore, it is reasonable to assume that interaction of exposure to air pollution with genetic risk of schizophrenia significantly contributes to the development of schizophrenia. However, no research has been conducted so far to investigate how genetic susceptibility modifies the association between air pollutants and schizophrenia risk.

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The current study

Using data derived from the UK Biobank, the current study aimed to explore the association between long-term exposure to air pollution and the development of schizophrenia in adults. We also assessed how genetic susceptibility modified this relationship.

Method

Study design and population

The UK Biobank recruited approximately 500 000 individuals between the ages of 37 and 73 from 22 different centres across the UK during the period 2006–2010.[18] It gathered biological and medical data from participants through touch-screen questionnaires, computer-assisted interviews and biological specimens.

The current study was conducted using data from the UK Biobank, under application number 69741. Ethical approval for the study was granted by the North West Multi-Centre Research Ethics Committee (reference no. 16/NW/0274), and all participants had previously provided written informed consent to the UK Biobank.

Air pollutants

We obtained data on annual average concentrations of the air pollutants $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) for each year during the study period from UK AIR, which is developed by the Department for Environment, Food and Rural Affairs (DEFRA) (uk-air.defra.gov.uk). The platform offered UK near-surface data on air pollution for the years 2001 through 2021. Adopting an air diffusion model, UK AIR models the concentrations of various air pollutants at a spatial resolution of 1 × 1 km. We associated the residential addresses gathered at baseline in time and space with ambient air pollution.[14] To ensure the reliability of the models, DEFRA compared the modelled and measured values of air pollutants, and the results demonstrated a satisfactory level of agreement. Detailed information regarding the performance of the model can be obtained at https://uk-air.defra.gov.uk/data/pcm-data.

Genetic data and PRS calculation

We derived the PRS for schizophrenia from the established PRS set in the UK Biobank PRS Release. Previous publications provide more information on the methods employed for calculating the PRS.[13,19] In summary, the UK Biobank used a standardised test subgroup and a predefined set of disease and trait definitions and applied Bayesian methods to derive the PRS algorithm, appropriately combining data from various ancestral and relevant characteristics. The UK Biobank determined the PRS value for each individual by summing the posterior effect size of each genetic variant multiplied by the allele gene dosage for the whole genome. We then categorised participants into three groups: low (lowest tertile), medium (middle tertile) or high (highest tertile).

Assessment of schizophrenia

The first occurrence of schizophrenia was determined by using data from medical history, linked death register data, hospital admissions data and primary care records. The related algorithms were provided by the UK Biobank. The diagnosis of schizophrenia was based on ICD-10 (F20).[20] Follow-up of all participants was conducted from enrolment to the occurrence of schizophrenia, death or 12 December 2020, whichever came first.

Covariates

To identify covariates that required adjustment in our multivariate analyses, we used an online directed acyclic graph (DAG) tool DAGitty (www.dagitty.net) to construct a DAG.[21] Considering prior knowledge and literature,[11,22] we incorporated a comprehensive range of covariates into the DAG for analysis, which included age, gender, ethnicity, employment, education, income, residential area, migration, social isolation, substance use, pregnancy and birth complications, Townsend deprivation index (TDI), cardiovascular disease, diabetes and lifestyle factors (alcohol consumption, smoking, healthy diet score and physical activity). By referring to the DAG (Supplementary Fig. 1, available at https://doi.org/10.1192/bjp.2024.118), we retained a minimal set of essential variables for adjustment, including age, gender (male or female), ethnicity (Black and minority ethnic or White), education background (degree level education; non-college level, i.e. below degree level; or none of above), employment (employed, retired, unemployed, homemaker or others), annual income (<£31 000 or ≥£31 000), TDI, social isolation (least isolated, moderately isolated or most isolated: see Supplementary material, Method 1) and residential area (urban or rural). Data on covariates were obtained from baseline assessments.

Statistical analysis

Baseline characteristics were computed and displayed as mean (s.d.) for continuous data, or frequency and percentages for categorical data. Missing data in covariates were addressed using the fully conditional specification (FCS) technique through multiple imputation. Student *t*-test, Mann–Whitney *U*-test, or χ^2-tests were used to assess the differences in baseline features between individuals with and without schizophrenia.

We used the Cox proportional hazards model, which included time-varying annual air pollution exposure data, to separately investigate the associations between $PM_{2.5}$, PM_{10}, NO_2, NO_X and the risk of developing schizophrenia. In the multivariate-adjusted models, the annual average concentrations of air pollutants for each participant were classified into tertiles, and the categorised air pollutant measure was treated as a time-varying variable. Using the first tertiles as the reference, the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated after adjusting for confounders including age, gender, ethnicity, employment, education, income, TDI, social isolation and residential area. In genetics-related studies, additional adjustments were made to include genotyping batch and the first ten genetic principal components (Supplementary Method 2). We further conducted a trend analysis by assigning tertiles as continuous variables in a Cox regression model. Additionally, restricted cubic spline (RCS) analysis was employed to explore the dose–response relationships between air pollution and schizophrenia risk.

