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Environmental VOC exposure and mental health

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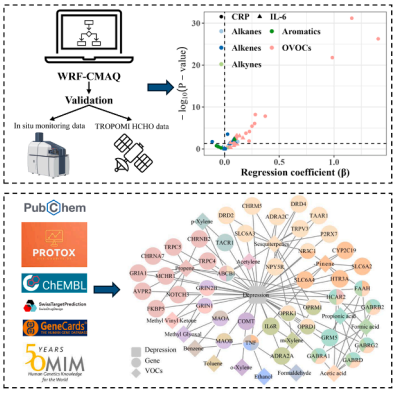
HIGHLIGHTS

- A national-scale, high-resolution VOCs exposure dataset was generated using CMAQ modeling for 33 species.
- Short-term ambient VOCs exposure was linked to systemic inflammation in 9195 psychiatric inpatients.
- OVOCs showed the strongest pro-inflammatory signals, especially formaldehyde and methacrolein.
- Network toxicology identified 43 VOCs-depression target genes that are enriched in neuroimmune and synaptic pathways.

GRAPHICAL ABSTRACT



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ABSTRACT

Volatile organic compounds (VOCs) are major atmospheric pollutants with potential neurotoxic effects, yet their impacts on population-level mental health remain understudied. Here, we develop an integrative framework that combines the Community Multiscale Air Quality (CMAQ) model, epidemiological analysis, and network toxicology to assess the mental health risks of ambient VOC exposure across China. We simulated the spatiotemporal distribution of 33 VOC species at a 36 km × 36 km resolution using CMAQ, driven by the Weather Research and Forecasting (WRF) model. Ground-based observations and satellite-derived formaldehyde validated model performance. Applying these model-based exposure estimates to a national psychiatric cohort of 9195 inpatients, we observed significant associations between short-term VOC exposure and elevated serum interleukin-6 levels (per IQR increase in total VOC: β = 0.09, 95% CI: 0.03, 0.16), particularly for oxygenated VOCs such as formaldehyde (β = 0.14, 95% CI: 0.06, 0.22) and methacrolein (β = 0.06, 95% CI: 0.01, 0.11). Network toxicology predicted

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high blood-brain barrier permeability (probability > 0.9) for most VOCs and identified 43 overlapping genes linked to both VOC exposure and major depressive disorder, enriched in neuroinflammatory and synaptic signaling pathways. Our findings provide multidimensional evidence linking ambient VOC exposure to neuroinflammatory responses and potential mental health risks, supporting the need for broader VOC monitoring and mechanistic research.

1. Introduction

Volatile organic compounds (VOCs) are a significant category of atmospheric pollutants emitted by both human-made and natural sources, including transportation, industrial processes, solvent use, and vegetation [1,2]. VOCs participate in complex photochemical reactions in the atmosphere and are key precursors to ozone (O_3) and secondary organic aerosols (SOA) [3]. In addition to their roles in the atmosphereand and many VOC species have been shown to be carcinogenic and mutagenic even at environmentally relevant levels [4,5].

Both short-term and long-term exposure to VOCs have been linked to various health issues, including skin and mucous membrane irritation, impaired immune function, and cardiopulmonary events [5]. Long-term exposure may lead to more severe health problems, such as reproductive disorders, adverse pregnancy outcomes, liver and kidney damage, cancer, and even death [6–11]. Although numerous studies have highlighted the toxicity of VOCs, the existing evidence still has several limitations. First, most available evidence comes from occupational cohorts, which may not accurately reflect exposure levels in the general population [12–14]. Nevertheless, findings that long-term, low-level VOC exposure may increase the risk of cardiovascular disease, mental illness, and mortality have raised concerns about the potential public health implications of chronic low-dose exposure [6,10,11]. Furthermore, previous studies have primarily examined BTEX compounds (e.g., benzene, toluene, and ethylbenzene) [6,10,11,15], whose carcinogenicity has already been firmly established [16,17]. In contrast, evidence on the health effects of most other VOC species, such as alkenes, halogenated hydrocarbons, and aldehydes and ketones, remains scarce [18,19]. This scarcity largely reflects limited VOC monitoring capacity and the lack of high-resolution, large-scale VOC datasets, which have constrained population-based investigations into their health impacts [15]. Meanwhile, with the growing need for population-based VOC exposure assessment, CMAQ has continued to evolve in recent years, and improvements in chemical mechanisms, source apportionment, and multiscale simulation have further enhanced its applicability for high-resolution, multispecies VOC exposure assessment [20].

Notably, a growing body of research has shown that VOCs can have significant neurotoxic effects [21–23]. Further epidemiological evidence indicates that VOCs, among various classes of environmental chemicals, show the strongest associations with depressive symptoms, suggesting their potential importance for mental health [24]. These findings still require validation in larger, population-based studies. Previous evidence suggests that the neurotoxic effects of VOCs are primarily mediated through neuroinflammatory pathways, such as glial cell activation and the release of inflammatory mediators, as well as the disruption of neuroimmune homeostasis [25]. Nevertheless, it is still necessary to identify which VOC species specifically trigger neuroinflammation, and to elucidate the relative contributions of individual compounds to adverse mental health. Furthermore, it is unclear whether the effects of VOCs on mental health involve biological pathways beyond neuroinflammation. Therefore, network toxicology, an emerging and increasingly integrative approach, has become a valuable framework for systematically identifying the mechanisms and targets involved in environmental exposure and mental health outcomes, particularly through its growing integration with transcriptomics, molecular docking, and experimental validation [26–30].

To fill these research gaps, we combine air-pollution modeling validation, hospital-based cohort studies, and molecular mechanistic analyses to provide a comprehensive assessment of how VOC exposure affects mental health. First, we generate a high-resolution, multispecies VOC dataset using the Community Multiscale Air Quality (CMAQ) model, and then validate the simulations against both ground-based measurements and satellite observations. Second, we combined these estimates with a nationwide cohort of hospitalized psychiatric patients to examine the association between short-term VOC exposure and inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), to identify VOC species most strongly associated with neuroinflammatory responses. Finally, we apply a network toxicology approach to identify the molecular targets and pathways that may mediate the associations between VOCs and depression.

