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Inhibitory neuron links the causal relationship from air pollution to psychiatric disorders: a large multi-omics analysis

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Abstract

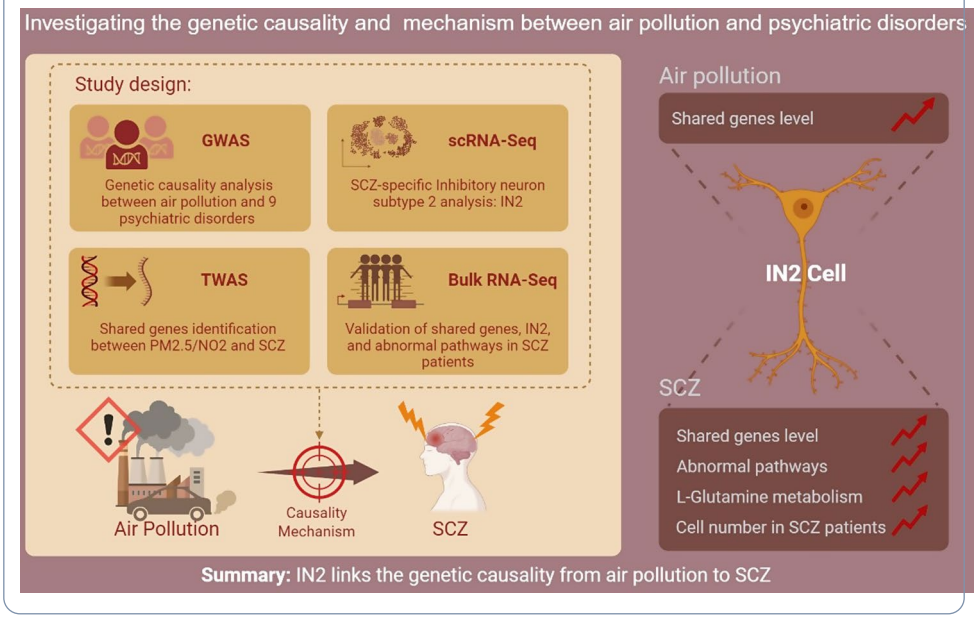
Psychiatric disorders are severe health challenges that exert a heavy public burden. Air pollution has been widely reported as related to psychiatric disorder risk, but their casual association and pathological mechanism remained unclear. Herein, we systematically investigated the large genome-wide association studies (6 cohorts with 1,357,645 samples), single-cell RNA (26 samples with 157,488 cells), and bulk-RNAseq (1595 samples) datasets to reveal the genetic causality and biological link between four air pollutants and nine psychiatric disorders. As a result, we identified ten positive genetic correlations between air pollution and psychiatric disorders. Besides, PM2.5 and NO_2 presented significant causal effects on schizophrenia risk which was robust with adjustment of potential confounders. Besides, transcriptome-wide association studies identified the shared genes between PM2.5/NO2 and schizophrenia. We then discovered a schizophrenia-derived inhibitory neuron subtype with highly expressed shared genes and abnormal synaptic and metabolic pathways by scRNA analyses and confirmed their abnormal level and correlations with the shared genes in schizophrenia patients in a large RNA-seq cohort. Comprehensively, we discovered robust genetic causality between PM2.5, NO_2, and schizophrenia and identified an abnormal inhibitory neuron subtype that links schizophrenia pathology and PM2.5/NO2 exposure. These discoveries highlight the schizophrenia risk under air pollutants exposure and provide novel mechanical insights into schizophrenia pathology, contributing to pollutant-related schizophrenia risk control and therapeutic strategies development.

Keywords Psychiatric disorders, PM2.5, NO_2, Mendelian randomization, Single-cell RNA analyses

Introduction

Psychiatric disorders were the most mysterious diseases in medicine for their unknown genetic mechanism and casual risky factors, raising heavy public burdens. These could be attributed to the neurophysiological complexity and the lack of effective research approaches [1]. However, their pathogenic factors or risky conditions are being

Graphical Abstract



consistently investigated. Air pollution has been a severe public health concern during the past decades and has been linked to the increased risk of various chronic diseases such as cardiovascular disease and cancers [2–5]. Urban dwellers are currently exposed to many detected outdoor air pollution gradients, including fine particulate matter (PM2.5), particulate matter of ≤10 mm in diameter (PM10), nitrogen oxides (NO_x), and indoor agents like nitrogen dioxide (NO_2) as reported [6], their long-term exposure was associated with destroyed lung function or higher asthma incidence during adulthood, as well as psychiatric disorders [7]. Air pollution exposures have raised much concerns and research interests in psychiatric disorder risk [8]. For instance, depression risk was observed to increase by pregnancy PM2.5 exposure [9], and the association between air pollution and schizophrenia risk has been proposed [10]. Whereas the non-causal observational studies and unpractical randomized controlled trials blocked the potential causality investigation and prevented public health decision-making [11].

Mendelian randomization (MR) is a Genome-wide association studies (GWAS)-based epidemiological approach. It utilizes randomized alleles (genetic variants) allocation to simulate randomized grouping in prospective randomized controlled trials. It maximally avoids confounders and reveals the causal relationship between the exposure and the outcome [12]. In principle, the MR analyses rely on three basic assumptions: First, the genetic variants should present a robust association with the exposure. Second, the genetic association between the exposure and outcome should be independent of confounders. Third, the genetic variants affect the outcome exclusively via the exposures [13, 14]. On these bases, MR avoids measurement errors due to the well-defined and stable genetic instrument variants (IVs) and could eliminate reverse causation because the disease cannot affect genotype. Besides, the environmental exposure proxying genetic variants is unlikely to be confounded by other factors [15]. These advantages make MR an appropriate and advanced approach to investigating causal associations between air pollution exposure and psychiatric disorder risk.

Despite inferring the pollutants to psychiatric risk causality, understanding their biological mechanism was also urgently required. Previous reports have shown their correlations with specific genetic patterns [16, 17]. *YWHAB* polymorphic locus rs6031849 could strengthen cumulative PM2.5's associations with schizophrenia relapse [17]. Also, the extent of PM2.5 exposure's influence on depression-related neural function networks could differ by polygenic risk in gene-by-environment interactions [16]. Gene expression transfers gene-level information to biological effects [18–21]. Experimentally, PM2.5 exposure increased Adra2b levels in the mice's brains, and Adra2b overexpression, in turn, could enhance the anxiety-like behavior under PM2.5 exposure [22]. Meanwhile, PM2.5 increased the microglia-related neuroinflammatory transcription [23] to potentially promote mental disorders progression [24]. However, the current understanding of how air pollutants affect psychiatric disorder pathology is still insufficient. The emerging high-throughput approaches offered effective investigation into gene-trait correlations. Transcriptome-wide association study (TWAS) links population gene expression with phenotypes [25], while bulk RNA-seq and single-cell RNA (scRNA) have provided more detailed expression-traits associations and cell-level clues [26]. Large bulk RNA-seq analyses discovered enriched excitatory and inhibitory neuron pathways associated with schizophrenia risk [27], and scRNA further identified schizophrenia populations with specific excitatory and inhibitory neuronal cell states [28]. Therefore, integrating RNA-based approaches with MR is beneficial in inferring air pollutants' causal and biological effects on psychiatric disorders.

In this study, we applied a linkage disequilibrium score regression (LDSC) and a two-sample MR (TSMR) to explore the genetic and causal association between the exposures of common air pollution gradients and nine psychiatric disorder risks and used multivariable Mendelian randomization (MVMR) to exclude the bias of common confounding factors (Fig. 1). Furthermore, the biological mechanism investigation was performed via the TWAS, scRNA, and RNA-seq cohort analyses. We aimed to determine whether air pollutants function as the casual risk of psychiatric disorders and reveal potential biological mechanisms, thereby benefiting public health decision-making and therapeutic management.

(**a**) LDSC and TSMR identifies genetic and causal associations between air pollution exposure and nine psychiatric disorders, and their confounders-adjusted association was examined by MVMR. (**b**) TWAS converged from GWAS to investigate the potential genes and biological processes involved in the association between air pollution exposure and nine psychiatric disorders. (**c**) ScRNA and RNA-seq cohort analyses validated the abnormally expressed genes from TWAS and their involved pathways. Created by Biorender.com.