We conducted a stratified analysis to examine the relationship of air pollution with the schizophrenia risk in three different genetic risk (low, intermediate and high) groups by adding a product term of air pollution and genetic risk to the model. We then calculated *P*-values for interaction (Supplementary Method 3). To assess the joint associations, we further categorised participants into nine groups according to air pollution exposure (tertiles) and genetic risk (tertiles) and evaluated the schizophrenia risk in different groups compared with those having low air pollution exposure and low genetic risk.

To ensure the robustness of our findings, several sensitivity analyses were conducted: (a) excluding schizophrenia events occurring within the initial 2 years of follow-up; (b) limiting our analysis to participants who have lived at their baseline address for more than 5 years; (c) analysing the completed data-set after removing participants with missing covariate data; (d) performing an analysis

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after further adjusting for lifestyle; (e) fitting a two-pollutant model for each air pollutant by incorporating various types of pollutant into the model; (f) restricting analyses to non-movers (those who did not move to a different residential area) during the follow-up period. Software R (version 4.2.0 for Windows) was used for statistical analyses.

Results

Among the 502 480 individuals initially included in the study, 917 individuals diagnosed with schizophrenia at baseline and 16 275 with incomplete genetic data were excluded. Eventually, 485 288 individuals were included in main analysis (Supplementary Fig. 2). At baseline, the average age of all individuals was 56.55 years (s.d. = 8.09) and 263 336 (54.3%) were female (Table 1). During a median follow-up period of 11.9 years, a total of 417 schizophrenia events were recorded. In comparison with those without schizophrenia, individuals with schizophrenia tended to be younger, male, live in urban areas, have lower employment rates, education levels and income levels, and have higher levels of social isolation. The mean (s.d.) levels of $PM_{2.5}$, PM_{10}, NO_2 and NO_x for participants during study period were 10.20 (s.d. = 2.16), 15.10 (s.d. = 2.97), 18.70 (s.d. = 6.80) and 28.20 (s.d. = 12.60) μg/m^3 respectively (Supplementary Table 1).

In the multivariable-adjusted model, significant links were identified between long-term exposure to air pollutants and increased schizophrenia risk (Table 2). The adjusted hazard ratios (95% CI) for the highest tertile compared with the lowest were 1.98 (95% CI 1.80–2.19) for $PM_{2.5}$, 2.30 (95% CI 2.08–2.55) for PM_{10}, 2.30 (95% CI 2.05–2.58) for NO_2 and 2.35 (95% CI 2.09–2.64) for NO_x (P for trend of all pollutants <0.001). The sensitivity analyses also yielded consistent results (Supplementary Tables 2–7). For instance, even after excluding missing covariates and further restricting analyses to non-movers during the follow-up period, the correlation between the four pollutants and schizophrenia risk remained robust (Supplementary Tables 4, 7). Additionally, RCS analyses were utilised to evaluate the dose–response curve linking air pollution and schizophrenia (Fig. 1), revealing evidence of non-linear associations (P for non-linearity <0.05). Supplementary Table 8 shows a significant relationship between PRS and the schizophrenia risk (hazard ratio = 1.65 (95% CI 1.50–1.81)).

As shown in Fig. 2, significant correlations were observed between the four air pollutants and schizophrenia risk in each genetic risk group. We observed significant interaction effects of genetic risk and NO_2 and NO_x exposure on schizophrenia risk (P for interaction <0.001), whereas no significant interaction was found for $PM_{2.5}$ and PM_{10}. Additionally, we fitted a model excluding the interaction terms between air pollution and PRS, and the analysis revealed that both air pollution and PRS still exhibited positive associations with schizophrenia risk (Supplementary Table 9). We also conducted an analysis to explore the joint effects of air pollutant exposure and genetic factors on schizophrenia risk (Fig. 3). The results revealed that individuals with both high genetic risk and high air pollution exposure had the highest risk of developing schizophrenia, surpassing those with low air pollution exposure and low genetic risk ($PM_{2.5}$: hazard ratio = 6.25 (95% CI 5.03–7.76); PM_{10}: hazard ratio = 7.38 (95% CI 5.86–9.29); NO_2: hazard ratio = 6.31 (95% CI 5.02–7.93); NO_x: hazard ratio = 6.62 (95% CI 5.24–8.37)). The effects of NO_2 and NO_x on schizophrenia risk were greater in the higher genetic risk compared with lower genetic risk group and the joint effect was larger than the additive