2. Method

2.1. Study design

We employed a multi-stage, integrated research framework that combined atmospheric modelling, epidemiological analysis, and network toxicology approaches. We estimated VOC exposure levels using the CMAQ model and validated these with monitoring data. We then linked the exposure levels to a nationwide cohort of hospitalised psychiatric patients. We quantified the association between short-term VOC exposure and inflammatory biomarkers (CRP and IL-6), and further applied network toxicology methods to identify VOC species associated with neuroinflammatory pathways and their potential molecular targets. Together, these research components, from exposure assessment and population-level analysis to elucidation of mechanisms, provided multilayered support for understanding the health effects of environmental VOC exposure.

2.2. In situ monitoring of ambient VOCs

To obtain high-time-resolution measurements of ambient VOCs, continuous online monitoring was conducted at a site on the Peking University campus (116.3109°E, 39.99287°N) from 11 November 2018–28 February 2019. During this period, 99 VOC species were measured, including 29 alkanes, 28 halocarbons, 16 aromatics, 13 oxygenated VOCs (OVOCs), and 10 alkenes, along with representative compounds such as isoprene, acetylene, and acetonitrile. VOC sampling and analysis were performed using a fully automated preconcentration gas chromatography-mass spectrometry/flame ionization detection (GC-MS/FID) system operating at an hourly resolution. The instrument featured dual-channel injection. After cryogenic dehumidification, air samples were routed to two parallel adsorption traps and preconcentrated at −165 °C. The trapped VOCs were then thermally desorbed at 100 °C, separated by gas chromatography, and quantified using both an FID and an MS detector. Each analytical cycle consisted of four steps: sample collection with internal standards, thermal desorption, chromatographic separation, and column backflushing. Quantification was based on a combination of external and internal calibration, with FID quantified by external calibration and MS by internal calibration. Multipoint calibration curves were established over the range of 0.2–16 ppbv, and only compounds with satisfactory linearity ($R^2 > 0.99$) were included in the quantitative analysis. Four stable internal standards, bromochloromethane (CAS 74–97–5), 1,4-difluorobenzene (CAS 540–36–3), chlorobenzene-d5 (CAS 3114–55–4), and 4-bromofluorobenzene (CAS 460–00–4), were used to correct for instrumental drift

and ensure measurement stability. During routine analysis, daily calibration was performed using a 2 ppbv standard gas, and both instrument and system blanks were regularly analyzed to assess instrument stability and potential contamination. Species-specific method detection limits (MDLs), together with detailed calibration procedures and QA/QC protocols, are provided in the Supplementary Material [31–33].

2.3. Spatiotemporal modeling of ambient VOCs using CMAQ

In this study, we employed the CMAQ model (version 5.0.2) to simulate the spatiotemporal distribution of ambient VOCs across mainland China at a horizontal resolution of 36 km × 36 km. Meteorological inputs were provided by the Weather Research and Forecasting (WRF) model (version 3.9.1.1), and emission inputs were processed using the Sparse Matrix Operator Kernel Emissions (SMOKE) model (version 3.6) [34]. Anthropogenic emissions were based on the 2017 AiMa Emission Inventory [35,36], which covers key source sectors including agriculture, biomass burning, fugitive dust, industry, power, transportation, residential, and solvent usage [37–39]. The final input emissions have been optimized/constrained using the 2019 air quality observations, applying the inverse method described in Du et al. Yunsong et al., [36]. Environmental statistics, pollution census, and local emission inventories were also considered in the updating process. BVOC emissions were estimated using the BEIS 3.61 model [40]. The SAPRC07tc mechanism represented the gas-phase chemistry, and aerosol processes were simulated using the AERO6 module [41,42]. The model employed 13 vertical layers extending from the surface to the tropopause, enabling a comprehensive simulation of VOC emissions, transformations, and transport [43,44]. CMAQ simulations were performed for 2019–2022. The model output included hourly concentrations of 33 VOC species, providing gridded exposure data to support downstream toxicological and epidemiological investigations. Detailed model configurations and key parameter settings for the CMAQ simulations are provided in Table S1. The 33 VOC species were selected from the CMAQ outputs to represent the major VOC categories relevant to this study, after consolidating redundant or overlapping entries during the screening process. Further details on the species selection are provided in Table S2 and the Supplementary Methods.

To assess model performance, observed VOC concentrations were extracted from in situ monitoring data and compared with CMAQ outputs using Pearson correlation coefficients. Additionally, we obtained daily tropospheric formaldehyde (HCHO) column densities from TROPOMI satellite retrievals spanning 2019–2022 [45]. For this conversion, column concentrations of formaldehyde (originally in mol/m^2) were converted to volumetric mixing ratios (ppbv) using the ideal gas law, assuming a 10 km column height, standard pressure (101325 Pa), and temperature (298 K). Formaldehyde was selected as a representative VOC, and grid-level temporal correlations between modeled and satellite-derived daily concentrations were calculated. A spatial correlation map was subsequently generated to evaluate the regional performance of the CMAQ simulations.

2.4. Associations between short-term VOCs exposure and inflammatory biomarkers

To investigate the potential biological pathways linking exposure to volatile organic compounds (VOCs) to psychiatric disorders, we examined the relationship between short-term VOC exposure and inflammatory biomarkers in a cohort of psychiatric inpatients. This cohort comprised 15,445 patients admitted between October 2016 and September 2024, who had received primary diagnoses based on ICD-10 codes F01-F99, which cover various mental and behavioural disorders. To minimise the impact of clinical interventions on inflammatory markers, fasting venous blood samples were collected from all patients the day after admission. CRP was measured by turbidimetric assay, and IL-6 by chemiluminescent immunoassay. Comprehensive biochemical and haematological parameters were recorded concurrently to assess overall inflammatory and metabolic status. For the present analysis, we included 9195 patients with complete data on IL-6, CRP, and residential address from 2019 to 2022. Daily VOC concentrations were simulated using CMAQ (spatial resolution 36 km × 36 km). The average VOC concentration over the seven days preceding hospitalisation was used as the individual short-term exposure level, assigned by the patient's residence administrative district code. Meteorological covariates (including daily mean temperature and relative humidity) were derived from ECMWF ERA5 reanalysis data and incorporated into the exposure-response model as potential confounders [46]. Detailed formulas and parameter settings are provided in Supplementary Methods. To complement the linear regression analysis, we further used a random forest model as a supplementary approach to rank the relative importance of individual VOC species in predicting inflammatory biomarkers. The model was implemented using the randomForestSRC package, with ntree = 500 and nsplit = 10.