Methods

MR Study design and data sources

MR analysis has been revealed as an important tool to link environmental exposure and psychiatric outcome risk with casual associations [29, 30]. Therefore, we used MR analysis to investigate the causality between air pollution exposure and psychiatric disorder risk. The flow chart of our study design is shown in Fig. 1. The summary-level GWAS data we used were collected from publicly available databases (summarized in

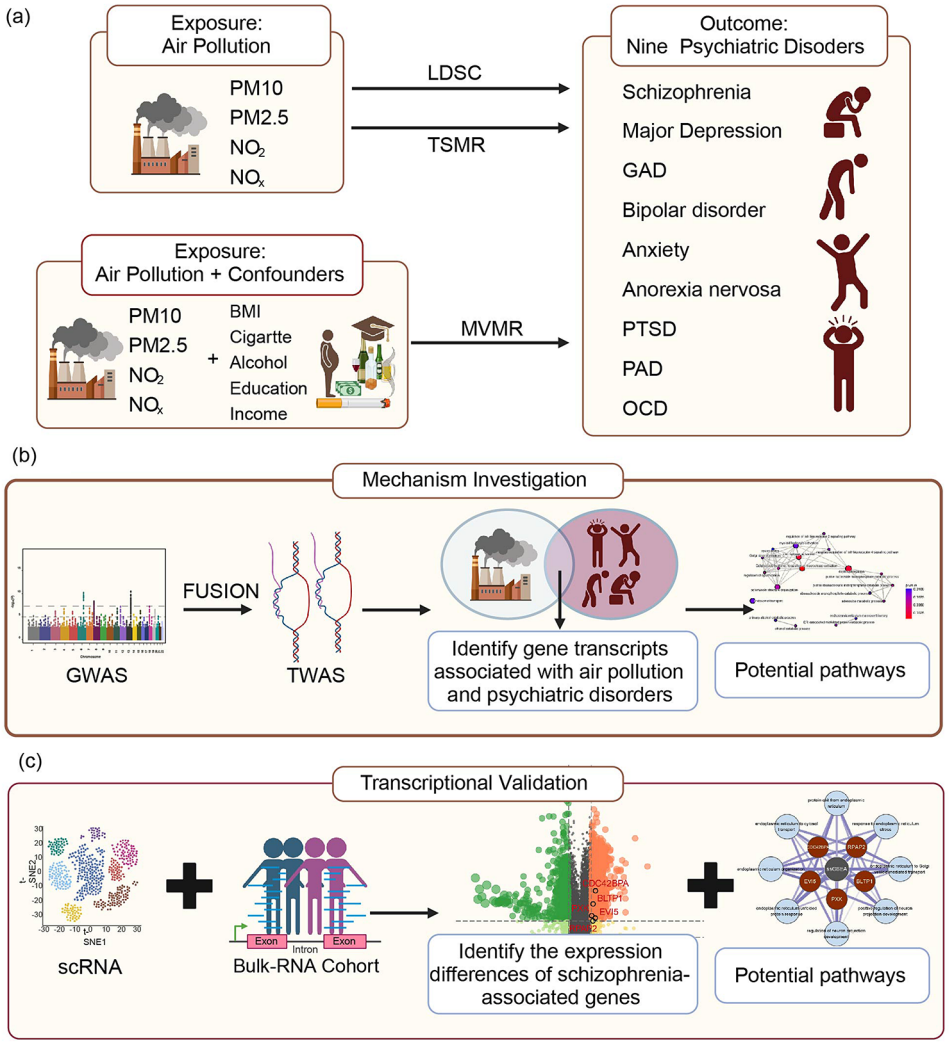


Fig. 1 The MR analyses design and data included in this study

Additional Table S1, sTable 1). No restriction of gender, age, income, or education level was set for these GWAS.

The GWAS data of participants under diverse air pollution exposure levels were derived from UK Biobank [31–33] and collected from the MRC IEU database (https://gwas.mrcieu.ac.uk/) [34, 35]. The residential air pollution range was evaluated in different locations in Great London with a land use regression for the annual average of 2010. The mean PM10 level was 16·24±1.90micro-g/m3, from 11.78 to 31.39 micro-g/m3, and the mean PM2.5 level was 9·99±1.06 micro-g/m3, from 8·17–21.31 micro-g/m3. The summary-level GWAS of PM10 and PM2.5 contained 423,796 individuals and 9,851,867 single-nucleotide polymorphisms (SNPs). The mean NO_2 level was 26·71±7·58 micro-g/m3, from 12·93–108·49 micro-g/m3 The mean NO_x level was 44·11±15·53 micro-g/m3, ranging 19·74–265·94 micro-g/m3. The summary-level GWAS of NO_2 and NO_x included 456,380 individuals and 9,851,867 SNPs.

We also retrieved the GWAS data for analyzing the potential confounders, and these include body mass index (BMI) [31], alcohol intake frequency [31], number of cigarettes previously smoked daily [31], education level (years of schooling) [34], and income level

(average total household income before tax) [31]. These potential confounders' GWAS data included 336,109, 462,346, 108,946, 766,345, and 397,751 participants respectively.

To avoid the bias generated by sample overlapping, the GWAS data of the psychiatric outcomes were obtained from databases outside the UK biobank. The psychiatric disorders were all diagnosed by ICD-10. The GWAS data for major depression (170,756 cases, 329,443 controls, 8,481,298 SNPs) [36], schizophrenia (52,017 cases, 75,889 controls, 7,659,768 SNPs) [27], anorexia nervosa (3495 cases, 10,982 controls, 10,641,224 SNPs), [37] and obsessive-compulsive disorder (OCD) (26,888 cases, 7037 controls, 8,409,517 SNPs) [38] were obtained from the PGC consortium, bipolar disorder (4501 cases, 192,220 controls, 16,380,409 SNPs), post-traumatic stress disorder (PTSD) (1103 cases, 198,110 controls, 16,380,382 SNPs), anxiety (20,992 cases, 166,584 controls, 16,380,449 SNPs), generalized anxiety disorder (GAD) (2163 cases, 198,110 controls, 16,380,388 SNPs) and phobic anxiety disorder (PAD) (2200 cases, 198,110 controls, 16,380,394 SNPs) were obtained from FinnGen (round 5) [39, 40]. This research utilized publicly available data, which waived the ethical approval requirement. Each study contributing to the GWAS contains details for ethical approval and participant consent in their original publications. This research requires no specific ethical approval.

Linkage disequilibrium score regression

We utilized the summarized GWAS data to perform the genetic correlations between the four air pollutant exposures and the nine psychiatric disorders via LDSC [40, 41]. LDSC evaluated the genetic correlation by leveraging the fact that the GWAS effect size estimation for a given SNP encompasses the effects of all SNPs in linkage disequilibrium (LD) with that SNP. First, all SNPs were harmonized with munge_sumstats.py. Then, the genetic correlations were estimated by the ldsc.py with pre-computed LD scores of 1000 Genome European data [42].

Selection for instrumental variables

A threshold (5e-6) was used to ensure sufficient IVs for robust analyses, which has been commonly used in MR research including psychiatric causality inference [43–49]. Then, we calculated F-statistics for each IV and excluded IVs with F-statistics < 10 to retain the strong instruments only [50, 51]. F statistics for each instrument in the exposures were calculated by $\frac{\frac{R2}{K}}{[(1-R2)(N-K-1)]}$, where K is the number of SNP, N is the sample size, R^2 is the variance explained by SNPs calculated by $2 * EAF * (1 - EAF) * \left(\frac{Beta}{SE}\right)^2$ [51]. These approaches were sequentially conducted to ensure the first assumption (exposure correlation assumption) of MR analyses was obeyed. Then, linkage disequilibrium analyses ($r^2 < 0.001$, distance < 10 MB) were conducted to select independent IVs further, eliminating the linkage disequilibrium effects. Finally, IVs significantly correlated with the outcome were excluded. These filtrations were performed to ensure the third assumption was obeyed.