Table 1 Baseline characteristics of participants included in study

	Total participants (n = 485 288)	Participants without schizophrenia (n = 484 871)	Participants with schizophrenia (n = 417)	P
Age, years: mean (s.d.)	56.55 (8.09)	56.55 (8.09)	55.57 (8.68)	0.013
Gender, n (%)				<0.001
Male	221 952 (45.7)	221 725 (45.7)	227 (54.4)	
Female	263 336 (54.3)	263 146 (54.3)	190 (45.6)	
Ethnicity, n (%)				<0.001
White	459 478 (94.7)	459 124 (94.7)	354 (84.9)	
Black and minority ethnic	25 810 (5.3)	25 747 (5.3)	63 (15.1)	
Employment, n (%)				<0.001
Employed	280 746 (57.9)	280 658 (57.9)	88 (21.1)	
Retired	163 670 (33.7)	163 520 (33.7)	150 (36.0)	
Unemployed, homemaker or others or others	40 872 (8.4)	40 693 (8.4)	179 (42.9)	
Education, n (%)				<0.001
Degree level education	158 934 (32.8)	158 837 (32.8)	97 (23.3)	
Non-college education[a]	242 472 (50.0)	242 278 (50.0)	194 (46.5)	
None of above	83 882 (17.3)	83 756 (17.3)	126 (30.2)	
Townsend deprivation index, mean (s.d.)[b]	−1.32 (3.08)	−1.32 (3.08)	1.60 (3.64)	<0.001
Household income, n (%)				<0.001
<£31 000	240 482 (49.6)	240 121 (49.5)	361 (86.6)	
≥£31 000	244 806 (50.4)	244 750 (50.5)	56 (13.4)	
Residential area, n (%)				<0.001
Urban	417 452 (86.0)	417 056 (86.0)	396 (95.0)	
Rural	67 836 (14.0)	67 815 (14.0)	21 (5.0)	
Social isolation, n (%)				<0.001
Least isolated	217 871 (44.9)	217 791 (44.9)	80 (19.2)	
Moderately isolated	197 020 (40.6)	196 836 (40.6)	184 (44.1)	
Most isolated	70 397 (14.5)	70 244 (14.5)	153 (36.7)	
Genetic risk category, n (%)				<0.001
Low risk	161 601 (33.3)	161 531 (33.3)	70 (16.8)	
Medium risk	162 087 (33.4)	161 975 (33.4)	112 (26.9)	
High risk	161 600 (33.3)	161 365 (33.3)	235 (56.4)	

a. Below degree level.
b. Positive values of the Townsend deprivation index indicate higher levels of deprivation, whereas negative values indicate lower levels of deprivation.

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Table 2 Associations between air pollutants and the risk of incident schizophrenia among participants in the UK Biobank[a]

Air pollutants	Hazard ratio (95% CI)	*P*	*P* for trend
$PM_{2.5}$			
Tertile 1	Ref.	–	<0.001
Tertile 2	1.59 (1.43–1.76)	<0.001	
Tertile 3	1.98 (1.80–2.19)	<0.001	
PM_{10}			
Tertile 1	Ref.	–	<0.001
Tertile 2	1.81 (1.63–2.01)	<0.001	
Tertile 3	2.30 (2.08–2.55)	<0.001	
NO_2			
Tertile 1	Ref.	–	<0.001
Tertile 2	1.43 (1.26–1.61)	<0.001	
Tertile 3	2.30 (2.05–2.58)	<0.001	
NO_x			
Tertile 1	Ref.	–	<0.001
Tertile 2	1.52 (1.35–1.72)	<0.001	
Tertile 3	2.35 (2.09–2.64)	<0.001	

$PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.
a. Cox regression models adjusted for age, gender, ethnicity, education, employment, household income, Townsend deprivation index, residential area and social isolation.

effect, which indicates a synergistic relationship. Additive effects were observed between the four air pollutants and the PRS (Supplementary Table 10 and Method 4).

Discussion

To the best of our knowledge, this is the first large-scale population study to comprehensively summarise the relationship between long-term exposure to air pollution and schizophrenia risk in adults. We found that long-term exposure to PM_{10}, $PM_{2.5}$, NO_x and NO_2 was related to increased schizophrenia risk. We also identified a positive correlation of PRS with the schizophrenia risk. The highest risk of developing schizophrenia was observed in participants with high PRS and exposure to high air pollution levels. Moreover, interactions were observed between genetic risk and two pollutants: NO_2 and NO_x.

Comparison with existing literature

Previous studies have explored the potential relationship between short-term exposure to air pollution and schizophrenia. However, the results were inconsistent. A systematic review conducted in 2022, which summarised 13 papers, found a positive correlation between short-term exposure to $PM_{2.5}$, PM_C (coarse fraction, diameter 2.5–10 μm) and PM_{10} and the risk of schizophrenia.[22] In the current study, we found similar results that long-term exposure to air pollutants, including particulate matter and nitrogen oxides, is linked to increased risk of schizophrenia. However, completely contrary results have been found in other studies. For instance, a study carried out in three subtropical Chinese cities reported that short-term $PM_{2.5}$ exposure did not exhibit any association with schizophrenia risk.[10] Additionally, although some studies have identified a positive effect of NO_2 on the increased risk of schizophrenia,[22] others have observed no significant results regarding the association of short-term exposure to NO_2 and NO_x and the risk of schizophrenia.[23] Unlike these studies on short-term pollution exposure, only one national study has used long-term air pollution exposure data and suggested positive associations between long-term exposure and schizophrenia in adults.[11]

