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Review Article

Affective disorder and brain alterations in children and adolescents exposed to outdoor air pollution

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ABSTRACT

Background: Childhood and adolescence are critical periods for the development of the brain. However, a limited number of studies have explored how air pollution may associate with affective symptoms in youth.
Methods: We performed a comprehensive review of the existing research on the associations between outdoor air pollution and affective disorders, suicidality, and the evidence for brain changes in youth. PRISMA guidelines were followed and PubMed, Embase, Web of Science, Cochrane Library, and PsychINFO databases were searched from their inception to June 2022.
Results: From 2123 search records, 28 papers were identified as being relevant for studying the association between air pollution and affective disorders (n = 14), suicide (n = 5), and neuroimaging-based evidence of brain alterations (n = 9). The exposure levels and neuropsychological performance measures were highly heterogeneous and confounders including traffic-related noise, indoor air pollution, and social stressors were not consistently considered. Notwithstanding, 10 out of the 14 papers provide evidence that air pollution is associated with increased risk of depression symptoms, and 4 out of 5 papers provide evidence that air pollution might trigger suicidal attempts and behaviors. Besides, 5 neuroimaging studies revealed decreased gray-matter volume in the Cortico-Striato-Thalamo-Cortical neurocircuitry, and two found white matter hyperintensities in the prefrontal lobe.
Conclusions: Outdoor air pollution is associated with increased risks of affective disorders and suicide in youth, and there is evidence for associated structural and functional brain abnormalities. Future studies should determine the specific effects of each air pollutant, the critical exposure levels, and population susceptibility.

1. Introduction

The rapid increase in urbanization, industrialization and development of transport infrastructure has led to severe air pollution. It is estimated that exposure to particulate matter (PM) causes approximately 2 million deaths per annum in America, and people with cardiovascular diseases are especially vulnerable (Pope et al., 2019). Sources of air pollution are varied and include industrial emissions, straw combustion, household biomass, trade-driven relocation, and traffic emissions (Wang et al., 2017). Accordingly, air pollution is a mixture of several pollutants, and PM10 (coarse particles between 2.5 μm and 10 μm), PM2.5 (fine particles between 100 nm and 2.5 μm), elemental carbon (EC), nitrogen oxide (NO), nitrogen dioxide (NO2), ozone (O3), and polycyclic aromatic hydrocarbons (PAHs) are the major components of pollution that threaten public health (Wang et al., 2017). Recently, attention has focused on the possibility that air pollution may contribute to a diverse range of central nervous system (CNS) diseases (Kim et al., 2020).

There is evidence from both animal and human studies that air pollution produces a dual effect of neuroinflammation and oxidative stress, which plays a crucial role in producing structural and functional brain changes. Air pollutants are believed to invade the CNS by two

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major pathways (Cipriani et al., 2018; Hahad et al., 2020), namely (1) neural transmission to specific brain regions via the nasal olfactory nerve, and (2) pulmonary gas inhalation followed by transmigration to the blood circulation and crossing the blood-brain-barrier (BBB). Notably, air pollutants in the alveolar structures of the lungs could contribute to the production of proinflammatory factors, leading to systematic inflammation and neuronal death (Block and Calderón-Garcidueñas, 2009; Rao et al., 2018). For example, a progressive reduction in neurons was found in mice treated with TNF-α (Qin et al., 2007). Once air pollutants enter the CNS, astroglia and microglia can be activated, resulting in the release of inflammatory mediators (TNF-α, IL-1β, and INF-γ) and causing oxidative stress (Araneda et al., 2008; Sama et al., 2007). The resulting chronic neurotoxicity may induce structural and functional alterations in the brain and lead to cognitive, behavioral, and affective changes.

Adverse impacts of air pollution exposure on depression, anxiety, and suicide have frequently been reported in adults and older populations (Qiu et al., 2023; Villeneuve et al., 2023; Zare Sakhvidi et al., 2022). There is concern that children and adolescents are especially vulnerable in view of their ongoing brain development (Danese and Baldwin, 2017). There is evidence that most adult psychopathologies started in childhood and adolescence (Kim-Cohen et al., 2003), and once brain neurologic injury occurs, the sequelae affect the entire life span (Copeland et al., 2015). Thus, mental health problems that emerge early in life may have a prolonged and profound impact in later years. Notably, affective changes greatly impact the individual quality of life and may lead to the risk of suicide, causing a large burden on society and families (Chen et al., 2021; Li et al., 2020; Tian et al., 2021). Therefore, it is crucial and urgent to study the effect of air pollution on affective disorders in children and adolescents.

Air pollution, and especially traffic-related air pollution (TRAP), is now ubiquitous, and because young people not only spend more time on outdoor activities but also breathe faster and live closer to the ground, they are more likely to experience greater impacts of exposure to air pollution than adults (Chen et al., 2019; Rajper et al., 2018; Saadeh and Klaunig, 2014). Moreover, while many countries have taken a series of actions to ensure that air pollution levels lie within a permissible range, often these actions cannot keep pace with the rise in fossil fuel use and urban development (Huang et al., 2017). Considering that whether postnatal exposure to air pollution increases the risk of psychiatric symptoms is not well understood, we conducted a review of the literature describing the epidemiology, pathophysiology, and neuroimaging of air-pollution-related affective disorders and brain changes in children and adolescents. We aimed to evaluate the strength of the association between air pollution and affective disorders and review the evidence of air-pollution-related brain alterations from a neuroimaging perspective in children and adolescents.

2. Methods

2.1. Literature search strategy

A systematic review was conducted and is reported according to the PRISMA guideline (Hutton et al., 2015). First, a search was performed to find relevant papers published in the PubMed, Embase, Cochrane Library, Web of Science, and PsychINFO databases from their inception to 30 June 2022. Terms related to air pollution (e.g., 'air pollution' and 'traffic-related air pollution') or specific air pollutants (e.g., 'black carbon', 'elemental carbon', 'PM10', 'PM2.5', 'PM1', 'NO2' and 'O3') were combined with terms related to population category (e.g., 'children' and 'adolescent') and their affective disorders or symptoms (e.g., 'affective disorder', 'depression', 'anxiety', 'suicide', and 'bipolar disorder') and neuroimaging studies, and English-language filters were applied. Titles, abstracts, and references from all the publications that were identified were examined by two reviewers (HSX and YC) independently, and the full texts of relevant studies were retrieved. In addition, the reference lists of the selected articles and prior similar reviews were manually researched. The complete search strategy can be found in the Supplementary Materials.