Two-sample mendelian randomization

Seven different methods [random-effect inverse-variance weighted (IVW) [52], weighted median, MR Egger [52–54], MR-RAPS [55] MR-PRESSO [56], Simple Mode, and Weighted mode] were conducted for two-sample MR. IVW was used as the main results, in which the weighted regression of the SNP-outcome effects and SNP-exposure

effects were calculated with the intercept constrained to zero. IVW [52] had the optimal statistical power but under the assumption that all instruments were valid and without pleiotropy. Weighted median and MR egger were used for supplementary results due to their more robust estimates in broader conditions, although less efficient [52–54], and MR-RAPS and MR-PRESSO are advanced in tackling pleiotropy [55, 56]. Moreover, the TSMR examined the association between SNPs and outcome, and the significant SNP was removed after ensuring that its removal exerted no effect on TSMR results according to the leave-one-out approach. Heterogeneity was analyzed by Cochran's Q test [57]. Steiger tests were conducted to examine the causal direction of SNPs [58]. Horizontal pleiotropy was analyzed by the MR Egger intercept test [59, 60], and leave-one-out analysis was used to evaluate whether a single SNP could affect the results, and this could detect the potential violation of the second and third assumptions that the genetic variants are independent of confounders and merely affect the outcome via the exposure [14].

Multivariate mendelian randomization

MVMR allowed for estimating the effects of multiple exposures on an outcome. The included exposures could be confounders, mediators, or colliders [61]. MVMR was also suitable for accounting for pleiotropic variants [62]. We used MVMR to estimate more direct effects of air pollution on psychiatric disorders, adjusting for BMI, alcohol intake frequency, the number of cigarettes previously smoked daily, education level, and income. This is also critical in identifying potential violence of the second assumption that the genetic associations are not correlated to potential confounders [63].

Transcriptome-wide association study (TWAS) and enrichment of biological pathways

To conduct transcriptomic imputation, we converted GWAS into TWAS by the FUSION method [64]. Expression quantitative trait loci (eQTL)-based linear model was used in FUSION to predict gene expression based on the reference panels of RNA-seq. European cortex samples of RNA-seq of Genotype-Tissue Expression version 8 (GTEx v8) [65], CommonMind Consortium's (CMC), and splicing reference [66] were used as reference panels in this study. An Omnibus test was performed to evaluate the combined association of a single gene in multiple reference panels. Genes significantly associated with air pollution and psychiatric disorders were identified in TWAS results. Combined P values of TWAS for air pollutants and psychiatric disorders were calculated by Fisher's Combined P-value (FCP) method. Additionally, we conducted biological pathway enrichment analyses for these genes based on the Gene Ontology database to further understand the potential biological mechanisms underlying air pollution and psychiatric disorders.

Single-cell RNA data processing and analyses

The 26 schizophrenia and control scRNA samples were obtained from gene expression omnibus (GEO, GSE228315) [67]. These samples were derived from either donor or engineered brain organoids. The control group contains eight iPSC samples derived from control donors and five control-engineered hPSC samples, and the SCZ group contains eight iPSC samples derived from SCZ patients and five SCZ-engineered hPSC samples. The quality control, doublets removal, data integration, reduction, and cell

annotation were conducted according to the previously published study [67]. The level of the shared genes in each cell was estimated using "AddModuleScore" function [68], and the functional enrichment was performed using "AUCell", "UCell", "singscore", and "ssgsea " algorithms [69, 70] from the "irGSEA" R package (https://github.com/chuiqin/irGSEA) [71]. We evaluated the metabolic communications among different cell clusters by "MEBOCOST" [72]. The BayesPrism [73] deconvolution was used to estimate the cell proportions in each bulk RNA-seq sample.

RNA-seq cohort processing and analyses

We retrieved the TPM expression matrix 'DER-02-PEC-Gene_expression_matrix' and clinical information 'PEC_capstone_data_map_clinical' of schizophrenia and control cases from http://adult.psychencode.org/#Derived, and the merged PsychENCODE and GTEx TPM matrix was then transferred into log2(TPM+1) matrix for the downstream analyses. The differentially expressed genes were identified using the "limma" R package, and the ssGSEA score of the shared genes was calculated by the "GSVA" [74] R package. To investigate the pathways associated with the shared genes in schizophrenia, we performed WGCNA [75] to filter genes with positive correlations with the shared genes and ssGSEA score. The gene module with the highest correlation was selected and the genes inside the module with gene significance>0.5 and module membership>0.9 [76] were harvested for functional enrichment. The functional enrichment was conducted using the "clusterProfiler" R package [77]. The correlations between shared genes, ssGSEA score, and the pathways were visualized using the "Cytoscape" software [78].

Statistical analyses

Analyses were conducted using the combination of 'TwoSampleMR' packages [79], 'ggplot2', 'clusterProfiler' [77], 'enrichplot', and 'DOSE' [80] in Rstudio version 4.2.2 and FUSION software. Normally-and non-normally-distributed parameters were tested by *student's t*-test and *Wilcoxon* test, respectively. Comparsion among multiple groups of normally- and non-normally-distributed data were examined by Anova and *Kruskal Wallis*-test, respectively. The correlations between normally distributed parameters were calculated by *Pearson's* correlation coefficient and were adjusted by the default 'holm' method. A false discovery rate ($FDR<0.05$) was performed to correct for multiple independent tests in TSMR [23, 52–56], TWAS [64] analyses, gene expression differences comparison, and differentially enriched pathways identification. Results with $FDR<0.05$ were regarded as statistically significant. Meanwhile, those $P<0.05$ with $FDR\geq0.05$ were regarded as suggestive [81, 82]. We used raw P values rather than FDR for MVMR analyses, considering these analyses exploratory and robustness tests for the TSMRs, consistent with previous studies [63, 83–85].

Results

TSMR identified the air pollutants-psychiatric disorders pairs with causal association

After filtration, 29, 58, 84, and 75 instrument SNPs were selected for PM10, PM2.5, NO_2, and NO_x, respectively (Additional Table S1, sTables 2, 3, 4 and 5). We then performed LDSC to evaluate the genetic correlation between the four air pollutant exposures and nine psychiatric disorder outcomes (Additional Table S1, sTable 6). PM2.5, NO2, and NOx exhibit significant positive genetic correlations with schizophrenia,

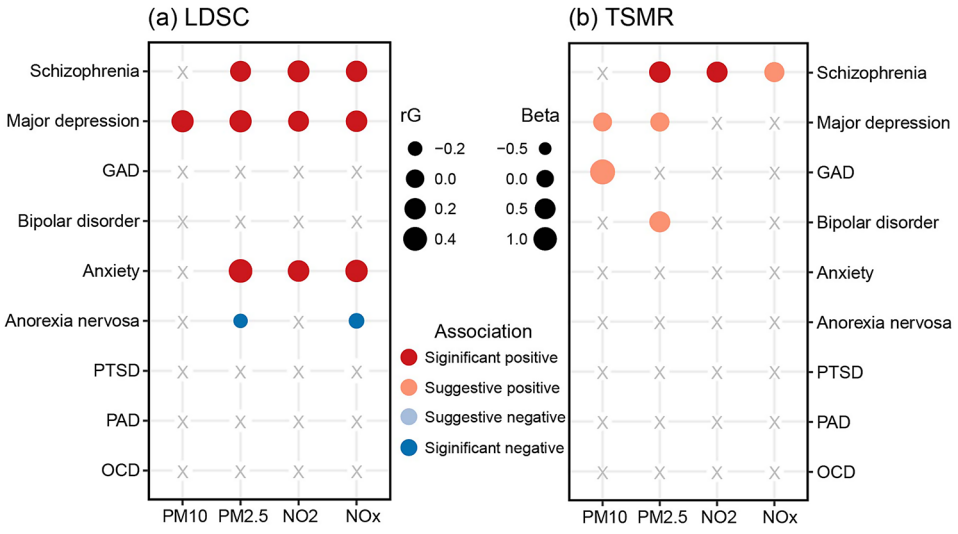


Fig. 2 LDSC genetic correlation and TSMR effect for each association between air pollutants and psychiatric disorders. (**a**) The LDSC dot map indicates the genetic correlations by dot size and statistical significance by color. (**b**) The TSMR dot map indicates the effect size by dot size and statistical significance by colors.