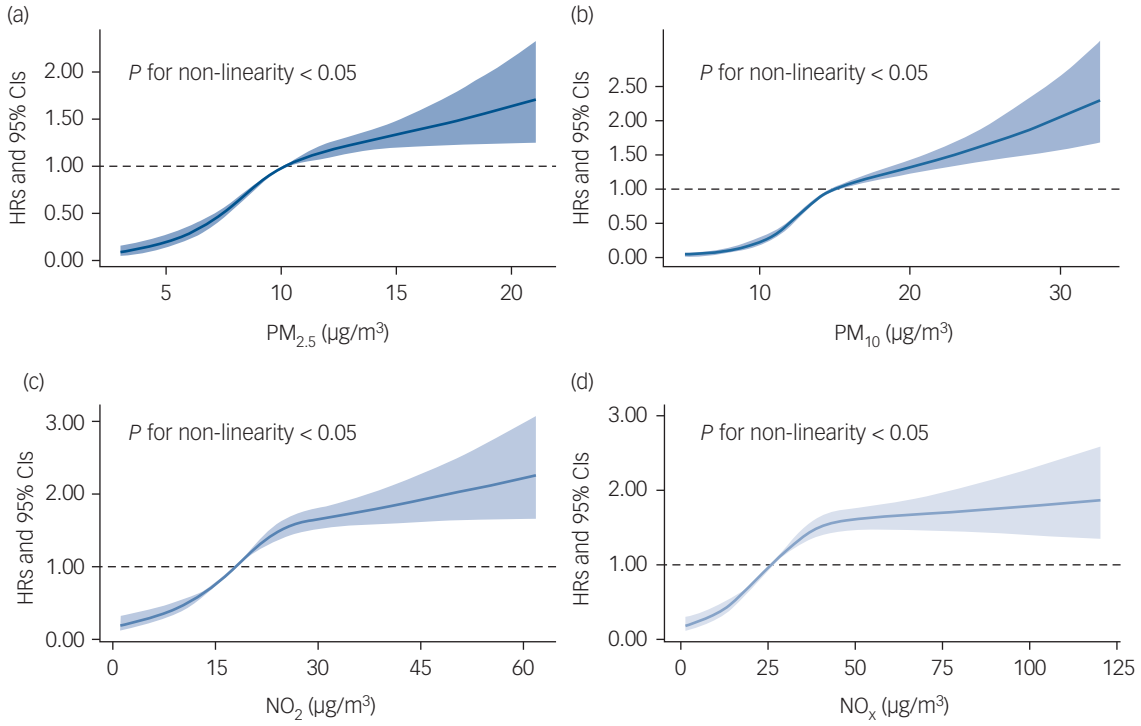

Fig. 1 Associations between long-term exposure to air pollutants and the risk of schizophrenia among participants in the UK Biobank.

A restricted cubic spline regression model with four knots (at the 5th, 35th, 65th and 95th percentiles) was used to estimate the dose–response relations between air pollutants and the risk of schizophrenia among participants. Hazard ratios ((HRs) solid lines) and 95% CIs (shaded areas) were adjusted for age, sex, ethnicity, education, employment, household income, Townsend deprivation index, residential area, social isolation. $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