2.2. Inclusion and exclusion criteria

All published papers which refer to cohort and cross-sectional studies and report neuroimaging changes and neuropsychological disorders associated with air pollution exposure in children and adolescents were considered. The qualified articles required the following three items: (1) children aged 1–12 and adolescents aged 12–18 years; (2) outdoor air pollution exposure; (3a) anxiety, depressive, and bipolar symptoms with or without suicidal attempt/behavior; and (3b) neuroimaging studies. Exclusion criteria were (1) reviews, comments, consensuses, editorials, guidelines, in-vitro studies, meta-analyses, ecological studies, and protocols; and (2) when exposure occurred during the prenatal period.

2.3. Quality assessment

The same two reviewers (HSX and YC) extracted the study data, including study design, participants (location, age, and sex), sample size, measured pollution exposure, psychiatric assessment, main findings, controlled confounders, and limitations for each of the studies that are included. Next, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institute of Health was applied to assess the quality of each study (NIH, 2021). The tool comprises a 14-item checklist focusing on the risk of bias, type I and type II errors, transparency, and confounding factors (Coelho-Júnior et al., 2021). Notably, Items 6, 7, and 13 do not apply in the case of cross-sectional studies, so the maximum score for cross-sectional studies is eleven whereas that for longitudinal studies is fourteen. A risk point of one was applied to the relevant Item when evaluation resulted in a response of "No", "Not applied", "Not reported" or "Cannot determine". The risk scores for all the Items were summed and the higher the total risk score the lower the quality of the study. The agreement rate for quality assessment between reviewers was 97 %, and disagreement was resolved by another senior investigator (ZYJ).

3. Results

From 2123 records resulting from the literature search, 28 papers published between 2008 and June 2022 were eventually included in the systematic review (Fig. 1). Of these, thirteen referred to investigations conducted in the Americas (USA, Mexico, and Columbia), ten in Europe (UK, Netherlands, Belgium, Spain, and Germany), and five in Asia (China and Korea). The sample size ranged from 20 to 54,923 individuals (mean = 5207, SD = 11,116). The age of participants ranged from 3 to 18 years old, and the male proportion ranged from 38 % to 59 % (mean = 49.5 %, SD = 4.1 %). Measures of air pollution included PM (40 %), nitrogen oxides (20 %), ozone (14 %), SO2 (9 %), elemental carbon (6 %), CO (6 %), PAHs (3 %), and lead (2 %).

3.1. Affective disorders and suicide

Fourteen of the included articles refer to the study of the potential association between exposure to air pollution and affective disorders/symptoms and 5 articles refer to the study of the potential association between air pollution and suicide/self-injury in children and adolescents (Table 1). Overall, it was revealed that the affective disorder associated with air pollution is depression with/without anxiety rather than mania or bipolar disorder. In particular, in ten out of fourteen studies a significant association was reported between outdoor air pollutant exposure and depression symptoms. In four of the studies, long-term exposure was found to be a significant predictive factor for the development of depressive symptoms (Rasnick et al., 2021; Roberts et al., 2019; Yolton et al., 2019; Zhang et al., 2021). Importantly, the effects of

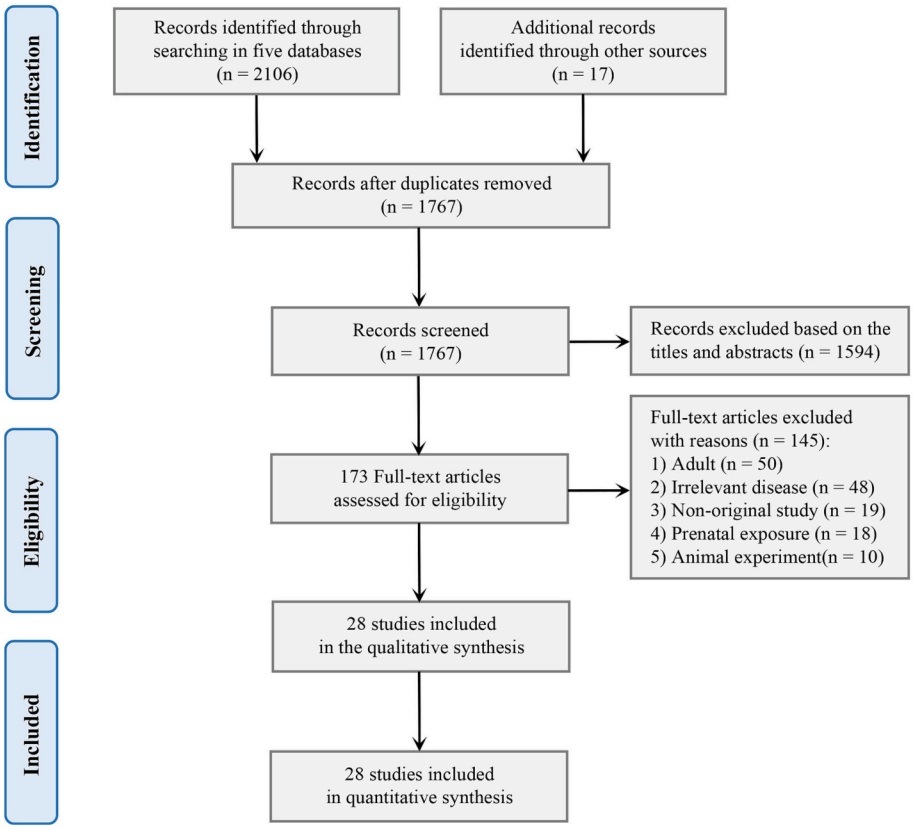

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow chart.

both short and long-term exposure appeared to be equivalent, suggesting that depressive symptoms might persist once the association has been established s (Shen et al., 2021). Other three studies investigated the relationship between specific air pollutants (NO2 and ozone) and depression symptoms (Latham et al., 2021; Manczak et al., 2022; Reuben et al., 2021). In one paper it was suggested that exposure to air pollution might function as a catalyst by heightening the physiological reactivity to social stressors in adolescence (Miller et al., 2019). Additionally, exposure to higher levels of PM was found to be associated with a decrease in physical activity, which in turn increased depressive symptoms in children (Kim et al., 2022). However, in four out of fourteen studies, and which refer to much larger multicenter cohorts, no significant relationship was found between outdoor air pollutant exposure and affective symptoms (Jorcano et al., 2019; Midouhas et al., 2019; Turner et al., 2022; Zhao et al., 2019). These negative results might be related to the possibility of more site-dependent heterogeneity.