Table 1 Significant TSMR results for air pollution and psychiatry disorders

Exposure	Outcome	nSNP	OR	LCI	UCI	*P*-value	FDR
PM10	Major depression	27	1.224	1.008	1.486	4.11E-02	2.11E-01
	GAD	28	3.804	1.128	12.831	3.13E-02	2.11E-01
PM2.5	Schizophrenia	51	1.87	1.254	2.79	2.15E-03	3.87E-02
	Bipolar disorder	55	1.711	1.035	2.829	3.62E-02	2.11E-01
	Major depression	46	1.268	1.037	1.551	2.08E-02	1.87E-01
NO_2	Schizophrenia	74	1.708	1.261	2.315	5.51E-04	1.98E-02
NO_x	Schizophrenia	71	1.477	1.077	2.026	1.55E-02	1.86E-01

Abbreviation: nSNP, number of single nucleotide polymorphism; OR, odds ratio; LCI, lower confidence interval; UCI, upper confidence interval; GAD, generalized anxiety disorder; FDR, false discovery rate

major depression, and anxiety. Also, a significant positive result between PM10 and major depression was observed (Fig. 2a). These preliminarily indicate their potential correlations. Further, we conducted TSMRs to calculate the effect size of four air pollutants on nine psychiatric disorders, thereby determining their causal correlations. As Fig. 2b shows, two significant positive causal associations were found, with PM2.5 & schizophrenia exhibiting the highest causal effect (OR: 1.870, 95%CI: 1.254-2·790, FDR < 0.05, $P<0.01$), followed by NO2 & schizophrenia (OR: 1.708, 95% CI: 1.261-2·315, FDR < 0.05, $P<0.01$). Besides, suggestive positive associations between NOx & schizophrenia (OR: 1.477, 95% CI: 1.077-2·026, $P<0.05$), PM10 & GAD (OR: 3·804, 95% CI: 1.128-12·831, $P<0.05$), PM10 & major depression (OR: 1.224, 95% CI: 1.008–1.486, $P<0.05$), PM2.5 & major depression (OR: 1.268, 95% CI: 1.037–1.551, $P<0.05$), and PM2.5 & bipolar disorder (OR: 1.711, 95% CI: 1.035-2·829, $P<0.05$) (Table 1). The results of other associations were recorded in Additional Table S1, sTable 7, and 8.

In the sensitivity analyses, the causal directions of the associations in TSMR were examined using Steiger tests. The results showed that the causal direction for all significant and suggestive positive associations identified by TSMR was correct (Additional Table S1, sTable 9). Additionally, heterogeneity was observed in some associations, while the main method, random-effect IVW we used, fitted the presence of heterogeneity

(Additional Table S1, sTable 10) [86]. The leave-one-out analyses showed no peculiar SNPs and the robustness of the results in all TSMR results (Additional Figure S1-S4). Moreover, pleiotropy was also not observed in all significant TSMR results (FDR < 0.05), as the *P*-values for pleiotropy tests were higher than 0.05 (Additional Table S1, sTable 11), showing that the basic assumptions of MR were obeyed.

MVMR identified the causal association without common confounder disruptions

The aforementioned TSMR methods have filtered out the likely causal associations between four air pollutants and nine psychiatric disorders. However, the effects of common confounders might disrupt these causal effects. Hence, we applied the MVMR approach to further identify the robust causal correlations after including the number of daily cigarettes, BMI, alcohol intake, education, and income level as confounders. We observed that PM2.5 and NO_2 exhibit consistent causal effects on schizophrenia after all confounding factors were included in MVMR analyses (Fig. 3; Table 2). In contrast, some suggestive effects of previously identified causal exposure in TSMR were interfered with by the inclusion of confounders. The aforementioned suggestive causal effect of PM10 on GAD attenuated towards null with the inclusion of BMI, alcohol intake, income, and number of cigarettes smoked daily, and that of PM10 and PM2.5 on major depression also failed to pass the MVMR as affected by either cigarette, BMI, income, education or alcohol inclusion (Additional Table S1, sTable 12). Similarly, PM2.5's causal effects on bipolar disorder were also adjusted as not robust after integrating cigarette, BMI, and education. Shortly, these results demonstrate that schizophrenia harbored the most robust independent cause by air pollutants without violating the MR assumptions mediated by confounders, at least for the five common confounding factors BMI, alcohol, cigarette intakes, income, and education.

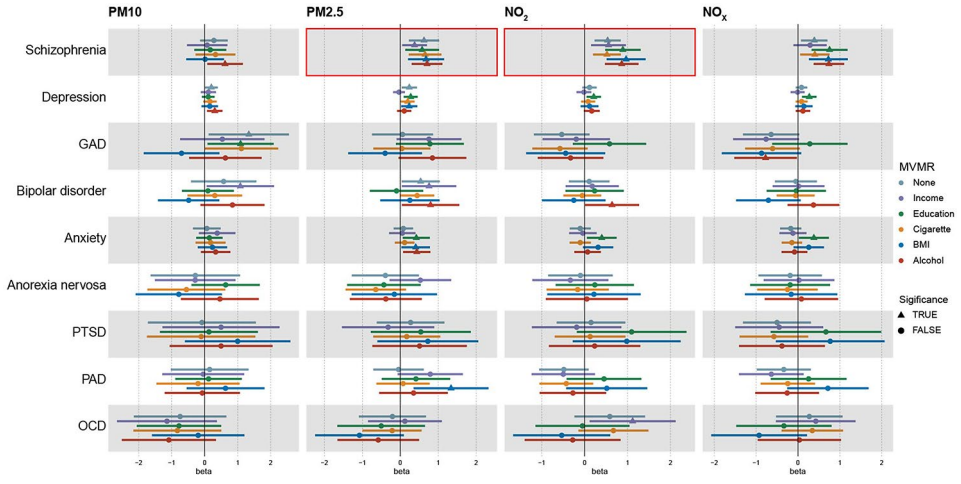


Fig. 3 MVMR of each causal association adjusted by confounders. The forest map describes the adjusted causal effect size of four air pollutants on nine psychiatric disorders by cigarette, BMI, alcohol, education, and income. The triangle and circle dot indicate that the effect size was significant and not significant after the confounder adjustment, respectively

Table 2 Significant MVMR results for air pollution and psychiatry disorders

Model	Exposure	Outcome	OR	LCI	UCI	*P*-value
PM10 & Alcohol	PM10	Schizophrenia	1.853	1.081	3.175	2.48E-02
PM10 & Alcohol		Major depression	1.358	1.076	1.713	9.95E-03
PM10 & Income		GAD	2.965	1.091	8.057	3.31E-02
PM10 & Education		Bipolar disorder	2.943	1.061	8.161	3.80E-02
PM2.5 & Alcohol	PM2.5	Schizophrenia	2.026	1.352	3.037	6.30E-04
PM2.5 & Cigarette		Schizophrenia	1.925	1.253	2.959	2.82E-03
PM2.5 & BMI		Schizophrenia	1.972	1.226	3.171	5.13E-03
PM2.5 & Education		Schizophrenia	1.780	1.140	2.778	1.12E-02
PM2.5 & Income		Schizophrenia	1.458	1.053	2.017	2.30E-02
PM2.5 & BMI		PAD	3.811	1.422	10.215	7.83E-03
PM2.5 & BMI		Major depression	1.264	1.020	1.565	3.20E-02
PM2.5 & Cigarette		Major depression	1.216	1.012	1.462	3.73E-02
PM2.5 & Education		Depression	1.317	1.096	1.581	3.22E-03
PM2.5 & Income		Bipolar disorder	2.137	1.045	4.369	3.74E-02
PM2.5 & Alcohol		Bipolar disorder	2.223	1.045	4.730	3.81E-02
PM2.5 & Alcohol		Anxiety	1.545	1.077	2.216	1.81E-02
PM2.5 & Education		Anxiety	1.527	1.069	2.181	1.99E-02
PM2.5 & BMI		Anxiety	1.503	1.032	2.188	3.35E-02
NO2 & Alcohol	NO2	Schizophrenia	2.372	1.606	3.503	1.41E-05
NO2 & Education		Schizophrenia	2.438	1.612	3.687	2.43E-05
NO2 & BMI		Schizophrenia	2.627	1.667	4.139	3.13E-05
NO2 & Cigarette		Schizophrenia	1.681	1.215	2.325	1.72E-03
NO2 & Income		Schizophrenia	1.744	1.163	2.616	7.11E-03
NO2 & Income		OCD	3.061	1.123	8.342	2.87E-02
NO2 & Education		Depression	1.236	1.045	1.463	1.35E-02
NO2 & Alcohol		Bipolar disorder	1.893	1.008	3.556	4.72E-02
NO2 & Education		Anxiety	1.490	1.053	2.108	2.42E-02
NOx & Alcohol	NOx	Schizophrenia	2.094	1.452	3.018	7.49E-05
NOx & Education		Schizophrenia	2.128	1.385	3.270	5.66E-04
NOx & BMI		Schizophrenia	2.065	1.300	3.282	2.15E-03
NOx & Cigarette		Schizophrenia	1.496	1.054	2.125	2.43E-02
NOx & Alcohol		GAD	0.462	0.219	0.975	4.28E-02
NOx & Education		Depression	1.310	1.101	1.559	2.33E-03
NOx & Education		Anxiety	1.463	1.021	2.095	3.81E-02