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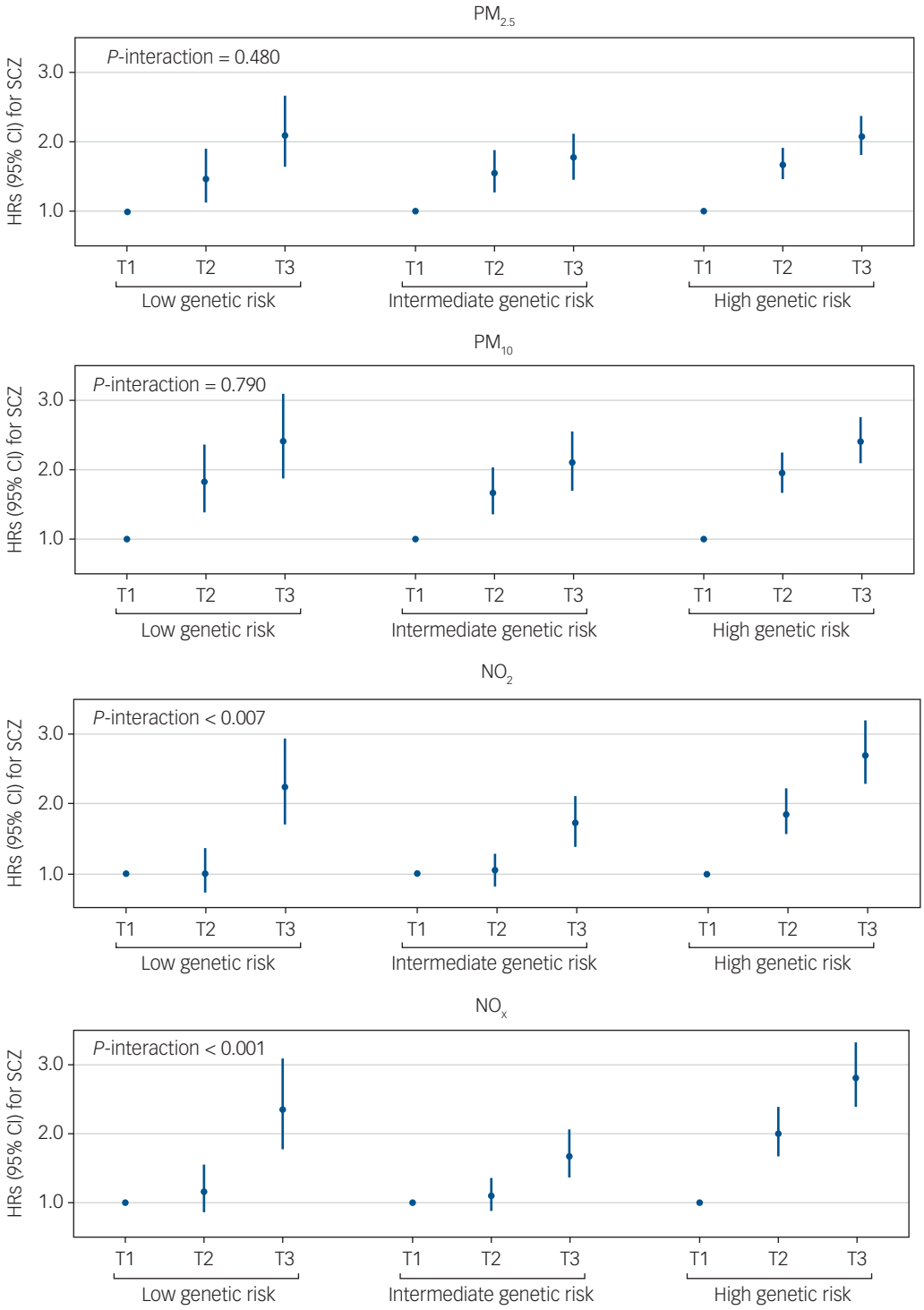

Fig. 2 Associations between air pollutants and the risk of incident schizophrenia (SCZ) stratified by genetic risk.

The *P*-interaction was evaluated using hazard ratios for the product term between air pollutants and effect modifiers. The genetic risk subgroup was defined according to the polygenic risk score, as low (lowest tertile), intermediate (middle tertile) and high (highest tertile). Hazard ratios ((HRs) data points) and 95% CIs (solid lines) were adjusted for age, gender, ethnicity, education, employment, household income, Townsend deprivation index, residential area and social isolation. $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

In our study, we assessed air pollution exposure by matching it to residential addresses with a spatial resolution of 1 × 1 km. This method has been widely adopted in previous research to investigate the relationship between air pollution and various diseases, including mental disorders.[5,14] A Danish study matched children's addresses with air pollution information, confirming a positive relationship between air pollution and schizophrenia risk.[11] Similar results were observed in our study of adults. Moreover, the consistency in methodologies across these studies, including our own, reinforces the reliability and relevance of using address-matched air pollution data to probe the intricate association of air pollution and mental illness. Our findings for the four air pollutants and schizophrenia risk provide new evidence for future insights.