In five published articles studying the potential association between outdoor air pollution and suicide/self-injury, four of them reported a statistically significant association based on the self-reports and ambulance records (Casas et al., 2017; Fan et al., 2019; Liu et al., 2019; Liu et al., 2018). However, one study found no association between any single air pollutant including NO2, PM10, CO, and ozone and suicide after adjusting for the influence of temperature, humidity, precipitation, and holidays (Fernández-Niño et al., 2018). It is notable that different scales were used to evaluate the severity of affective disorder and suicide, and the most commonly used scales were the Children's Depression Inventory, Child Behavior Checklist, Strengths and Difficulties Questionnaire, and Behavior Assessment System for Children. Another limitation is that the effects of individual components in the mixed air pollutants have not been analyzed in most studies.

3.2. Neuroimaging evidence of brain alterations under air pollution

Nine of the included articles refer to neuroimaging studies of the potential association between exposure to air pollution and brain changes in children and adolescents (Table 2). In all studies, the magnetic resonance imaging (MRI) technique was employed, and the most commonly used sequences were T1-weighted and T2 Flair images. Significant associations were found in both gray/white matter structure and resting-state brain function (Fig. 2). In particular, an extensive reduction was found in the volume of the orbital frontal cortex, cingulate cortex, hippocampus, caudate, and insula (Cserbik et al., 2020; Lubczyńska et al., 2020; Miller et al., 2021; Mortamais et al., 2017). The white matter was also reduced in volume in some regions, and white matter hyperintensities were found in the prefrontal lobe, suggesting that exposure to air pollution may have caused neuroinflammation (Calderon-Garciduenas et al., 2011; Calderon-Garciduenas et al., 2008; Calderon-Garciduenas et al., 2012). In terms of brain function, a study found that a higher level of pollution was associated with reduced functional connectivity between the medial frontal cortex and angular gyrus (Pujol et al., 2016). Furthermore, in one study it was reported that recent TRAP exposure was associated with increased myo-inositol in the brain and symptoms of generalized anxiety (Brunst et al., 2019).

3.3. Quality assessment

The overall quality score of the eight cross-sectional studies was good, with risk scores of between 2 and 3. In all studies, the research question was defined (item 1), the study population was described (item 2), participants were recruited from the same or similar population (item 4), multiple measurements were performed (item 10), dependent variables were defined (item 11) and potential confounding variables were adjusted (item 14). Notably, only in one study did the participation rate of eligible persons exceed 50 % (item 3), and in another study, a

Table 1
Characteristics of studies of air-pollution-related affective disorder and suicide in children and adolescents.

Study	Participants Age (years ± SD)/Male (%)	Measured pollutants	Study design	Psychiatric assessment	Controlled confounders	Main findings	Limitations	Risk score
Affective disorder/symptoms								
Roberts et al. 2019	London 284 children, (12.0 ± NA), 54 %	$PM_{2.5}$, NO_2	Longitudinal, twin study	CDI, MASC DSM-4	Sex, ethnicity, SES, psychiatric history, victimization, and smoking	Pollution exposure at the age of 12 was associated with increased odds of major depressive disorder six years later.	1) Sample size. 2) genetic factors. 3) A single-site pollution measurement.	3/14
Yolton et al. 2019	Greater Cincinnati, USA 344 adolescents, (12.2 ± 0.8), 55 %	$PM_{2.5}$ Elemental carbon	Prospective cohort	BASC-2, CDI	Sex, age, race, PRQ, lead, cotinine, and SES	TRAP exposure during early life and childhood was associated with self-reported depression.	1) Limited pollutants. 2) Genetic factors.	5/14
Miller et al. 2019	Northern California 144 adolescents, (12.2 ± 1.4), 45 %	$PM_{2.5}$	Cross-sectional	TSST, YSR	Sex, age, pubertal stage, BMI, minority status, and SES	$PM_{2.5}$ exposure heightened adolescent physiological reactivity to social stressors, especially for those experiencing anxiety and depression.	1) Community-level air pollution. 2) Social stress	3/11
Zhang et al. 2021	Louisville, Kentucky, USA 235 adolescents, (10.8 ± 2.5), 55 %	PM_{10}	Cross-sectional	CBCL	Age, gender, ethnicity, and SES	Age and square root of traffic proximity showed positive associations with affective problems	1) Spatial sampling errors. 2) A week-long sample of PM_{10}.	3/11
Shen et al. 2021	Changsha, Wuhan, China 20,079 adolescents, (18.3 ± 0.8), 51 %	$PM_{2.5}$, PM_{10}, CO, NO2, SO2, O3, BC	Retrospective cohort	PHQ-2, GAD-2	Age, sex, SES, education, smoking, alcohol, physical activity, BMI, humidity, temperature, UV radiation, and night artificial light	1) Short and long-term effects of BC were comparable on depression. 2) BC and mixed environmental exposures were associated with depressive symptoms.	1) Recall bias. 2) Specific populations. 3) Annual mean pollution levels.	4/14
Latham et al. 2021	UK 2232 children, (10–18 years), 49 %	$PM_{2.5}$, PM_{10}, NO2, NO_X	Longitudinal, cohort	DSM-4	Sex, psychiatric history, SES, urbanicity, and smoking	The risk of developing major depressive disorder at 18 was elevated most by the exposure to NO_X and PM2.5.	1) Uncontrolled noise. 2) A single-site pollution measurement. 3) Specific populations.	4/14
Reuben et al. 2021	England and Wales 2039 adolescents, (10–18 years), 47 %	$PM_{2.5}$, NO_X	Longitudinal twin study	General psychopathology	SES, smoking, psychiatric history, and emotional/behavioral problems	NOx exposure was associated with an increase in general psychopathology.	1) Observational design. 2) Uncontrolled preschool exposure, noise, and CO.	3/14
Rasnick et al. 2021	Greater Cincinnati, USA 263 children, (12.0 ± NA), 54 %	Lead, $PM_{2.5}$	Prospective cohort	BASC-2	Education, lead, greenspace, and SES	1) Depression was positively correlated with the lead before 5 years old. 2) No sensitive windows were identified for increased depression.	1) Blood lead. 2) Collinearity among pollutants.	5/14
Manczak et al. 2022	San Francisco, USA 213 adolescents, (9–13 years), 43 %	O_3	Longitudinal	CDI, YSR	Sex, age, minority status, life stressors, income, education, and neighborhood disadvantage	Higher ozone predicted steeper increases in depressive symptoms in adolescents.	1) Study design. 2) Non-clinical diagnoses. 3) Single averaged ozone assessments.	5/14
Kim et al. 2022	Korea 4704 children, NA, 47 %	$PM_{2.5}$	Cross-sectional	SCL	Sex, age, education, family background characteristic, and living areas	Higher levels of PM are associated with a decrease in physical activity, which in turn increases children's depressive symptoms.	1) Study design. 2) Omitted variable bias. 3) Non-clinical diagnoses. 4) Unevenly distributed samples.	3/11
Zhao et al. 2019	Munich and Wesel 2827 adolescents, (15.2 ± 0.3), 49 %	PM_{10}, NO_2, O_3	Cross-sectional	DST	Age, sex, education, income, smoking, screen time, outside time, and psychopathology	Both short- and long-term exposure to O_3 were not associated with depressive symptoms.	1) Study design. 2) Subjective reports of depression. 3) Specific populations.	2/11
Jorcano et al. 2019	6 European areas 1896 children,	$PM_{2.5}$, PM_{10} NO_2, NOx, PAHs	Prospective cohort	CBCL, SDQ	Age, income, education, tobacco, alcohol, BMI, and emotional/ behavioral problems	Postnatal air pollution exposure was not related with depressive, anxious,	1) Time window. 2) Limited pollutants. 3) Different	4/14