Abbreviation: nSNP, number of single nucleotide polymorphism; OR, odds ratio; LCI, lower confidence interval; UCI, upper confidence interval; BMI, body mass index; GAD, generalized anxiety disorder; PAD, phobic anxiety disorder

TWAS discovered shared genes significantly associated with air pollution and psychiatric disorders

We converted the GWAS results to TWAS in order to discover the genes with significant correlations with both air pollution and psychiatric disorders. The detailed gene information and statistical summary of significant associations identified by TSMR and MVMR are listed in Additional Table S1 (sTables 13–17). We depicted the chromosomal location identified of shared genes between PM2.5 & schizophrenia, NO2 & schizophrenia, respectively, and those between the two associations (Fig. 4A, 4B). As a result, 13 shared genes were found between PM2.5 and schizophrenia, and 15 shared genes were found between NO_2 and schizophrenia in the same direction. Seven shared genes (*SULT1A1*, *ZNF680*, *RPAP2*, *NT5C2*, *KIAA1109*, *FANCL*, and *ALG1L11P*) were found in both PM2.5 & schizophrenia and NO2 & schizophrenia with the same direction. Notably, these seven shared genes between the two significant associations are located on different chromosomes, suggesting their independent effects in exposure-outcome

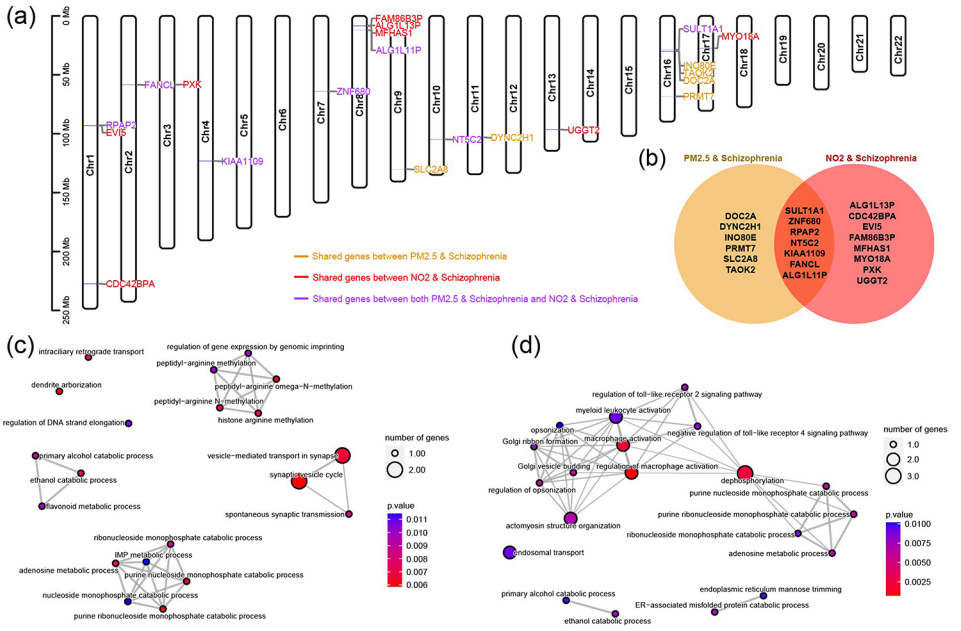


Fig. 4 The shared genes involved in the significant causal association between air pollutants and psychiatric disorders. (**a**) The chromosome graph shows the location of shared genes recognized by TWAS within each significant association. (**b**) The Venn diagram depicts the shared genes and the common shared genes between both PM2.5 & schizophrenia and NO2 schizophrenia. (**c**) Functional enrichment of shared genes within PM2.5 & schizophrenia (c) and NO2 & schizophrenia association (**d**), respectively

interactions (Fig. 4a). In order to further investigate the biological processes in which these shared genes are potentially involved, we input these genes to conduct functional enrichment analyses based on the database of GO terms. The results showed that synapse-related and histone arginine methylation processes were enriched by 13 shared genes between PM2.5 & schizophrenia (Fig. 4c), while macrophage and endoplasmic reticulum-related processes were also observed by 15 shared genes between NO2 & schizophrenia (Fig. 4d). The detailed enrichment results were recorded in Additional Table S1, sTables 18–19. Importantly, nucleoside and alcohol metabolic processes enrichment were found in both two associations (Fig. 4c, 4d), implying that their metabolic disturbance might be the mechanism underlying pollutants-mediated schizophrenia risk.

To further examine whether the IVs used in TSMR were located in the shared genes, we annotated the location of each IV (Additional Table S1, sTable 2–5). None of the IV was located at the shared genes, except rs10094026, which is located at the intron of MFHAS1, significantly correlated with NO2 (P=7·70E-7) but not significantly correlated with schizophrenia (P=4·58E-1). After excluding this IV, NO2 still showed significant correlation and minor alteration in TSMR by IVW (OR: 1.739, 95% CI:1.280-2·362, $P<0.01$). Besides, leave-one-out tests also confirmed the robustness of the result after leaving rs10094026 (Additional Fig. 3).

ScRNA analyses identified abnormally expressed shared genes and their involved pathways in a schizophrenia-derived neuron subtype

The abnormal shared genes between air pollution and schizophrenia risk indicate an influenced cell population during the pathological development. To investigate the potential cell type that turns abnormal and might mediate the causality, we analyzed

the transcriptional expression of shared genes in schizophrenia/control scRNA samples. The scRNA cells were annotated to 27 defined clusters with corresponding cell-specific markers, consistent with a previous publication [67] (Additional Figure S5a), the completed cell annotation, as well as the group allocation, were shown in Additional Figure S5b and S5c, respectively. We first compared the expression differences of the shared genes on each cell type between the healthy donor and schizophrenia-derived samples. We found that five shared genes that show a positive genetic correlation with air pollution & schizophrenia (*RPAP2*, *KIAA1109*, *CDC42BPA*, *EVI5*, and *PXK*) were upregulated in the IN2 cluster (inhibitory neuron subtype2) from the schizophrenia group (Fig. 5a), suggesting that the IN2 cells were affected in pollutants-induced schizophrenia development. To dive into the IN2 cells, we extracted and clustered the IN2 cells according to their high variable features first, and divided them into two levels according to the median scores calculated by the shared genes' expression. We noticed that after the IN2 cells were clustered into C0 and C1, the C1 cluster exhibited a remarkably higher proportion of high-level cells, as well as a higher expression of the five genes (Fig. 5b). This implies that the five genes contribute greatly to the cell fate influence of IN2. Further, we compared the biological heterogeneity between the low-level and high-level IN2 cells, the high-level cells presented elevated biological processes including neuron-neuron synaptic transmission, plus end-directed organelle transport along microtubule etc.