2.5. Network toxicology analysis

To investigate the potential molecular mechanisms linking volatile organic compound (VOC) exposure to mental health outcomes, we conducted a network-based toxicology analysis focusing on key VOC species identified in CMAQ simulations. First, we retrieved structural information, including Simplified Molecular-Input Line-Entry System (SMILES) representations and 2D/3D molecular structures, from the PubChem database for subsequent toxicity assessment and target prediction. Using the ProTox 3.0 platform, we generated toxicological profiles encompassing toxicity rankings, median lethal dose (LD_{50}), target-organ toxicity (e.g., neurotoxicity and blood–brain barrier permeability), and cytotoxicity metrics to identify VOC species potentially associated with the central nervous system [28,47]. To predict potential targets, compound SMILES strings or compound names were submitted to ChEMBL (version 35), SwissTargetPrediction, and STITCH (version 5) databases to obtain candidate target genes [48]. To focus the analysis on mental health, we curated genes associated with major depressive disorder (MDD) from the GeneCards and Online Mendelian Inheritance in Man (OMIM) databases. MDD was selected as it is the most prevalent mental disorder globally, with well-defined pathophysiological mechanisms [49]. It serves as a paradigmatic model for studying environment-related neuropsychiatric mechanisms. Candidate genes potentially mediating the neuropsychiatric effects of VOCs were identified by intersecting the predicted VOC target genes with the MDD-associated genes. We performed functional enrichment analysis of these candidate genes using the GO, KEGG, and Reactome databases to identify pathways associated with neuroinflammation, immune dysregulation, oxidative stress, and other central nervous system-related mechanisms. Pathways with adjusted $p < 0.05$ were considered statistically significant. Finally, Cytoscape was used to construct a VOC-target-function-disease interaction network to visualise the potential molecular link between environmental VOC exposure and mental health risk. All databases used in this study were accessed in July 2025.

3. Results

3.1. Validation of CMAQ-simulated VOC concentrations using ground and satellite observations

We validated the CMAQ-simulated VOC concentrations against in situ GC-MS measurements collected in Beijing from November 2018 to February 2019 (Fig. 1). The CMAQ-simulated TVOC time series captured the overall temporal patterns observed in the measurements and reasonably well reflected the timing of major pollution events. However, the simulations tended to underestimate peak concentrations and showed slight delays during periods of high exposure (Fig. 1**A**). At the chemical-group level, the CMAQ-simulated concentrations showed

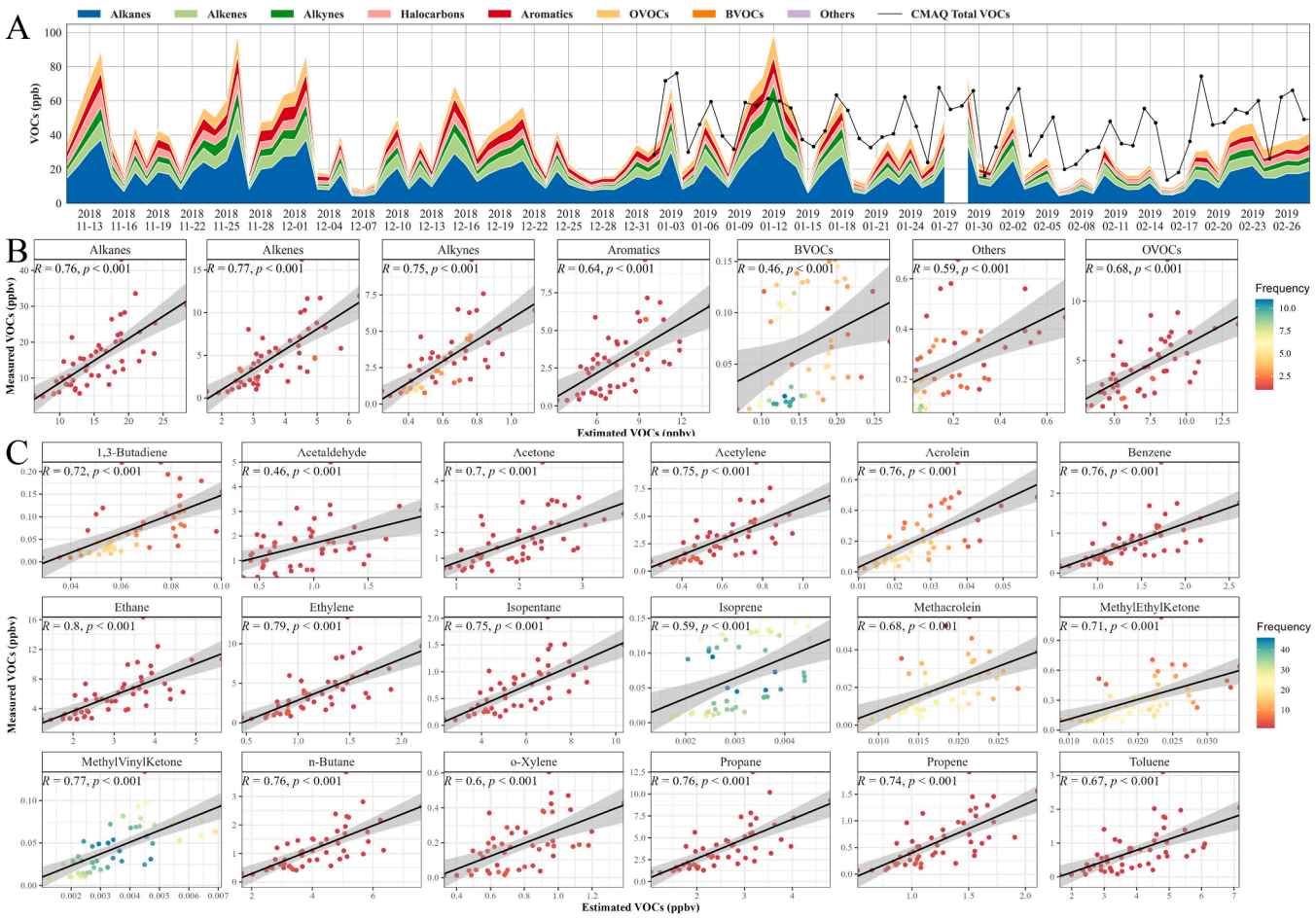

Fig. 1. CMAQ-simulated trends, composition, and validation of VOC subgroups. A, Temporal variation and relative composition of volatile organic compound (VOC) subgroups simulated by CMAQ from December 2018 to February 2019. B, Correlation between CMAQ-estimated and observed concentrations for six VOC categories, with linear fits and 95% confidence intervals. C, Correlation between CMAQ-estimated and observed concentrations for 18 selected VOC species, with linear fits and 95% confidence intervals.