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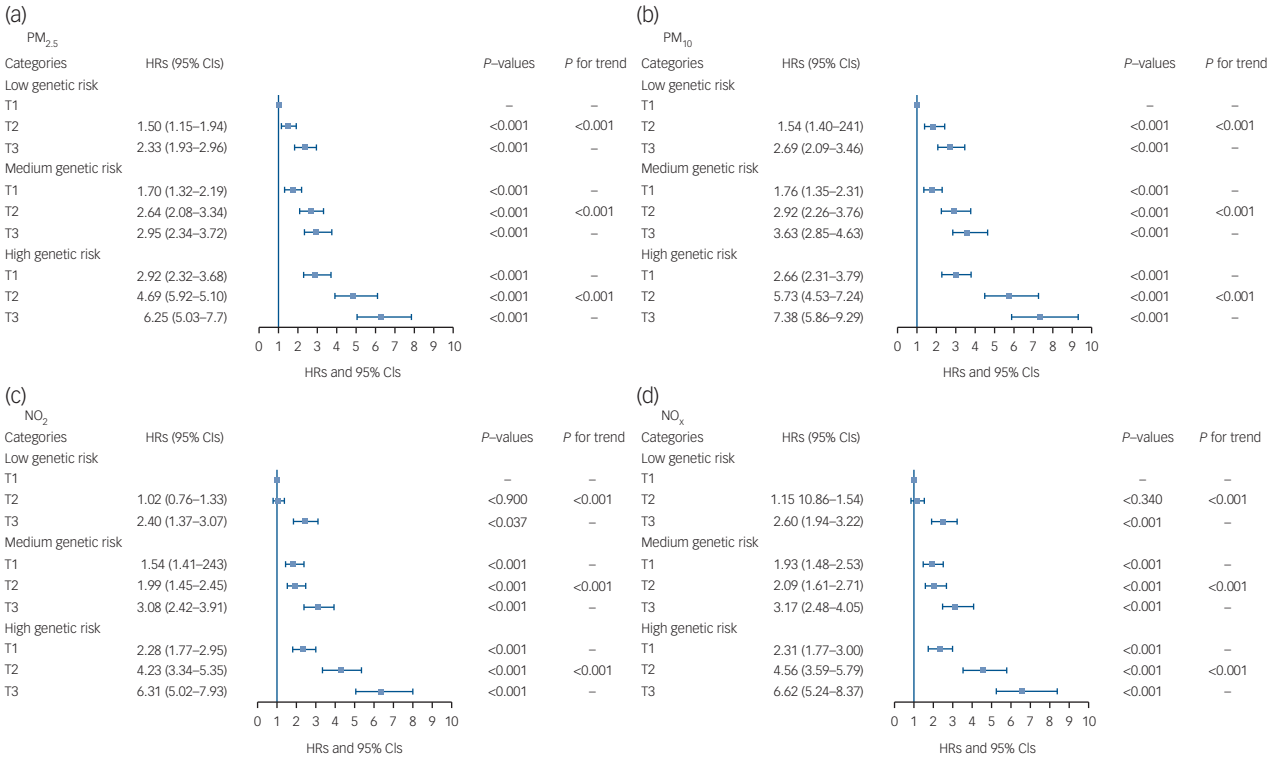

Fig. 3 The joint associations of long-term exposure to air pollutants and polygenic risk score with the risk of incident schizophrenia among participants in the UK Biobank.

Cox regression models adjusted for age, gender, ethnicity, education, employment, household income, Townsend deprivation index, residential area, social isolation, genotyping batch and the first ten genetic principal components. $PM_{2.5}$, fine particulate matter with diameter <2.5 μm; PM_{10}, particulate matter with diameter <10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; HRs, hazard ratios; T1–T3, first, second and third tertile.

Potential confounders

There are other confounders that can influence the risk of schizophrenia. For instance, evidence shows that metropolitan indoor environments may contribute significantly to overall exposure to adverse environmental conditions, particularly for people in industrialised nations.[24] Despite this, most population-based epidemiological studies have primarily focused on outdoor exposure, owing to data availability, neglecting indoor conditions. Quantifying relationships between indoor environments and health remains a substantial challenge. Furthermore, although the current study indicates a positive association between long-term air pollution exposure and increased schizophrenia risk, observational research design does not support the view that air pollutants causally affect the schizophrenia risk. Considering the facts that unmeasured and unknown potential covariates may exist and associations do not mean causality, the results should be interpreted with caution. Further research is warranted to examine the causality of air pollution in relation to schizophrenia risk using methods of causal inference such as intervention studies.

Derivation of the schizophrenia PRS

The PRS calculated by aggregating multiple variants has the capacity to evaluate genetic susceptibility and identify people with high genetic risk.[13] The current study used a standard set of PRS for schizophrenia generated by the UK Biobank. The UK Biobank PRS Release provides well-validated PRS across multiple diseases. The UK Biobank's PRS algorithm was developed using trait-specific meta-analyses based on a Bayesian approach, appropriately pooling data across various ancestries and related traits; these tools are especially valuable as PRS algorithms move beyond simple linear combinations of variant weights.[19] Furthermore, although validating the performance of PRS or comparing different PRS algorithms presents considerable challenges, the UK Biobank has developed and released a robust PRS evaluation tool to facilitate comprehensive and comparable assessments of predictive performance across various PRS in the UK Biobank data-set. Broad benchmark tests have shown that the PRS in the UK Biobank Release outperforms a series of published PRS. Additionally, the UK Biobank is set to routinely update its PRS Release, with goals to improve performance and enlarge the range of traits included. This approach anticipates the ongoing development of improved PRS scores as both data and methodologies progress, facilitating continuous research and advancements in clinical model development.

Biological mechanisms underlying the link between air pollution and schizophrenia

Suggested mechanisms underlying the increased schizophrenia risk due to air pollutants are currently limited and still being explored. Research indicates that air pollution can reach and affect the brain by various pathways, including through the nasal pathway and olfactory bulbs or through respiration, systemic circulation and the blood–brain barrier.[25] Air pollutants have the potential to induce neuroinflammation, endothelial dysfunction and microglia activation and cause cerebrovascular injury,[7,25] thereby promoting mental disorders, including schizophrenia. Experimental studies conducted on mice have demonstrated that PM_{10} can trigger inflammation and endothelial dysfunction in the brain.[26] Air pollution has also been shown to affect central nervous system (CNS) function by activating microglia, with ensuing oxidative stress and neuroinflammation,[25] which may increase the schizophrenia risk.