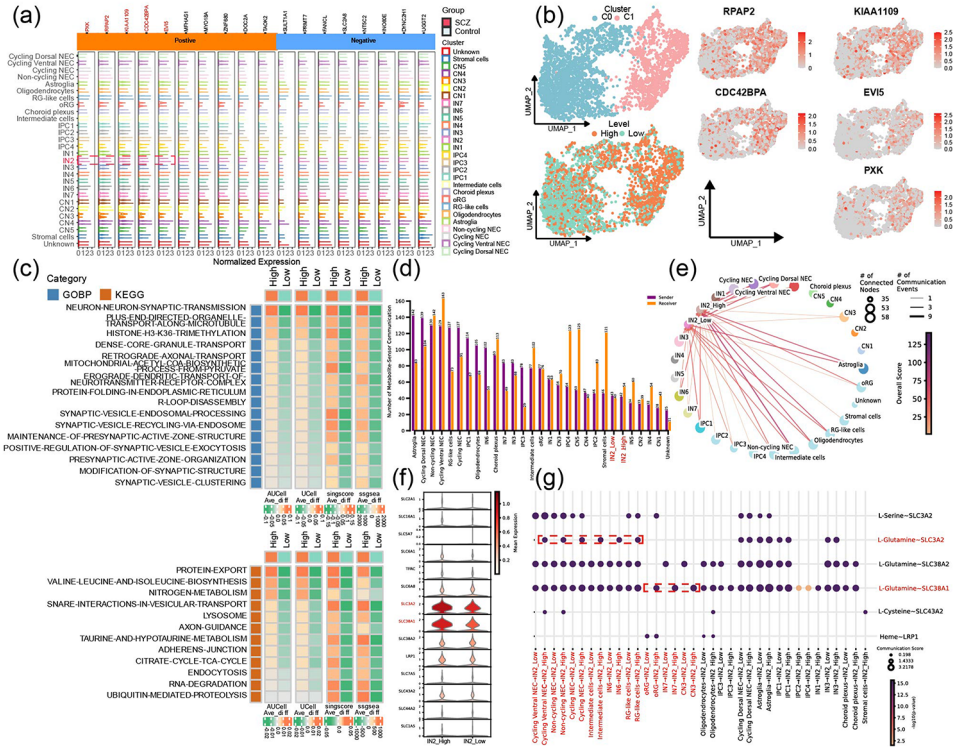


Fig. 5 Single-cell analyses identify schizophrenia-specific cells with abnormal levels of shared genes, pathways, and metabolic patterns. (**a**) The stacked violin plot compares the expression differences of shared genes between schizophrenia and control cases in all cell clusters. (**b**) The scatter plot depicts the different levels of five shared genes and their integrated score between IN2 subtypes. (**c**) Comparison of functional heterogeneity between the high-level and low-level IN2 cells. (**d**) Comparison of the number of metabolite-sensor communication among all cell clusters. (**e**) The circle plot describes the frequencies of communication events estimated from other cell clusters to the high-level and low-level IN2 cells. The arrows indicate the communication direction. (**f**) Comparison of metabolite sensor expressions between the high-level and low-level IN2 cells. (b) The communication network of metabolite-sensor communication from other cells to the high-level and low-level IN2 cells

and protein export, valine leucine and isoleucine biosynthesis pathways etc. (Fig. 5c), indicating their abnormal synaptic activities and metabolic process. Hence, we therefore compared their metabolic crosstalk differences with other cell clusters. We found that the high-level IN2 exhibits a higher number of metabolite-sensor communication with several cell clusters like oRG and RG-like cells etc. (Fig. 5d,e). Specifically, we identified that the receptor genes *SLC3A2* and *SLC38A1* are highly and upregulated in the high-level IN2 cells (Fig. 5f). When final metabolite-sensor communications were estimated, we noticed that high-level IN2 cells showed significantly higher levels of L-Glutamine-SLC3A2-mediated communications from cycling ventral NEC, non-cycling NEC, cycling NEC, intermediate cells, IN6, and RG-like cells, compared to the low-level IN2 cells. Additionally, they also received significantly stronger L-Glutamine-SLC38A1-mediated communications from oRG, IN7, and CN3 cells (Fig. 5g), suggesting that synaptic and metabolic abnormality might be caused in IN2 cells expressing higher expression of the five shared genes.

RNA-seq cohort analyses validated the abnormal expression of five shared genes and their involved pathways in schizophrenia cases

Finally, we employed an RNA-seq cohort with a large number of schizophrenia and control individual cases to validate the abnormal level of the shared genes, pathways, and the schizophrenia-related IN2 subtypes in schizophrenia patients. We confirmed that *RPAP2*, *KIAA1109 (BLTP1)*, *CDC42BPA*, *EVI5*, and *PXK* are consistently upregulated in schizophrenia patients compared to control cases (Fig. 6a,b). Meanwhile, we evaluated the cell proportions in each sample, and we noticed that the high-level IN2 cell proportion was higher in schizophrenia patients, while the low-level IN2 cell proportion was lower (Fig. 6c). After dividing schizophrenia patients into IN2_high and IN2_low groups according to the high-level IN2 cell level, we confirmed that patients with higher high-level IN2 cell proportion harbored elevated expression of *RPAP2*, *KIAA1109*, *CDC42BPA*, *EVI5*, and *PXK* (Fig. 6d), indicating their close association with IN2 cells. To further verify the pathways that are associated with the five genes and their ssGSEA score, we subsequently conducted weighted gene co-expression network analysis (WGCNA) to identify genes that are highly associated with *RPAP2*, *KIAA1109*, *CDC42BPA*, *EVI5*, *PXK*, and ssGSEA level. To obtain the most relevant genes, we collected the genes from the turquoise module with the highest correlation that harbored gene significance > 0.5 and module membership > 0.9 (Fig. 6e). Subsequently, functional enrichment analysis was performed according to the harvested genes. We noticed that pathways related to the endoplasmic reticulum and neuron projection were enriched (Fig. 6f) and their correlations with the five shared genes and the ssGSEA score were shown (Fig. 6g). We then calculated the correlation between the five genes, pathways levels, and the high-level IN2 cell proportion and their strong positive correlations were confirmed (Fig. 6h), implying that IN2 cells with abnormal transcriptional alterations were associated with schizophrenia development.

Discussion

Air pollution has been raised as a severe environmental problem found to affect multi-system dysfunctions, including cardiovascular [87, 88], respiratory diseases [89], neurologic diseases [90], cancers [91, 92], and autoimmune diseases [93], and its correlations