relatively strong correlations ($p < 0.05$) with observations for alkanes ($R = 0.76$), alkenes ($R = 0.77$), and alkynes ($R = 0.75$), and moderate agreement for aromatics ($R = 0.64$) and OVOCs ($R = 0.68$). By contrast, BVOCs exhibited a weaker correlation with the observed values ($R =$

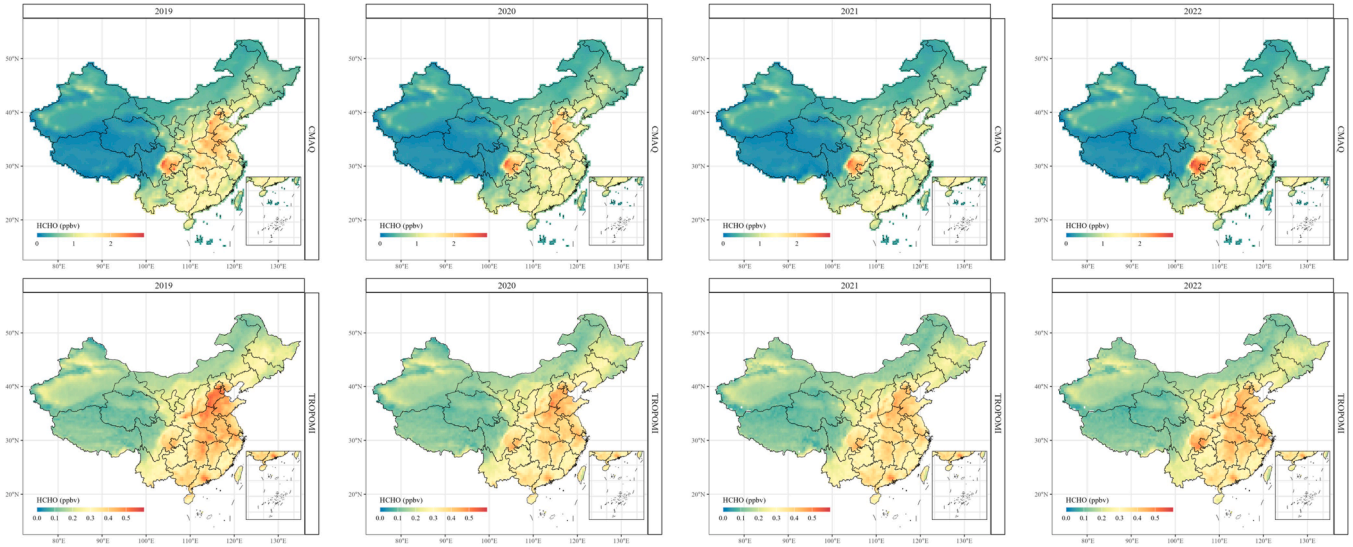

Fig. 2. Spatial distribution of CMAQ-simulated and TROPOMI-retrieved formaldehyde (HCHO) across China. Annual mean concentrations of formaldehyde (HCHO) simulated by CMAQ (top row) and retrieved from Sentinel-5P (bottom row) for the period 2019–2022. Each map presents the annual mean concentration for the corresponding year.

0.46) (Fig. 1**B**). At the level of individual compounds, ethane, ethylene, acetylene, benzene, and propane all exhibited high correlations ($R \geq 0.75$). Conversely, correlations were markedly lower for more reactive VOCs, including acetaldehyde and isoprene.

We further compared CMAQ-simulated near-surface HCHO concentrations with tropospheric HCHO column densities retrieved by the TROPOMI satellite (Fig. 2). Overall, the surface HCHO concentrations simulated by CMAQ showed strong spatial consistency with satellite observations, with both datasets revealing a clear southeast-northwest gradient. This spatial pattern remained broadly stable from 2019 to 2022, with only minor year-to-year variations in the intensity and extent of a few high-concentration areas. Correlation analyses showed that CMAQ-simulated HCHO and TROPOMI-retrieved values were positively correlated across most regions, with the strongest agreement observed in the North China Plain, northeastern provinces, and the eastern coastal areas (Figure S1). Figures S2-S7 present the spatial patterns and seasonal variability of TVOCs and the individual VOC groups.

3.2. Associations between VOC exposure and inflammatory biomarkers

We included 9195 psychiatric inpatients (63.3% female), the majority of whom were diagnosed with affective disorders (International Classification of Diseases, 10th Revision [ICD-10]: F30–F39) or schizophrenia spectrum disorders (F20-F29) (Table 1). Participants were primarily located in eastern and central China (Fig. 3**A**). Total VOC exposure was positively associated with serum interleukin-6 (IL-6) levels ($\beta = 0.09$; 95% CI: 0.03, 0.16), whereas no overall association was observed with C-reactive protein (CRP, $\beta = 0.04$; 95% CI: −0.06, 0.15) (Fig. 3**B;** Table S3). At the subclass level, OVOCs showed the strongest and most consistent associations with both IL-6 ($\beta = 0.12$; 95% CI: 0.05, 0.19) and CRP ($\beta = 0.22$; 95% CI: 0.10, 0.34), suggesting a predominant role of oxygenated compounds in systemic inflammation. At the compound level, several OVOCs were robustly linked to inflammatory biomarkers. Formaldehyde (IL-6: $\beta = 0.14$; 95% CI: 0.06, 0.22; CRP: $\beta = 0.37$; 95% CI: 0.24, 0.50), propionaldehyde and larger aldehydes (IL-6: $\beta = 0.11$; 95% CI: 0.05, 0.18; CRP: $\beta = 0.25$; 95% CI: 0.15, 0.36), acetic acid (CRP: $\beta = 1.41$; 95% CI: 1.15, 1.66), and C3 + organic acids (CRP: $\beta = 1.16$; 95% CI: 0.97, 1.36) exhibited the strongest positive associations. Additional OVOCs, including methanol, acetaldehyde, acetone, and methylglyoxal, also showed consistent effects with both IL-6 and CRP. By contrast, most alkanes, alkenes, and aromatic hydrocarbons exhibited weak or insignificant associations with CRP, whereas isoprene displayed moderate positive correlations. In the random forest analysis, methanol, formaldehyde, and propionaldehyde emerged as the most influential predictors of IL-6 levels, while C3 + organic acids and methylglyoxal contributed most strongly to CRP prediction. When the data were stratified by ICD-10 diagnostic categories (Fig. 3D and S8), the positive correlation between VOC exposure and IL-6 remained significant across the main diagnostic groups. The associations were especially pronounced among patients with affective disorders and those with schizophrenia spectrum disorders, lending further support to the robustness of the results. Season-stratified subgroup analyses showed that the effect estimates were generally higher in the cold season than in the warm season, although no clear statistically significant seasonal difference was observed (Figure S9).