(*continued on next page*)

Table 1 (*continued*)

Study	Participants Age (years ± SD)/Male (%)	Measured pollutants	Study design	Psychiatric assessment	Controlled confounders	Main findings	Limitations	Risk score
	(7–11 years), 51 %					or aggressive symptoms in 7–11 children.	evaluation methods of pollutants.	
Midouhas et al. 2019	Four UK countries 11,625 children, (3.0 ± NA), 51 %	NO_2, SO_2	Longitudinal, cohort	SDQ	Age, sex, ethnicity, weight, income, education, and maternal health	1) NO_2 and SO_2 exposures in infancy were not associated with emotional symptoms at 3 years old. 2) Green space amount was not related to emotional problems.	1) Uncontrolled noise, indoor pollution, and season. 2) Spatial resolution	5/14
Turner et al. 2022	Cincinnati, USA 97 children, (15.4 ± 1.2), 46 %	Ultrafine particles	Cross-sectional	PROMIS	Sex, age, education, income, season, medication, physical activity, community features.	Ultrafine particles are associated with physical symptoms of stress response instead of depression among adolescent.	1) Study design. 2) Limited pollutants. 3) Specific populations.	3/11
Suicide/self-injury								
Casas et al. 2017	Belgium 71 suicides, (5–14 years), NA 482 suicides, (15–19 years), NA	PM_{10}, O_3	Retrospective	NA	Season, age, sex, suicide modes, and time lag	PM_{10} may have strong trigger-suicide effects in children at 5–14 years.	1) Exposure data from monitoring stations. 2) Mixed effects of all air pollutants.	4/14
Liu et al. 2018	Jiangsu, China 54,923 adolescents, (16.2 ± NA), 48 %	$PM_{2.5}$ CO, NO_2, SO_2, O_3	Cross-sectional	FSM	Gender, income, education, maltreatment, pocket money and school level	Air pollutants may increase the incidence of non-suicidal self-injury in adolescent students, especially in male students.	1) Retrospective design 2) Uncontrolled confounders	3/11
Fernández et al. 2018	Four Colombian cities 1942 suicides, (0–18 years), NA	$PM_{2.5}$, PM_{10} NO_2, SO_2, O_3	Retrospective	NA	Age, sex, meteorological variables, and holidays	No association was found between examined air pollutants and suicide:	1) Group-level model. 2) Exposure data from monitoring stations.	5/14
Liu et al. 2019	Beijing, China 4470 suicide-related ADPE for 7 years, (0–18 years), NA	$PM_{2.5}$	Retrospective	NA	Calendar time, public holiday, temperature, and humidity	Suicide-related ADPE was positively associated with exposure to $PM_{2.5.}$	1) A single-site pollution measurement. 2) Collinearity among pollutants.	4/14
Fan et al. 2019	Guangdong, China 21,780 adolescents, (15.4 ± 1.9), 47 %	$PM_{2.5}$	Cross-sectional	CESD, PSQI	Age, sex, nationality, income, living status, smoking, and drinking	$PM_{2.5}$ exposure and sleep disturbance were positively associated with suicide attempts respectively.	1) Observational design. 2) Recall bias. 3) Sampling errors. 4) Specific populations.	3/11

Abbreviations: ADPE, ambulance dispatch for psychiatric emergency; BASC-2, Behavior Assessment System for Children-2; BC, black carbon; CBCL, Child Behavior Checklist; CDI, Children's Depression Inventory; CESD, Center for Epidemiologic Studies Depression Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; DST, Depression Screener for Teenagers; FSM, Function of Self-Mutilation; GAD-2, Generalized Anxiety Disorder Scale-2; MASC, Multidimensional Anxiety Scale for Children; NA, not available; PAHs, polycyclic aromatic hydrocarbons; PHQ-2, Patient Health Questionnaire-2; PROMIS, Patient Reported Outcomes Measurement Information System; PRQ, Parenting Relationship Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SCL, Symptom Checklist; SDQ, Strengths and Difficulties Questionnaire; SES, socio-economic status; TSST, Trier Social Stress Test; YSR, Youth Self-Report.

power calculation was performed to justify the sample size (item 5). No studies described whether assessors were blinded to exposure measures (item 12).

The overall quality score of the twenty longitudinal studies was good, with risk scores of between 3 and 7. In all studies, the research question was defined (item 1), the study population was described (item 2), participants were recruited from the same or similar population (item 4), outcomes were observed over a sufficient timeframe (item 7), different levels of air pollutants were examined (item 8), independent variables were specified (item 9), and dependent variables were defined (item 11). Notably, in only four studies did the participation rate of eligible persons exceed 50 % (item 3), and in four studies a power calculation was performed to justify the sample size (item 5). No studies could determine that the exposure to air pollution preceded the development of symptoms (item 6). In three studies it was not reported whether air pollutants were assessed more than once (item 10), and in only four studies it stated that the assessors of health were blinded to the measures of air pollution exposure (item 12). In two studies it was not reported whether statistical models were adjusted to take account of the potential confounding factors (item 14). The results of the detailed assessment of the quality of the cross-sectional and longitudinal studies can be found in the Supplementary Materials.