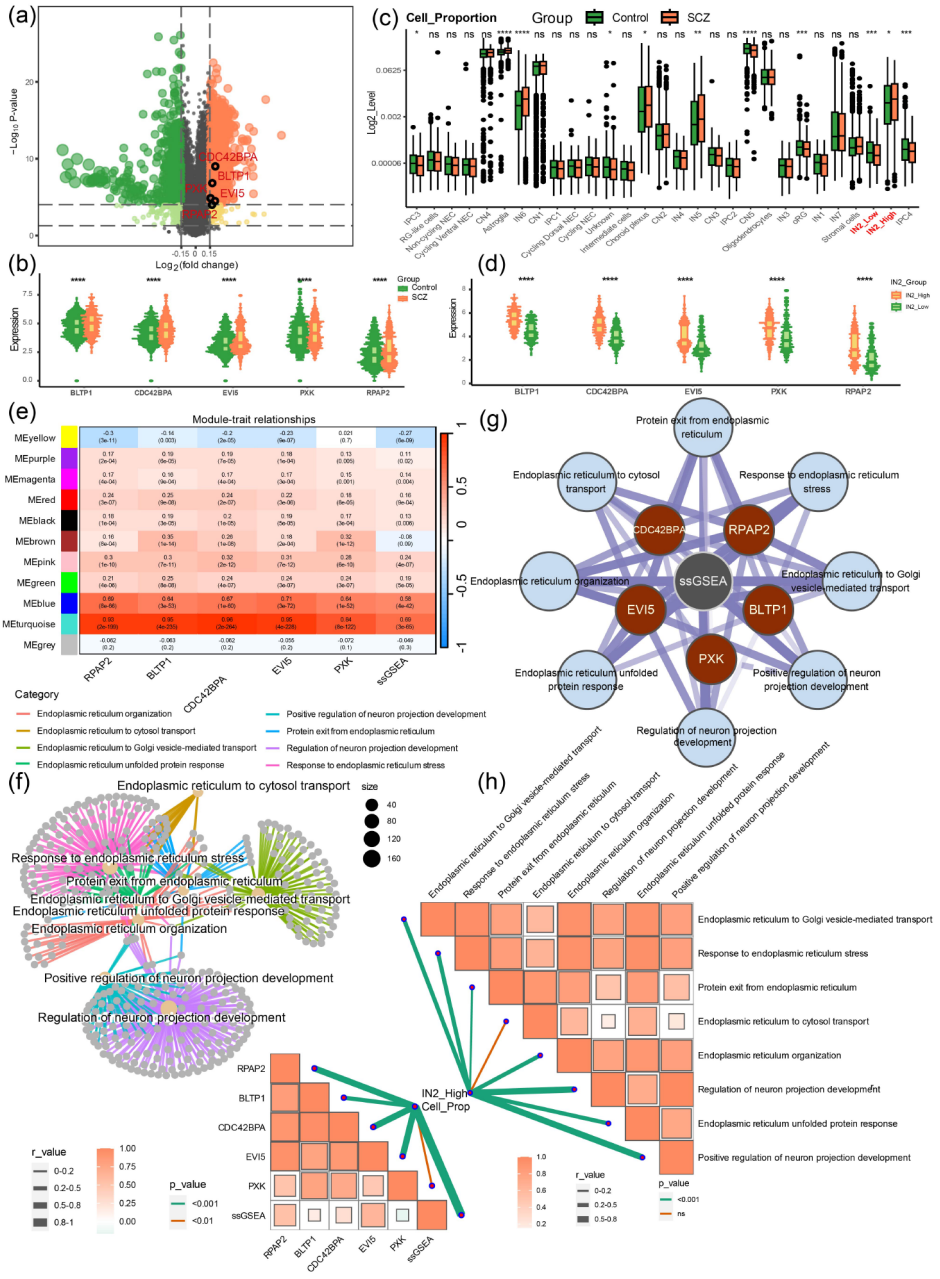


Fig. 6 RNA-seq validates the abnormality of shared genes, cell types, and functional enrichment in schizophrenia patients. (**a**) The volcano plot shows the differentially expressed genes between normal and schizophrenia cases in the RNA-seq cohort. (**b**) Comparison of the five shared genes between normal control and schizophrenia cases. (**c**) Deconvolution of scRNA cell proportion in bulk RNA-seq sample from schizophrenia and control patients. (**d**) Comparison of five shared genes between the IN2-high and IN2-low groups pf schizophrenia patients. (**e**) WGCNA modules and their correlations with the five shared genes and their ssGSEA score. (**f**) The functional annotation of the harvested genes from WGCNA. (**g**) The correlation network exhibits the correlations between the five shared genes, ssGSEA score, and the enriched pathways. The line width and color depth indicate the correlation value, the solid line indicates a positive correlation and the dashed line indicates a negative correlation. (**h**) The correlations of IN2_high cell proportion with five shared genes and pathways

with psychiatric disorders have also been widely observed. Though much observational research has consistently supported the association between air pollutant exposure and mental disorders, their clear causal associations are still unrevealed due to intrinsic approache limitations. The results from observational research were usually biased by

multiple confounders like BMI, cigarette smoking, and alcohol drinking [94], and spurious associations could thus be concluded. To overcome this limitation, we conducted MR to explore their causal associations. We found five suggestive positive as well as two significant positive causal associations via TSMR and excluded common confounders in the causal effects on schizophrenia by PM2.5 and NO_2 using MVMR. Robust causal correlations between other psychiatric disorders (such as anxiety, PAD, and PTSD) and air pollution were not found. Our results accorded with but also contradicted some previous preclinical and systematic review reports [10, 94], indicating the potential bias or interspecies biological/pathological heterogeneity might have disrupted the true associations.

We compared our MR results with previously published research to clarify which exposure to outcome associations are robustly developed and which are not. A recent systemic review including 13 Asia articles has proposed the concerns of short-term air pollution exposure's risk for schizophrenia. They found that PM2.5, PM10, and NO2 exposure correlated to increased schizophrenia risk with consideration of age, country, pollutant concentration, and temperature. [10] However, we noticed that PM10 does not present causal effects on schizophrenia during TSMR analyses, suggesting that the MR analyses might provide the possibility to overcome potential biases. While for PM2.5 and NO2, two recently published MR studies proposed causality clue between PM2.5 and schizophrenia [95, 96], which is consistent with our results. Moreover, we discovered NO2 as another independent risk exposure to schizophrenia and further validated PM2.5's and NO2's causal effects on schizophrenia without bias of BMI, smoking, education, incomes, and alcohol intake. However, limitations should be presented in that we did not include Asian cases, and the contradictory discoveries were not adjusted by case area. This might have differentiated pollutants' effects on schizophrenia risk. Isobel et al. [94] have also conducted a meta-analysis to investigate the correlation between air pollution exposure and depression, anxiety, and bipolar disorder. Their study showed that long-term PM2.5 has a significant positive association with depression, while we found it not significant after adjusting the TSMR via multiple testing corrections. However, we recommended that attention should still be paid to these suggestive associations because of the possibility of overcorrection from traditional MR and adjustment of P-values [97].

A subsequent TWAS analysis was performed to present the transcriptional explanation for genetic casual associations. For schizophrenia, many genes are involved in its associations with either PM2.5 or NO2. Notably, four genes (*SULT1A1*, *INO80E*, *TAOK2*, and *DOC2A*) were located on 16p11.2, whose copy number variant was associated with schizophrenia risk [98]. *SULT1A1* encodes a sulfotransferase that inactivates dopamine via sulfation. It has been detected as a candidate psychosis suppressor in the methamphetamine-treated mice brain, which resembles a positive symptom of schizophrenia [99]. This was consistent with our results. *INO80E*, a chromatin remodeling INO80 complex subunit coding gene, has been identified as a schizophrenia-associated gene [98]. The alteration of DNA open chromatin region affected by chromatin-remodeling-complex was associated with schizophrenia risk SNPs, and the CRISPR editing of these SNPs affected neurodevelopment [100], indicating that chromatin remodeling is important during schizophrenia development. However, the role of *INO80E* in schizophrenia pathology is still unclear due to the limited research. Dendritic spine maturation is critical for synapse integrity. Synapse dysfunction could disrupt synaptic transmission

and contribute to schizophrenia development [101]. *TAOK2* is a serine/threonine kinase coding gene and its alteration blocked the phosphorylation the cytoskeletal GTPase Septin7, which prevents dendritic spines maturation [102] and thereby probably promotes schizophrenia. *DOC2A* also codes proteins involved in calcium-dependent neurotransmitter release, and its depletion or duplication was found in schizophrenia cases [103], suggesting its abnormality promotes the schizophrenia process. Interestingly, PM2.5 has been discovered to induce synapse damage and dysfunction [104, 105], and this shows its probability of causing schizophrenia progression by disturbing synapse function. But its association with *DOC2A* or *TAOK2* remains unclear. On other chromosome regions, *PRMT7* encodes a protein arginine methyltransferase with histone methylation capability. Histone methylation is a well-recognized epigenetic abnormality in schizophrenia because it disrupts oligodendrocytes and myelination function [106]. Long-term PM2.5 exposure was found to increase the H3K4 and H3K9 methylation in macrophages, decreasing their IL-6 and IFN-β secretion [107], indicating *PRMT7*'s role in PM2.5-mediated schizophrenia risk. Also, *PRMT7* was abnormally expressed in schizophrenia tissues and was highly associated with schizophrenia [108]. *NT5C2* encodes a cytosolic 5'-nucleotidase to regulate purine/pyrimidine balance and it was a target of either schizophrenia risk miRNA variants or risk SNP cis-regulation [109, 110]. Additionally, the level of CDC42 Binding Protein Kinase alpha and UDP-glucose/glycoprotein glucosyltransferase 2, encoded by *CDC42BPA* and *UGGT2*, respectively, were found elevated in the schizophrenia samples [111, 112]. Shortly, we discovered genes potentially involved in schizophrenia development, as previous evidence suggests, while their roles in PM2.5- or NO2-mediated schizophrenia risk have not been noticed. Hence, we provided novel clues for the genetic engagements in air pollution and schizophrenia interaction.