Table 1
Baseline characteristics of study participants.

Variables	All participants	Male	Female
Sample size [n(%)]	9195 (100.0%)	3373 (36.7%)	5822 (63.3%)
Age [mean (SD)], years	27.1 (13.7)	28.4 (13.6)	26.4 (13.8)
ICD10			
F00–09	50 (0.5%)	26 (0.8%)	24 (0.4%)
F10–19	404 (4.4%)	315 (9.3%)	89 (1.5%)
F20–29	1598 (17.4%)	725 (21.5%)	873 (15.0%)
F30–39	5199 (56.5%)	1592 (47.2%)	3607 (62.0%)
F40–48	718 (7.8%)	394 (11.7%)	324 (5.6%)
F50–59	843 (9.2%)	119 (3.5%)	724 (12.4%)
F60–69	7 (0.1%)	1 (<0.1%)	6 (0.1%)
F70–79	6 (0.1%)	3 (0.1%)	3 (0.1%)
F80–89	20 (0.2%)	16 (0.5%)	4 (0.1%)
F90–98	350 (3.8%)	182 (5.4%)	168 (2.9%)
CRP [mean (SD)], mg/L	2.4 (3.3)	2.6 (3.4)	2.3 (3.3)
IL-6 [mean (SD)], pg/mL	2.5 (2.0)	2.6 (2.2)	2.5 (1.9)
Total VOCs [mean (SD)], ppbv	32.2 (16.9)	30.8 (16.6)	33.1 (16.9)
Alkanes [mean (SD)], ppbv	15.0 (9.1)	14.2 (8.9)	15.5 (9.1)
Alkenes [mean (SD)], ppbv	2.0 (0.9)	1.9 (0.9)	2.0 (0.9)
Alkynes [mean (SD)], ppbv	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
Aromatics [mean (SD)], ppbv	5.1 (3.2)	4.8 (3.2)	5.3 (3.2)
OVOCs [mean (SD)], ppbv	9.7 (4.4)	9.5 (4.4)	9.8 (4.4)
Temperature [mean (SD)], ℃	13.3 (11.1)	13.5 (11.0)	13.1 (11.2)
Relative humidity [mean (SD)], %	57.2 (17.1)	57.6 (17.1)	56.9 (17.1)

Summary statistics for all participants and by sex. Values are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. ICD-10 codes represent the distribution of primary psychiatric diagnoses. Exposure levels to total and subclassified VOCs (ppbv), inflammatory biomarkers (CRP, IL-6), and meteorological covariates (temperature and relative humidity) are also reported.

3.3. Toxicological properties and network toxicology analysis

Toxicological analysis indicated that most of the 33 VOC species simulated by CMAQ were predicted by ProTox 3.0 to have a high blood-brain barrier permeability (probability > 0.9), suggesting their potential to reach the central nervous system (Fig. 4**A**). Several compounds (including formaldehyde, methyl ethyl ketone, and p-xylene) were predicted to have high neurotoxicity, mutagenicity, and respiratory toxicity. Some also showed cardiovascular toxicity and endocrine-disrupting properties. We built a network toxicology framework that combined VOCs, their target genes, and depression-related pathways, and identified 43 key genes that appear to link VOC exposure with MDD. Key regulatory genes such as DRD2, HTR3A, GRIN1, SLC6A4, and IL6R occupied central positions within the network (Fig. 4**B and** Figure S10). Functional enrichment analysis revealed that these genes were significantly overrepresented in several pathways, including those involved in neurotransmitter transport, synaptic signalling, G protein-coupled receptor activity, and neuropsychiatric disorders. GO annotation also showed that these genes were enriched in the postsynaptic density, dendritic structures, and neuronal projection sites, suggesting that they may play a role in synaptic signal transduction and information exchange (Fig. 4**C and** Table S4).

At the level of chemical grouping, gene sets associated with alkenes, aromatics, and all components showed significant enrichment across multiple neural functional pathways (Figures S11-S13). KEGG pathway analysis revealed distinct patterns of action among different VOCs in biological processes related to MDD. Propionic acid and sesquiterpenes primarily exert their effects via neurotransmitter receptors and synaptic signalling pathways, including those associated with glutamatergic, GABAergic, and cholinergic synapses. Methylglyoxal showed the strongest associations with dopaminergic synapses, circadian rhythm processes, and pathways linked to neurodegeneration. However, methylvinylketone and acetic acid were more frequently associated with addiction, calcium signalling, and inflammatory pathways. Despite these diverse pathways, genes such as GRIN1/GRIN2B, GABRA1/GABRB2, CHRNA7, and DRD2 emerged as key co-affected targets, forming a core molecular pathway linking VOC exposure to MDD (Fig. 5).