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Mice experiments have also found that NO_2 can generate reactive nitrogen species (RNS) and reactive oxygen species (ROS), damaging mitochondria in the brain.[27] Population studies have further revealed that environmental $PM_{2.5}$ can increase the risk of relapse in schizophrenia through the mediation of cytokines, including IL-17 and IL-13.[6] The above evidence indicates that each pollutant may act through distinct mechanisms and have varying associations with schizophrenia. Future exploration is required to understand the specific biological mechanisms by which various air pollutants contribute to the pathogenesis of schizophrenia.

Genetic susceptibility to schizophrenia

Existing studies have established that schizophrenia's aetiology is multifactorial, with a substantial genetic component. GWAS have reported that numerous common variants, each with a minor impact, are associated with schizophrenia. Over 100 loci have been found to be significantly linked to schizophrenia.[12] PRS has been demonstrated to be associated with the risk of schizophrenia and it accounted for approximately 7.7% of the variability in schizophrenia case–control status.[28] In the current study, we examined the role of genetic factors in the connection between air pollution and schizophrenia, and observed that genetic susceptibility exacerbates the increased schizophrenia risk in relation to air pollution, especially in participants with high genetic susceptibility. The cellular mechanisms underlying the joint effect of air pollution and genetic factors on schizophrenia are not elucidated. However, previous studies have summarised the association of genetic factors and air pollutants in relation to other mental diseases,[14] and a few studies also indicated that genetic factors may affect schizophrenia through a common mechanism in air pollution such as the *YWHA* gene family,[16] implying that air pollutants and genetic variations might lead to schizophrenia by means of shared mechanistic pathways such as oxidative stress, neuroinflammation and endothelial dysfunction.

Strengths and limitations

The study included some notable strengths that enhance its validity and reliability. A large sample and a prospective study design were employed to enhance the statistical power. Furthermore, reliable nationwide data on time-varying exposure to air pollutants were used. Finally, a novel aspect of the study was the investigation of the interaction and joint impact of air pollutants, genetic factors and schizophrenia risk, which has never been conducted previously. Based on these strengths, we discovered that air pollution has a more extensive impact than previously believed. It affects not only physical health but also significantly affects mental health. The findings emphasise the need for disease prevention and mental health improvement through reductions in air pollution. Moreover, our study reaffirms the positive correlation between air pollution exposure and schizophrenia risk. These findings offer new insights into managing schizophrenia, which is a hidden yet significant public health challenge causing daily difficulties and considerable societal expense. These findings enhance our understanding of the environmental factors linked to this condition and underscore the pressing need for better air pollution control measures.

Nevertheless, some limitations of our study need to be acknowledged. First, in the UK Biobank, a swift and efficient recruitment process yielded a sample of 500 000 participants. However, this efficiency was accompanied by a response rate of 5.5%, raising the possibility of selection bias. However, the actual difference in these estimates is small, and consequences of potentially underestimating such risks are expected to be minimal.[29] Second, since we did not directly measure personal exposure to air pollution, there may be methodological issues regarding ecological fallacy and potential misclassification errors in exposure. One of the methods to reduce the ecological fallacy is the use of the smaller spatial units. In this study, we estimated the concentrations of ambient air pollution at a spatial resolution of 1×1 km, which is a reasonably fine precision of exposure modelling. However, it should be noted that the existence of an ecological fallacy cannot be completely avoided with this measure. Third, the UK Biobank data-set has only limited information on the composition of air pollution, and consequently, uncertainty remains regarding the specific components of air pollution that may be most harmful. Fourth, the identification of incident schizophrenia cases based only on registered medical information and healthcare records may not capture all cases accurately. It is possible that individuals with milder forms of schizophrenia may not seek medical attention, leading to underreporting of schizophrenia cases. Fifth, the identification of incident schizophrenia cases in the UK Biobank cohort relied on the ICD-10 coding system. The use of ICD-10 codes in administrative databases presents an opportunity for studying medical conditions and a variety of diseases in a large 'real-world' setting.[30] However, it is important to acknowledge inherent limitations in population studies using ICD-10 codes, which can include the possibility of misclassification or underdiagnosis. These inaccuracies are generally unrelated to air pollutant levels and often result in less precise estimates while also potentially biasing the risk estimates downwards.[31] Sixth, despite adjusting for numerous potential confounding variables in our analysis, there is still a possibility of residual confounding from unmeasured or unknown factors. Seventh, although we used a time-varying analysis, which is an effective method of avoiding introducing immortal time bias, it remains possible that immortal time bias may have influenced the quantitative results, and caution should be exercised in extrapolating these findings. Eighth, all individuals included in the study were drawn from the UK Biobank, with the predominant proportion being White, which could potentially reduce the generalisation to diverse populations. Therefore, it is imperative to validate the existing results in other ethnicities. Finally, we did not account for the impact of indoor air pollution, owing to the lack of relevant data in the UK Biobank. Although ambient sources contribute the most to indoor air pollution levels and the effect of indoor sources may not be as significant as that of outdoor sources,[32] we should be aware that the time spent indoors has continuously increased with the scale-up of cities, a better understanding of the contribution of the indoor environment on mental health is necessary to protect human health now and in the future.