Given that transcriptional changes can enhance the association between genetic abnormalities and genotypic transformation, we analyzed the shared genes in bulk tissues and single-cell clusters. Five shared genes (*BLTP1/KIAA1109*, *CDC42BPA*, *EVI5*, *PXK*, and *RPAP2*) are upregulated in the schizophrenia bulk cases and IN2 cell cluster, a subcluster of GABAergic neurons. *BLTP1/KIAA1109* gene variation was associated with neuron migration and embryonic abnormality [113], while whether it leads to *BLTP1/KIAA1109*-deficiency phenotype remains unknown. Overexpressed CDC42BPA protein level [111] was observed in schizophrenia samples, and its association with ATF4-mediated endoplasmic reticulum (ER) stress was recently reported [114] in the Alsheimer disease model, this is similar to what we obtained that *CDC42BPA* was positively correlated with the endoplasmic reticulum activities in schizophrenia cases, indicating *CDC42BPA* could participate in ER-mediated schizophrenia risk. *Pxk* encodes a secretory protein MONaKA that binds to and limits the function of Na^+, K^+-ATPase, it was found to cause Na^+ extrusion efficiency thus disrupting the hippocampal neural energy balance [115], suggesting that transcriptional change of *Pxk* might exert widespread damage on neuron function like synaptic activities, which is consistent with our elevated enrichment result in the high-level IN2 neurons. GABAergic neuron dysfunction in schizophrenia pathology has gained increasing attention [116], recent large data reports have discovered clues that suggest the involvement of inhibitory neuron activity in schizophrenia risk [27, 28]. Interestingly, we also discovered that the high-level IN2 neurons highly expressed *SLC3A2* and *SLC38A1*, and received a high level of communication mediated

via L-Glutamine. As GABAergic neurotransmission relies on the system-A-mediated glutamine transmission [117], the regulated *SLC38A1* might indicate that the activity of IN2 was disordered. Importantly, a higher level of this GABAergic neuron subtype was observed in schizophrenia patients, and its association with abnormal pathways and shared genes was verified, demonstrating that it links the genetic causality from air pollution to schizophrenia. So far, no direct evidence has been published regarding the associations between transcriptional changes of shared genes and schizophrenia pathology, especially in inhibitory neurons, our discoveries provide novel clues for the biological mechanism of schizophrenia risk.

We should emphasize that the results of MR analyses were strictly based on three assumptions: (1) The instrument variants present strong associations with exposures. (2) The genetic association should be free of confounding factors. (3) The instrument variants affect the outcomes exclusively on exposures. Therefore, our study has applied a series of approaches to ensure our results obeyed these assumptions. We excluded IVs with associations with outcomes and with $F<10$ to confirm that the retained IVs are strongly associated with air pollution exposure. Besides, we also include linkage disequilibrium analyses and horizontal pleiotropy analyses to ensure the second and their assumptions were not violated. Considering the existence of potential confounders, BMI, cigarette, and alcohol drinking, in the pollutants-disorder association, we applied MVMR to exclude their confounding effects while evaluating the causal correlations, as a previous study shows [63]. We finally validated the shared genes and pathways in scRNA and bulk-RNA data at the transcriptional level to strengthen the association between genetic variation and schizophrenia phenotype. However, there are still some limitations in this study. The major one is that some unavoidable confounding factors are retained. For instance, the population from different cohorts might introduce biases from population heterogeneity. Although we include as many confounding factors in MVMR analyses as we can, including BMI, cigarette smoking, alcohol drinking, education, and income levels, many other potential confounders might also act as potential confounders and need to be further revealed, such as diet factors. Additionally, the scarcity of transcription data pertaining to air pollution and the unrealizable prospective or experimental verification have constrained the exploration of potential links between schizophrenia-related genes and air pollution.

Comprehensively, we used LDSC, TSMR, and MVMR to identify robust causal associations between four common air pollutant exposures and the common psychiatric disorder outcomes, as well as their effect size. We found that the independent causal effects of schizophrenia by PM2.5 and NO2 could be established. Further, we applied TWAS analyses and discovered the shared genes and pathways between PM2.5 & schizophrenia and NO2 & schizophrenia risk, respectively. Finally, the scRNA and bulk RNA-seq data then identified an inhibitory neuron subtype with abnormal level of the shared genes and pathways. These findings confirmed the risk of air pollution exposure for schizophrenia and identified a critical neuron cell type participating in the pathological process. Therefore, more attention should be paid to schizophrenia risk control under air pollution exposure.

Abbreviations

PM	Particulate Matter
NOx	Nitrogen Oxides
NO2	Nitrogen Dioxide

IVs	Instrument Variants
LDSC	Linkage Disequilibrium Score Regression
TSMR	TWO-SAMPLE MR
MVMR	MULTIVARIABLE MENDELIAN RANDOMIZATION
TWAS	Transcriptome-Wide Association Study
ScRNA	SINGLE-CELL RNA SEQUENCE
SNPs	Single-Nucleotide Polymorphisms
GWAS1	Genome-Wide Association Studies
BMI	Body Mass Index
OCD	Obsessive-Compulsive Disorder
PTSD	Post-Traumatic Stress Disorder
GAD	Generalized Anxiety Disorder
PAD	Phobic Anxiety Disorder
LD	Linkage Disequilibrium
IVW	Random-Effect Inverse-Variance Weighted
eQTL	Expression Quantitative Trait Loci
GTEx	Genotype-Tissue Expression
CMC	COMMONMIND CONSORTIUM
FCP	FISHER'S COMBINED P-VALUE
GEO	Gene Expression Omnibus
IN2	Inhibitory Neuron Subtype 2

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Author contributions

X.L: Resources, Methodology, Software, Formal Analysis, Writing - Original Draft, and Writing - Review & Editing. J.W: Resources, Methodology, Software, Formal Analysis, Writing - Review & Editing, and Writing - Review & Editing. C.Q: Methodology, Visualization, and Writing - Review & Editing. N.Z: Visualization, Methodology, and Writing - Review & Editing. Z.D: Methodology, Software, and Writing - Review & Editing. H.Z: Validation, Software, and Writing - Review & Editing. P.L: Methodology and Writing - Review & Editing. M.M: Methodology, Validation, and Writing - Review & Editing. Z.L: Validation and Writing - Review & Editing. F.F: Conceptualization, Supervision, Project administration, and Writing - Review & Editing. Q.C: Resources, Conceptualization, Supervision, and Writing - Review & Editing. All authors read and approved the final manuscript.

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Data availability

The datasets analyzed during the current study are available in the [UK Biobank] repository [https://biobank.ndph.ox.ac.uk], [PGC consortium] repository [https://pgc.unc.edu/], [FinnGen] repository [https://github.com/FINNGEN/pheweb/], CommonMind Consortium's repository [https://www.nimhgenetics.org/resources/commonmind], GTEx repository [https://www.gtexportal.org/home/], GEO repository [https://www.ncbi.nlm.nih.gov/gds/?term=], and PsychEncode repository [http://adult.psychencode.org/#Derived]. The GWASs used in this study were available in the [MRC IEU] repository [https://gwas.mrcieu.ac.uk/] etc. Detailed information on UK, PGC, and FinnGene cohorts can be found in sTable 1 of Additional Table S1. Code availability statementAll code during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

This research utilized publicly available data, which waived the ethical approval requirement. Each study contributing to the GWAS contains details for ethical approval and participant consent in their original publications. This research requires no specific ethical approval.

Consent for publication
All authors consented to the submission and publication of this study.

Competing interests
The authors declare no competing interests.

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