4. Discussion

Our study systematically assessed the potential impact of

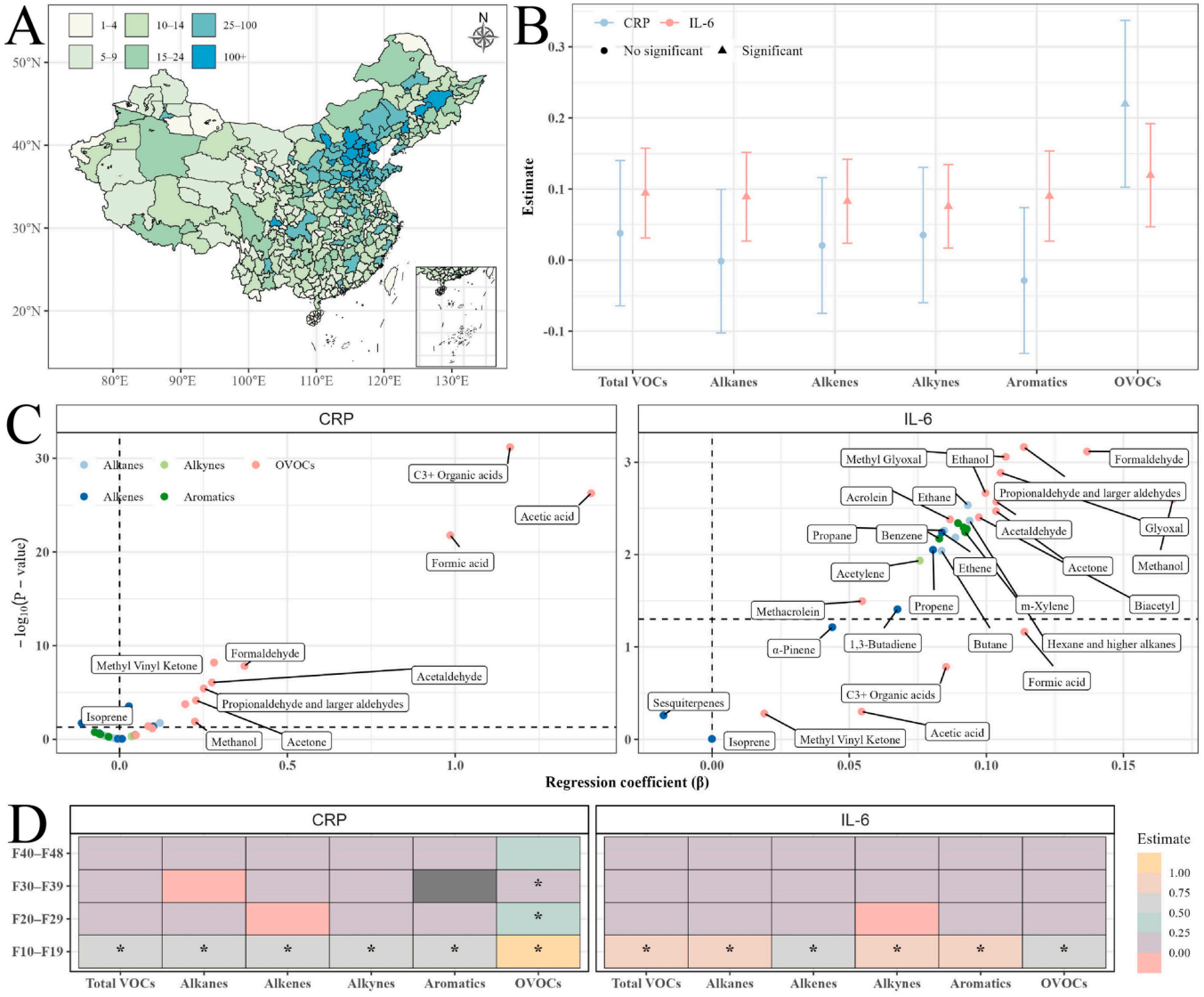

Fig. 3. Associations between VOCs exposure and inflammatory biomarkers across China. A, Spatial distribution of the study population across China. **B**, Regression estimates (β and 95% CI) for the associations between total and subgroup VOC exposure and circulating levels of C-reactive protein (CRP) and interleukin-6 (IL-6). Models were adjusted for age, sex, temperature, and humidity. **C**, Compound-specific associations for CRP (left) and IL-6 (right), showing regression coefficients on the x-axis and $-\log_{10}(p \text{ value})$ on the y-axis. Triangles indicate statistically significant associations. **D**, Subgroup analysis of VOC-inflammation associations stratified by mental disorder subtypes. Asterisks denote $p < 0.05$.

environmental VOCs on mental health through chemical transport modeling, toxicological characterization, and a clinical cohort study. CMAQ-simulated concentrations demonstrated good spatio-temporal consistency with ground-based monitoring and satellite observations. In a cohort of 9195 hospitalized psychiatric patients, short-term VOC exposure was significantly associated with higher serum IL-6 concentrations, with the most pronounced associations observed for OVOCs, including formaldehyde, methanol, methylglyoxal, and propionaldehyde and larger aldehydes. Although total VOC exposure was not significantly associated with CRP, OVOCs showed consistent positive associations with CRP concentrations, particularly acetic acid, C3+ organic acids, formaldehyde, methyl vinyl ketone, and propionaldehyde and larger aldehydes. Toxicological predictions indicated that multiple VOCs exhibit high blood-brain barrier permeability and potential neurotoxicity. Further network toxicology analysis identified 43 target genes associated with VOC exposure and depression, primarily enriched for pathways related to neurotransmitter transmission, synaptic signaling, and neurotransmitter transport. Our findings suggest that environmental exposure to environmental VOCs may represent a modifiable risk factor for adverse mental health outcomes and underscore the pivotal role of integrated modeling approaches in exposure assessment and mechanistic research.

CMAQ simulations of TVOC concentrations successfully captured key spatiotemporal variation patterns, including those of major chemical subclasses. The simulations accurately reproduced the observed temporal trends, chemical composition patterns, and regional distribution patterns. Alkanes consistently accounted for the largest fraction, followed by aromatics and OVOCs. Alkenes, alkynes, and BVOCs contributed less. Comparisons of in situ measurements showed good overall agreement across most subclasses. However, peak concentrations during high-pollution episodes were consistently underestimated, and the model performed comparatively poorly for reactive OVOCs, BVOCs, and certain alkenes and alkynes. Several factors may account for these discrepancies. First, simplified chemical mechanisms in CMAQ (e.g., CB6 or SAPRC07tc) do not accurately capture the complex pathways of secondary OVOC formation, resulting in structural biases in their estimates [50]. A considerable number of reaction pathways involving both known and unidentified VOCs remain unresolved, and field