4. Discussion

This systematic review summarized the effects of outdoor air pollutants on affective disorders and related suicide events as well as brain structural/functional alterations evident in MRIs in children and adolescents. The results of epidemiological studies consistently showed that air pollution increases the risk of depression and suicide-related events.

Table 2
Characteristics of neuroimaging studies of air-pollution-related brain changes in children and adolescents.

Study	Participants Age (years ± SD)/male (%)	Measured pollutants	Neuropsychiatric assessment	MRI features (Field/ sequence)	Study design	Controlled confounders	Main findings	Limitations	Risk score
Calderon et al. 2008	Mexico City 23 children, (10.7 ± 2.7), 48 % Polotitlán (low polluted) 13 children, (10.7 ± 2.1), 38 %	PM, O_3, LPS-PM	WISC-R	1.5 T T2, T2 FLAIR	Prospective cohort	Age and gender	Children from Mexico City showed delayed cognitive development, and half of them had prefrontal WHM.	Undefined.	6/14
Calderon et al. 2011	Mexico City 20 children, (7.1 ± 0.7), 50 % Polotitlán (low polluted) 10 children, (6.8 ± 0.7), 40 %	$PM_{2.5}$, PM_{10}, LPS NO_2, SO_2, O_3, CO	WISC-R	1.5 T T1, T2 FLAIR	Prospective cohort	Age, sex, and white blood cell count	Children from Mexico City showed progressive cognitive deficits and smaller white matter volume in the right parietal and bilateral temporal areas.	Undefined.	5/14
Calderon et al. 2012	Mexico City 10 children with WHM and 10 without. Polotitlán (low polluted) 10 children without WHM.	$PM_{2.5}$, PM_{10}, LPS, NO_2, SO_2, O_3, CO	WISC-R	1.5 T T1, T2 T2 FLAIR	Prospective cohort	Age and gender	Mexican children with WHM showed better cognitive performance and larger white and gray matter volume in the temporal, parietal, and frontal regions than those without. Mexico children without WMH displayed serum pro-inflammatory defensive responses.	Sample size.	7/14
Pujol et al. 2016	Barcelona, Spain 263 children (9.7 ± 0.9), 52 %	$PM_{2.5}$, NO_2 Elemental carbon	ANT, n-Back task	1.5 T T1, DTI, MRS RS-fMRI	Prospective cohort	Age, sex, academic achievement, obesity, vulnerability index, and distance to school	Heavier pollution was associated with lower functional integration in both inner and stimulus-driven brain regions. Air pollution exposure was not associated with brain anatomy, structure, or membrane metabolites.	Head movements during scans.	4/14
Mortamais et al. 2017	Barcelona, Spain 242 children (7–10 years), 51 %	$PM_{2.5}$, PAH, BPA	ANT ADHD (DSM-4)	1.5 T, T1	Prospective cohort	Socio-demographic factor, home address, and education	PAH and BPA exposures were associated with decreased caudate nucleus volume. ADHD symptoms were not associated with BPA exposure.	1) Specific populations. 2) Indirect estimates of PAH. 3) Limited pollutant kinds.	3/14
Brunst, et al. 2019	Greater Cincinnati Region 145 children (12.0 ± NA), 59 %	$PM_{2.5}$ Elemental carbon	SCAS	3 T T1, T2, MRS	Prospective cohort	Race, income, age, and serum cotinine levels.	Recent TRAP exposure was related with increased myo-inositol in the brain, and elevated TRAP exposure and myo-inositol were associated with increased generalized anxiety symptoms.	1) Limited brain areas for MRS. 2) Uncontrolled residual confounders.	4/14
Cserbik, et al. 2020	USA 10,343 children (10.0 ± 0.6), 52 %	$PM_{2.5}$	ORRT, PSMT FAT, PVT, DCST LSWMT, PCPST	3 T, T1	Cross-sectional	Age, sex, race, education, income, handedness and MRI device	$PM_{2.5}$ exposure was associated with hemispheric specific differences in gray matter volume across cortical, subcortical, and cerebellum brain regions, as well as cortical surface area	1) Study design. 2) Ecological confounding effects.	2/11

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Table 2 (*continued*)

Study	Participants Age (years ± SD)/male (%)	Measured pollutants	Neuropsychiatric assessment	MRI features (Field/ sequence)	Study design	Controlled confounders	Main findings	Limitations	Risk score
							and thickness in specific brain regions. No associations were fund between sex/ $PM_{2.5}$ and task performance.		
Lubczynska, et al. 2020	Rotterdam, Netherlands 3959 children (9–12 years), 50 %	$PM_{2.5}$, PM_{10}, NO_2, ultra-fine particles	NA	3 T, T1	Prospective cohort	Sex, age, education, income, smoking, BMI, alcohol, and parity.	Air pollution exposure during childhood was related with smaller corpus callosum and hippocampus, and prenatal exposure could induce wider gray-matter abnormalities.	1) A single MRI scanning. 2) Uncontrolled confounders. 3) Exposure information from monitoring stations.	4/14
Miller et al. 2021	San Francisco and San Jose Bay Area 115 adolescents (11.5 ± 1.1), 44 %	$PM_{2.5}$	TESI, LSI	3 T, T1	Longitudinal cohort	Age, sex, and SES	1) $PM_{2.5}$ was negatively associated with volumetric change in widespread brain regions. 2) There were interactive effects of early life stress and $PM_{2.5}$ on brain volume changes.	1) Developmental window. 2) Uncontrolled confounders. 3) Study design.4) Sample size.	4/14

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ANT, Attentional Network Test; BPA, benzo [α] pyrene; DCST, Dimensional Card Sorting Task; DSM, Diagnostic and Statistical Manual of Mental Disorders; DTI, diffusion tensor imaging; FAT, Flanker Attention Test; FLAIR, fluid-attenuated inversion recovery; LPS, lipopolysaccharides; LSI, Life Stress Interview; LSWMT, List Sorting Working Memory Test; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NA, not available; ORRT, Oral Reading Recognition Test; PAH, polycyclic aromatic hydrocarbons; PCPST, Pattern Comparison Processing Speed Test; PM, particulate matter; PSMT, Picture Sequence Memory Test; PVT, Picture Vocabulary Test; RS-f, resting-state functional; SCAS, Spence Children's Anxiety Scale; TRAP, Traffic-Related Air Pollution; TESI, Traumatic Events Screening Inventory; WISC-R, Wechsler Intelligence Scale for Children–Revised; WMH, white matter hyperintense.