Conclusions

To conclude, long-term exposure to air pollution was positively associated with an increased schizophrenia risk. Additionally, interactions between NO_2 and NO_x and genetic susceptibility were observed, and the joint effect is larger than the additive effect, indicating a synergistic relationship. In the future, more exploration is needed to provide new evidence that may contribute to changes in policy-making and individual behaviour aimed at reducing the risk of schizophrenia in the population.

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Supplementary material

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Data availability

The data-set can be accessed from the UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). The data on air pollution can be obtained through the DEFRA (https://uk-air.defra.gov.uk/data/pcm-data).

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Author contributions

R.L., R.C. and Y.T. conceived the study. R.L., D.L. and Y.T. contributed to the study design. Y.T. prepared and cleaned the data. R.L. and Y.M. conducted the data analysis. R.L. and Y.T. drafted the manuscript. R.L., R.C., D.L., Y.M., L.T. and Y.T. critically revised the manuscript for intellectual content. All authors approved the final version of the manuscript. R.C. and Y.T. act as guarantors.

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Declaration of interest

None.

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EXTRA CONTENT ONLINE

Reflection

Bark of the giant Sequoia tree

Chinenye Omesili

As the rays of the sun flooded my bedroom from the half-closed grey wooden blinds, I woke up from a deep and rejuvenating sleep, feeling refreshed. This was a stark contrast to the non-refreshing sleep associated with chronic fatigue syndrome – why the dawn?

As I stretched my limbs, I noticed that they were slightly stiff, but not rigid. In my mind, I ran through the Simpson Angus scale to ensure that I was not experiencing any symptoms of drug-induced Parkinsonism symptoms, but quickly reminded myself I was not on any medication. With that in mind, I got out of bed ready to face the day – why the feelings?

I quickly freshened up and prepared breakfast for my little children. Their regular morning gibberish filled my head. The words of Winnicott's theory on 'good enough mother' drifted into my head, but I shook them off and turned the pancake in the pan. On several occasions, I paused to check if I was experiencing a form of thought disorder or an auditory hallucination – why the thoughts?

Dropping the children off at school, I drove to work, enjoying my 40 min of non-clouded consciousness – a world of sanity. Despite experiencing a flight of thoughts, tangentiality and emotional dysregulation all at once, I regularly find solace in the little inspirational card hanging from my rear-view mirror serving as a soundboard for my frustrations. The transference and countertransference energy exchange between us can be cynical, but then who cares – why the silence?

I got to work euphoric but not to the extent that a diagnosis of F30.1 (International Classification of Disease 10th edition, code for manic episodes) comes into play. I whistled into the ward walking on cloud nine, greeting all and sundry, peers and patients alike. Obviously, a cup of tea to kick-start the day – why the joy?

Ward rounds started with new admissions reviewed. Cases ranging from unspecified dementia to drug-induced psychosis, with a sprinkle of Patau's syndrome and bipolar, with me getting all the diagnostic criteria mixed up and asking insurmountable questions. My notepad was open and my pen scribbling away like a reed brush dipped in ink on papyrus. I circled and underlined to place emphasis. Whether or not I get to read them afterwards is any one's guess – why the ambivalence?

In the depth of all of this, I skipped my lunch (and other times ate quickly to avoid my stomach embarrassingly rumbling incoherent pressured speech). I spent my day chasing results, letters and specialists. Some days fly by, running faster than a cheetah, while other days stand still like a catatonic person, taking 3 h to move from one hour to the next. Let me not indulge in my opinions on the British weather and its unstable personality trait. So unpredictable with an attitude of a child with conduct disorder and a flavour of ADHD – why the fiery temper?

How I ended up back at my doorstep was unfathomable. My bag hung down from my shoulder like someone at the extreme end of bipolar, with its zip expressing exhibitionist disorder. One thing was certain – the creases of tiredness on my face could allow a stream to flow. I retired to bed wearing the clothes of exhaustion. I bet I could pass as having REM sleep behavioural disorder. Fortunately, there is no need for a dopamine active transporter (DaT) scan. I know I was just a tired trainee worn out from my day-to-day activities, but I will continue as I am thicker than the bark of the Sequoia tree – Alas, here is the truth.

All in all, I will always choose psychiatry.

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