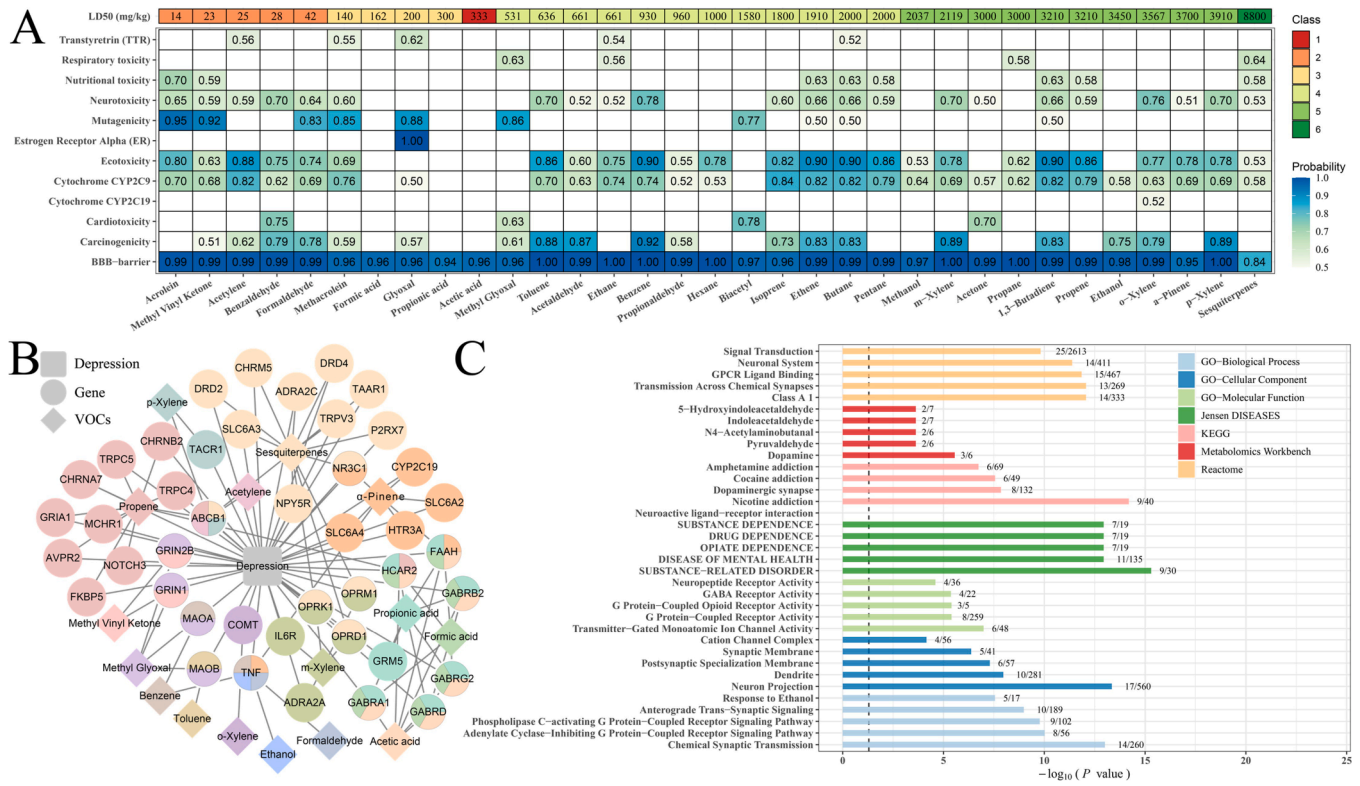

Fig. 4. Identification of VOCs associated with mental disorders through network toxicology analysis. A, Predicted toxicological profiles of 33 volatile organic compounds (VOCs) across 12 endpoints using ProTox 3.0, including neurotoxicity, mutagenicity, endocrine disruption, and blood–brain barrier permeability. LD_{50}-based toxicity classes are shown at the top. **B**, Network linking VOCs, genes, and mental disorders. Hexagons represent VOCs, circles represent genes, and the diamond node denotes mental disorders, with a focus on depression-related pathways. **C**, Functional enrichment of VOC-associated genes implicated in mental disorders, with pathways drawn from GO, KEGG, Reactome, and Jensen DISEASES databases.

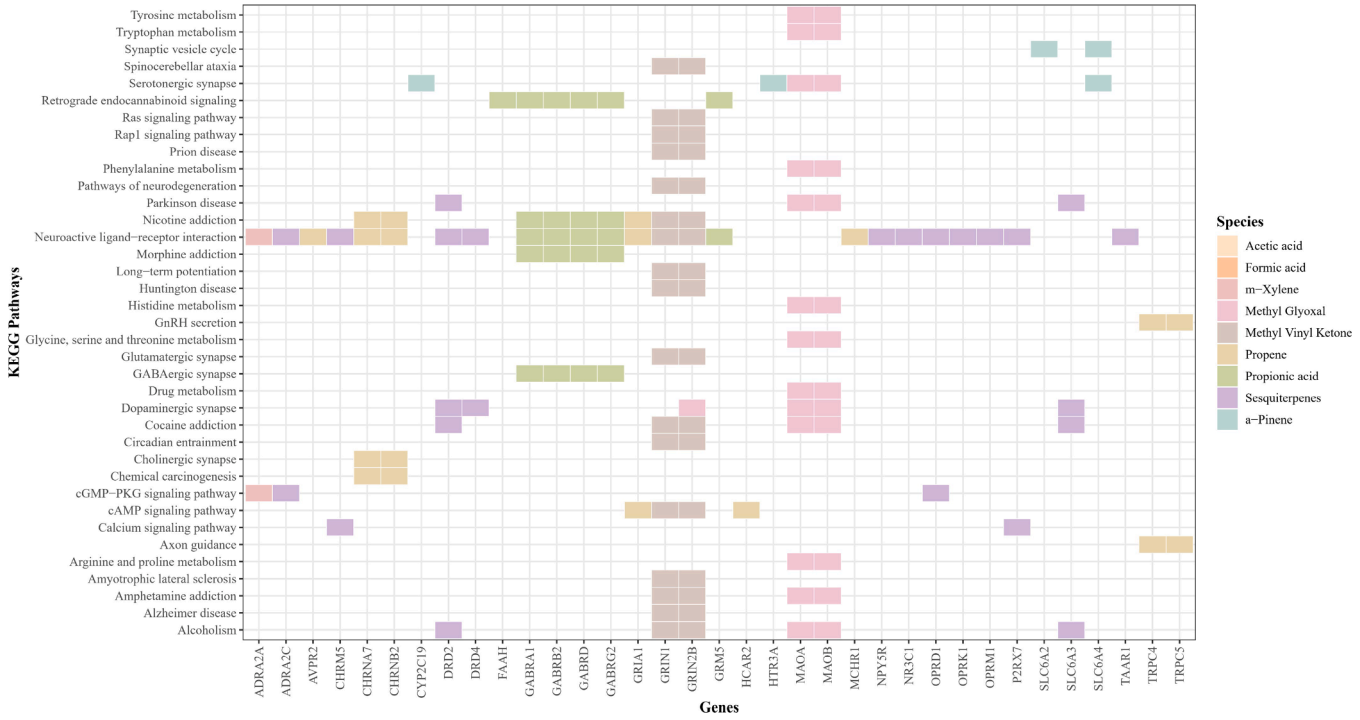

Fig. 5. VOC-specific gene enrichment across neural KEGG pathways. This diagram depicts the KEGG neural pathways mapped to gene targets for individual VOC species. Each row represents a KEGG pathway, each column represents a gene, and each colour indicates a specific VOC species. Coloured blocks indicate the presence of an interaction among a VOC, a gene, and a pathway.