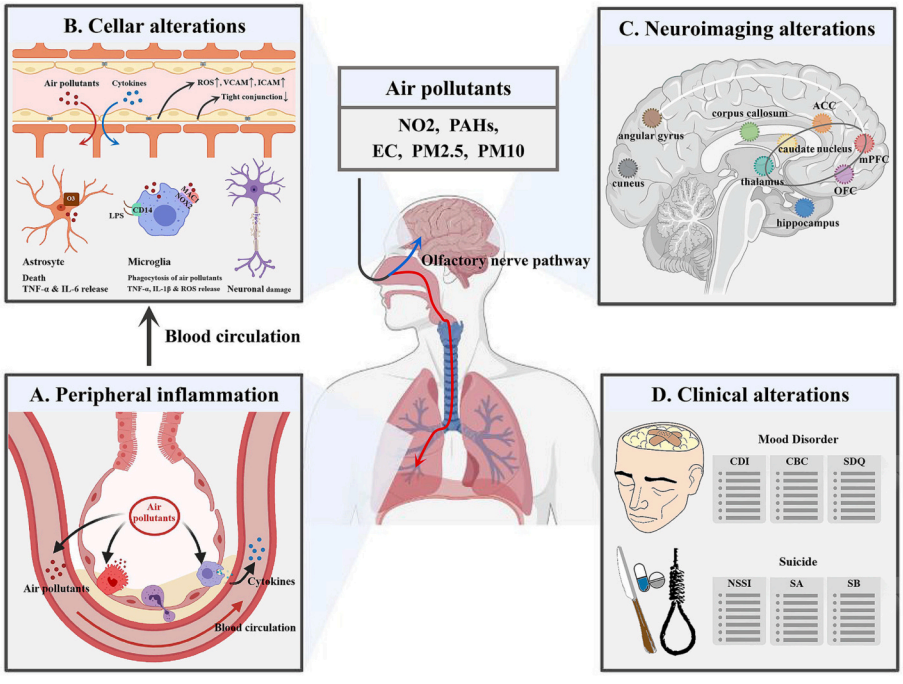

Fig. 2. A proposed model of how air pollution leads to affective disorder and symptoms in children and adolescents (created with BioRender.com and Skribbl). **(A)** The invasion of air pollutants and peripheral inflammation. In the lung alveoli, air pollutants translocate into the blood circulation through simple diffusion and promote phagocytosis and the release of cytokines. **(B)** Cellular alterations in the CNS after chronic exposure to air pollution. In the peripheral circulation, the deposition of air pollutants and cytokines (TNF-α, IL-6, and IL-1β) leads to endothelial cell damage by increasing levels of ICAM/ VCAM and decreasing the expression of tight junctions, which increases the permeability of the blood–brain barrier. Astrocytes may participate in the release of TNF-α/IL-6 and seem to be damaged in the CNS. Microglia recognize air pollutants through pattern recognition receptors (such as the LPS-CD14 interaction) and are activated to phagocytose them and release inflammatory mediators of TNF-α/IL-1β. The MAC1-NOX2 pathway is vital for the production and release of ROS by microglia. Finally, a double hit of oxidative stress and immune injury brings about axonal damage and neuronal death. **(C)** Brain structural and functional alterations revealed by MRI. White matter shows decreased volume in the corpus callosum. Gray matter shows extensive decreased volume in the Cortico-Striato-Thalamo-Cortical neurocircuitry (black loop). The functional connectivity between the medial prefrontal cortex and angular gyrus was decreased (white curve). **(D)** Air-pollution-related affective disorder, symptoms and suicide. The Children's Depression Inventory, Child Behavior Checklist, Strengths and Difficulties Questionnaire, and ambulance records are usually used to evaluate depression and suicidal events.

Abbreviations: ACC, anterior cingulate cortex; CNS, central nervous system; MAC1, CD11b and CD18; EC, elemental carbon; LPS, lipopolysaccharide; mPFC, medial prefrontal cortex; NOX2, nicotinamide adenine dinucleotide phosphate-oxidase; NSSI, non-suicide self-injury; OFC, orbital frontal cortex; PAHs, polycyclic aromatic hydrocarbons; ROS, reactive oxygen species; SA, suicide attempts; SB, suicide behaviors.

In addition, neuroimaging studies revealed that exposure to air pollution is associated with the alterations in brain structure, function, and metabolism. Of these, the decreased gray-matter volume in the CSTC neurocircuitry may underlie clinical changes in cognition, behavior, and emotion. Although the results must be interpreted cautiously, due to methodological heterogeneity and potential unmeasured confounding factors, there is relatively clear evidence that exposure to outdoor air pollution is associated with poor emotional wellbeing and compromised brain health. Large-scale longitudinal studies should be performed to investigate the particular effects of specific components within the air pollution mixture and the neurobiological mechanisms that may underly the associated affective disorders.

4.1. Air pollution and CNS function

Air pollution is a mixture of several pollutants, of which PM10, PM2.5, EC, NO, NO2, ozone, and PAHs are the major components threatening public health. The pollutants may enter the CNS by the neural transmission along the nasal olfactory nerve and blood-gas exchange in the lung (Cipriani et al., 2018; Hahad et al., 2020). Particulate Matter (PM10 and PM2.5) may cross the nasal brain barrier through direct contact with either olfactory receptor neurons or the trigeminal nerve (Fig. 2). In the lung, the particles can reach the CNS by translocation into the blood circulation (Wilson et al., 2018). Additionally, PM can indirectly disrupt the BBB integrity by mediating systematic inflammation during its interaction with lung tissues and immune cells. Furthermore, PM has been observed in olfactory bulb neurons, trigeminal nerves, and cerebral cortex in both mouse models of air pollution and clinically healthy, cognitively and neurologically normal children and young adults (Calderón-Garcidueñas et al., 2008; Wang et al., 2008).

Activation of microglia is a major link between immune injury and neurotoxicity in the CNS. Microglia are resident innate immune cells that usually exist in a resting state in the human brain. However, air pollutant invasion causes microglia to be activated and produce proinflammatory effects in three main pathways. First, air pollution components such as diesel exhaust particles (DEPs) and lipopolysaccharide can be directly bound to microglia and identified by various pathogen-associated molecules (Jayaraj et al., 2017). For example, the MAC1 receptor can bind with DEPs which leads to H2O2 production, resulting in the loss of neuron function (Levesque et al., 2013). In addition, the lipopolysaccharide recognition molecule, CD14, has been found to be elevated in the human olfactory bulb and frontal cortex after chronic exposure to air pollution (Calderón-Garcidueñas et al., 2008). Second, peripheral and systematic inflammation can activate the central immune system and lead to neuronal death (Qin et al., 2007). Third, components of damaged neurons may directly activate microglia, and thus, a vicious cycle is formed whereby activated microglia release large amounts of reactive oxygen species and inflammatory mediators, including TNF-α, IL-1β, and INF-γ, leading to neuronal death (Block et al., 2004; Sama et al., 2007).

Astrocytes are the main components of glial cells in the CNS. They play a critical role in the formation of the BBB, immune function, and nutritional support and have been suggested to participate in the inflammatory response to air pollution. For example, the expression of brain glial fibrillary acidic protein has been found to be increased in humans exposed to air pollution, suggesting that astroglia were activated (Calderón-Garcidueñas et al., 2008). Upregulated expression of IL-6 and TNF-α was also observed in astrocytes in mice exposed to ozone, suggesting that astrocytes also participate in the inflammatory response (Araneda et al., 2008). Furthermore, astrocytes that had been cultured in-vitro were damaged after short-term exposure to high-concentration of ozone (Zhou et al., 2008). At present, the role of astrocytes is relatively unclear under the circumstances of air pollution, and future studies need to explore its interaction with PM and microglia.

4.2. Air pollution-related affective disorder and suicide

Exposure duration and dose are key factors in the air pollution-related affective disorder in youth. Three prospective cohort studies emphasized the key role of early-life exposure in the subsequent depression in adolescents (Rasnick et al., 2021; Roberts et al., 2019; Yolton et al., 2019). Proximity to coal-fired power plants has been also identified as a risk factor for affective disorder in children (Zhang et al., 2021). In terms of long-term exposure, two recent meta-analyses consistently revealed statistically significant associations between exposure to PM2.5/NO2 and increased depression risks with low heterogeneity (Borroni et al., 2022; Braithwaite et al., 2019). In short-term (less than 1 month) exposures, compared with PM10, NO2, and SO2, the evidence for PM2.5-related depression is the most robust without publication bias and the influence of any single study (Borroni et al., 2022). Notably, some studies even found increased numbers of hospital visits for depression when the exposure duration was less than 1 week (Chen et al., 2018; Szyszkowicz et al., 2009). These findings are more likely to be associated with depression relapse induced by acute exposures since air-pollution-related brain changes often occur gradually (The Lancet, 2018). Therefore, for healthy teenagers, it is important for future studies to determine the exposure concentration and time that can cause brain changes and depression symptoms, which would contribute to environmental monitoring and pollution prevention.

The effects of a single component of air pollution on depression symptoms have been preliminarily explored in youth. Two large-scale longitudinal studies produced the consistent finding that nitroxide exposure was associated with an increased risk of depression in adolescents (Latham et al., 2021; Reuben et al., 2021). Another longitudinal study found that the level of exposure to ozone could be used to predict the severity of depressive symptoms in adolescents (Manczak et al., 2022). In adult studies, the evidence for depression associated with the exposure to nitroxide is also relatively clear, whereas the relationship between ozone and depression remains indeterminate, no matter whether long or short-term exposure (Fan et al., 2020; Zeng et al., 2019). At present, chronic ozone inhalation has been found to bring about oxidative stress in the brain and depression symptoms in rat experiments (Mokoena et al., 2015). Considering that outdoor ozone concentration is usually higher than indoor, children and adolescents might be more vulnerable to ozone exposure because of their more outdoor activities (Eftekhari et al., 2021; Salonen et al., 2018).

Air pollution is linked with suicide attempts or behaviors. According to the records of ambulance dispatch and self-reports, positive associations were revealed between exposure to PM2.5/ozone and suicide-related events in children and adolescents (Casas et al., 2017; Fan et al., 2019; Liu et al., 2019). Additionally, a cross-sectional study revealed that a positive correlation existed between the air pollutants of PM2.5, CO and non-suicidal self-injury, but no correlation existed for NO2 or SO2 (Liu et al., 2018). In adult studies, meta-analyses have consistently revealed an increased risk of suicide associated with the exposure to PM and nitrogen oxides, whereas the effects of ozone and CO on suicide remained relatively controversial (Heo et al., 2021; Liu et al., 2021). Importantly, the increased risk of suicide mortality associated with air pollutants persists in the lag days of three, suggesting the necessity of avoiding air pollution consecutively (Davoudi et al., 2021). To be clear, brain changes followed by abnormal behaviors tend to be associated with long-term exposures, so more evidences are still needed to better clarify the relationship between an acute exposure and suicide-related events in youth. Furthermore, future research is required to determine the role of air pollutants in more comprehensive suicide-related adverse events, including self-injury, suicidal thoughts, and suicidal behaviors.

In summary, the majority of studies examined in this systematic review reported the associations between air pollution and affective disorders or suicide. One reason for the inconsistent findings might be that no unified scales or diagnostic criteria were used to evaluate affective

symptoms/disorders, and this hampers the ability to perform a combined analysis of the different studies. Meanwhile, compared with a clinical diagnosis of depression, which tends to be more accurate and conservative, self-reports might bias the evaluation results of air-pollution-related depression symptoms. Considering that depression is a strong predictor of suicide, subgroup analyses should be performed according to the health status of adolescents when investigating the air-pollution-related suicide events. Furthermore, potential confounding factors and covariates including social characteristics, traffic-related noise, and family history of psychiatric disorders were not consistently identified and corrected in the statistical analyses. At present, the precise pathways between the outdoor air pollution and these adverse consequences are not well established because the exact neurobiological mechanisms remain largely unknown. Therefore, in this paper, we carefully chose our words to ensure that we are describing the associations rather than causality. Future studies should contribute further to this line of research by further animal experiments and autopsy studies.