measurements for highly reactive compounds are scarce, further increasing uncertainty [51,52]. Second, current emission inventories lack detailed source attribution for specific VOC precursors such as aldehydes, alcohols, and organic acids, and underestimate contributions from industrial processes and biogenic sources [53–55]. Third, the model's coarse spatial resolution (36 km × 36 km) smoothes fine-scale concentration gradients and fails to resolve urban-scale pollution hotspots, thereby affecting both the magnitude and spatial variability of simulated concentrations. Estimates of near-surface concentrations may also be affected by uncertainties in meteorological data, such as inaccurate measurements of the height of the planetary boundary layer [56]. Despite its limitations, CMAQ provides a reliable analytical framework for multi-component exposure assessment and supports population-scale health impact studies. Future improvements should include further refining emission inventories, particularly for industrial and biogenic VOC sources, incorporating greater detail into chemical mechanisms to describe secondary formation processes, enhancing spatial resolution, and expanding VOC monitoring networks to strengthen model calibration and validation. Such advances will improve CMAQ's capacity to characterise the health impacts of environmental VOC exposure, particularly on neuropsychiatric and immune-related health outcomes [50,57].

In this study, we combined the high-resolution VOC simulations with a nationwide cohort to explore the association between VOC exposure and systemic inflammation. Several VOC species, including formaldehyde, methacrolein, and ethanol, were positively associated with circulating IL-6 and CRP levels, suggesting that ambient exposure may contribute to psychiatric pathophysiology via inflammation-mediated pathways [58–60]. Toxicological predictions further indicate that most VOCs exhibit high blood-brain barrier permeability and may interact with key molecular targets involved in neurotransmission, synaptic signaling, and immune regulation, including DRD2, GRIN1, and IL6R [61,62]. Functional enrichment analysis further confirmed that these targets were significantly involved in multiple neurobiological processes and pathways associated with psychiatric disorders, supporting the hypothesis that VOCs may exert effects through a coordinated axis of inflammation, neural circuitry, and behavior. Beyond traditional exposure-outcome correlation analysis, our network toxicology approach enables mechanism inference without the use of animal models. By integrating chemical structural information with standardized databases, it maps potential compound-gene-disease associations [26]. In scenarios lacking comprehensive monitoring data, we employed CMAQ to construct multi-component VOC exposure models, providing a feasible and scalable framework for environmental health research. By linking simulated exposures to real biomarker data, this multistage strategy provides a replicable pathway for identifying environmental factors that affect mental health, particularly in research contexts with limited exposure measurements or complex chemical compositions. Despite lingering uncertainties, our research highlights the potential of integrated modeling in advancing environmental epidemiology.

Our study has several limitations. First, estimates of VOC exposure relied on CMAQ model simulations rather than direct measurements. Although CMAQ showed good agreement with observations for the main VOC categories, its performance was relatively weaker for more reactive species, and the ground-level validation of speciated VOCs relied on a single monitoring site in Beijing. Moreover, the model may not fully capture short-term pollution peaks, which could lead to exposure misclassification and bias in the risk estimates. Second, our study only examined the association between short-term exposure to VOCs and systemic inflammation, without explicitly addressing the joint effects of VOC mixtures. Further longitudinal cohort studies and experimental models are required to confirm these associations and their underlying mechanisms. Third, we assessed only two peripheral inflammatory biomarkers. While these markers are widely used indicators of systemic inflammation, they cannot fully capture immune activity within the central nervous system. In addition, the relationship between these biomarkers and the severity of neuropsychiatric disorders was not examined in the present study. Future studies should therefore incorporate more tissue-specific biomarkers and detailed clinical measures of symptom severity [25,63]. Fourth, the network toxicology results were based on database mining and bioinformatics predictions, and therefore require further validation in cellular and animal models to confirm the regulatory effects of VOCs on the identified target genes and their roles in neuroinflammatory processes. Finally, the study population consisted of psychiatric inpatients receiving treatment, who represent a high-risk group. This population may differ markedly from the general population in terms of health status, behavioural characteristics, and exposure patterns. Therefore, the findings may not be fully generalisable to the wider population, and their external validity should be interpreted with caution.

5. Conclusion

Our study reveals an association between exposure to environmental VOCs and systemic inflammation in individuals with psychiatric disorders, suggesting that environmental pollutants may contribute to mental health risks via inflammation-mediated pathways. We identified strong links between various VOC species, particularly OVOCs such as formaldehyde and methacrolein, and increased levels of inflammatory markers, including IL-6 and CRP. Network toxicology further revealed that these compounds may interact with key molecular targets in neurotransmitter transport and synaptic signalling, providing a mechanistic basis for potential pathways through which VOCs influence brain function. Our findings highlight the need to enhance VOC monitoring capabilities, optimise exposure models, and conduct more comprehensive longitudinal studies to better understand the impact of air pollution on mental health. Such efforts will provide a basis for developing targeted prevention strategies for high-risk populations.

Environmental Implication

This study explores the impact of volatile organic compounds (VOCs) on mental health. By combining high-resolution atmospheric modeling with clinical data from over 9000 hospitalized patients in China, we found that short-term exposure to oxygenated VOCs, particularly formaldehyde and methacrolein, was linked to increased interleukin-6 (IL-6) levels, a biomarker associated with psychiatric symptoms. Further toxicological and network analyses suggested that these VOCs may disrupt brain pathways involved in neuroinflammation, neurotransmission, and immune regulation. These findings emphasize the importance of including mental well-being in environmental health assessments and guiding the development of targeted air quality standards and pollution control strategies.

Author Contributions

J.G., S.F., R.H., and X.W. had full access to all data and took responsibility for the integrity of the data and the accuracy of the analyses. J.G., S.X., and J.L. conceived and designed the study. Data were acquired, analysed, and interpreted by all authors. Statistical analyses were done by J.G., R.H., and X.W. The manuscript was drafted by J.G., F. S., Y.S., G.Y., Y.W., D.S., and X.L., and critically revised by S.L., S.X., and J.L. All authors reviewed and approved the final version.

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Declaration of Competing Interest

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

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None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2026.142143.

Data availability

Data will be made available on request.

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