4.3. Neuroimaging of brain changes associated with air pollution

Previous studies have shown that air pollution produced the disruption of the BBB, oxidative stress, and deposition of PM in the CNS (Boda et al., 2020; Costa et al., 2019). Aided by neuroimaging, it is possible to identify the brain regions that are specifically affected (Lui et al., 2016; Zundel et al., 2022). Overall, extensive abnormalities of gray matter in the Cortico-Striato-Thalamo-Cortical (CSTC) neurocircuitry have been found in children exposed to air pollution. Specific findings included the decreased cortical surface of the frontal pole, thinner superior frontal, orbitofrontal, anterior cingulate cortex, and lower volumes of nucleus accumbens, caudate nucleus and thalamus (Brunst et al., 2019; Cserbik et al., 2020; Lubczyńska et al., 2020; Mortamais et al., 2017). Consistently, in adult studies, it was also found that more exposures to PM and nitrogen oxides were associated with lower gray-matter volume in this circuit (Cho et al., 2020; Gale et al., 2020). The CSTC circuit is responsible for integrating and processing neural information projected from the prefrontal cortex to the striatum and thalamus, finally returning to the initial prefrontal regions (Zhu et al., 2018; Zhu et al., 2016). It is closely concerned with attention allocation, emotional regulation, and impulsive behaviors (Bonath et al., 2018; Ho et al., 2015; Qu and Telzer, 2017). Abnormal gray-matter structure in this circuit in children and adolescents exposed to air pollution may be responsible for delayed cognitive development and unstable emotion.

Air-pollution-related structural white matter abnormalities have been initially explored in youth. In three cohort studies, white matter lesions in the prefrontal lobe, reduced white matter volume in the parietal and temporal lobe, and delayed cognitive development have been found in children living in a large polluted city (Calderon-Garciduenas et al., 2011; Calderon-Garciduenas et al., 2008; Calderon-Garciduenas et al., 2012). These findings suggest the presence of air-pollution-related neuroinflammation and its potential association with cognitive impairment in youth. Moreover, organic carbon exposure was found to be related to smaller corpus callosum volume in children, which may be related to a reduction in inter-hemispheric communication and function (Lubczyńska et al., 2020). Similarly, the smaller white-matter volume including the corpus callosum was found in female adults living in locations with higher levels of cumulative exposure to PM2.5 (Chen et al., 2017). At present, only volume is considered in the measures of air-pollution-related white matter abnormalities, whereas the integrity assessed by tract-based spatial statistics, the connectivity assessed by graph theory, and the myelination assessed by neurite density indices remain largely unknown. Therefore, further studies should utilize multi-shell diffusion-weighted imaging and novel analytical techniques to help further understand how air pollution impacts the maturation and development of white matter in children and adolescents.

Air-pollution-related brain functional alterations have gained increasing attention. Using blood oxygen level dependent imaging techniques, exposure to TRAP was found to be associated with lower functional integration in the default mode network (DMN) in children (Pujol et al., 2016). Similarly, in an adult study, living near high-traffic roads was also found to be associated with the less segregated DMN (Glaubitz et al., 2022). The DMN is mainly composed of the medial prefrontal cortex, posterior cingulate cortex and angular gyrus, which is activated in the resting state without tasks and is closely related to emotional processing and self-introspection (Raichle, 2015). Abnormalities in the DMN might be the potential neural substrates underlying affective disorders and anxiety (Xue et al., 2023; Zhou et al., 2020). Additionally, the changes in the prefrontal cortex (PFC)-amygdala circuit should be in-depth studied because it is strongly implicated in the internalizing psychopathology (Janiri et al., 2020; Xie et al., 2022). Concretely, future studies can consider conducting seed-based functional connectivity and amygdala subregion function analyses to further reveal the role of the PFC-amygdala circuit in the air-pollution-related depression and anxiety symptoms.

In summary, neuroimaging provides strong evidence for air-pollution-related brain structural and functional changes. Notably, most of these findings were revealed based on a cross-sectional design with between-group comparisons. In the future, this field would benefit from additional longitudinal studies using a pre- and post-exposure design to determine the trajectory of air-pollution-induced brain changes. In addition to studying the effect of the exposure itself, neuroimaging studies are also required to explore the impacts of green space on brain structure and function. Green space not only can directly improve air quality, but also may improve brain and mental health (Diener and Mudu, 2021; Ye et al., 2022). A systematic review also reported that greater greenness was positively associated with larger regional brain volumes and brain structural integrity (Besser, 2021). These benefits of green space on brain health might contribute to reducing the onset of depression, anxiety, and internalizing symptoms in children and adolescents (Liao et al., 2020). Furthermore, in view of the brain plasticity and ongoing brain development, it will be interesting and necessary to investigate the longitudinal brain alterations of migrating from air-polluted to green space areas.

5. Conclusion

Epidemiological studies have highlighted the association between air pollution and neuropsychological and behavioral symptoms in children and adolescents. However, although the association seems to be well established, the strength and specificity of the effects remain to be determined. Additional work to understand the confounders and covariates of these associations is needed including social characteristics, traffic-related noise, indoor air pollution, green space, and family history of psychiatric disorders. More importantly, neuroimaging will continue to play a crucial role in investigations of identifying the brain biological mechanisms that underpin these associations. In particular, neuroimaging makes it possible to visualize the specific region and degree of structural brain damage and evaluate the changes in brain function that may occur in people exposed to air pollution. High priority should be given to determining the pathogenesis of air pollution-related neuropsychiatric symptoms and the role of different components of air pollution. By using neuroimaging, it will be possible to explore the relationship between the environment and human brain health, and to obtain robust evidence for environmental governance.

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CRediT authorship contribution statement

Hongsheng Xie contributed to Methodology, Software, Formal analysis, Investigation, Data Curation, Writing (Review & Editing). **Yuan Cao** contributed to Methodology, Validation, Investigation, Resources, Writing (Original Draft). **Jiafeng Li** contributed to Data Curation, Writing (Review). **Yichen Lyu** contributed to Data collation, Investigation, Writing (Review). **Neil Roberts** contributed to Writing (Review & Editing). **Zhiyun Jia** contributed to Conceptualization, Visualization, Supervision, Funding acquisition, Writing (Review & Editing).

Conflict of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.03.082.

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