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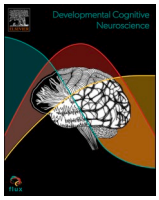

Clearing the air: A systematic review of studies on air pollution and childhood brain outcomes to mobilize policy change

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ABSTRACT

Climate change, wildfires, and environmental justice concerns have drawn increased attention to the impact of air pollution on children's health and development. Children are especially vulnerable to air pollution exposure, as their brains and bodies are still developing. The objective of this systematic review was to synthesize available empirical evidence on the associations between air pollution exposure and brain outcomes in developmental samples (ages 0–18 years old). Studies were identified by searching the PubMed and Web of Science Core Collection databases and underwent a two-phase screening process before inclusion. 40 studies were included in the review, which included measures of air pollution and brain outcomes at various points in development. Results linked air pollution to varied brain outcomes, including structural volumetric and cortical thickness differences, alterations in white matter microstructure, functional network changes, metabolic and molecular effects, as well as tumor incidence. Few studies included longitudinal changes in brain outcomes. This review also suggests methodologies for incorporating air pollution measures in developmental cognitive neuroscience studies and provides specific policy recommendations to reduce air pollution exposure and promote healthy brain development by improving access to clean air.

Climate change, wildfires, and environmental justice concerns have drawn increased attention to the impact of air pollution on children's development (Miller, 2022; Trentacosta and Austin, 2022). Outdoor air pollution is a mixture of particulate matter, gasses, and other organic and inorganic compounds that humans can inhale from the air (Calderón-Garcidueñas et al., 2015a). Particulate matter originates from the burning of gas, coal, oil, forests, industrial activities, fuel from vehicles, etc. Traffic-related air pollution in particular has been linked to adverse behavioral, cognitive, and motor development in children (de Prado Bert et al., 2018).

Reviews have documented the effects of air pollution on children's physical health, starting with preterm birth and low birth weight (Li et al., 2017; Stieb et al., 2012) and continuing with increased risk of developing respiratory, cardiovascular, and cutaneous diseases across the lifespan (Manisalidis et al., 2020). In addition, there is accumulating evidence linking air pollution to brain development outcomes in children and adolescents (Herting et al., 2019; Volk et al., 2021; Xie et al., 2023) including indices of brain function (Cotter et al., 2023), structure (Cserbik et al., 2020) and pathological outcomes such as tumors of the central nervous system (Danysh et al., 2015).

Furthermore, epidemiological findings have linked exposure to air pollution with increased risk of neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder (ADHD; Costa et al., 2019; Ha, 2021; Thygesen et al., 2020) and cognitive deficits in various domains, including intelligence and inhibitory control (Calderón-Garcidueñas et al., 2011b; Guxens et al., 2018). Overall, these findings may explain why children who have greater exposure to airborne fine particulate matter grow up to have lower earnings as adults (Swetschinski et al., 2023), suggesting broader impacts of air pollution on society and the need for policy change to mitigate these broader impacts.

Children and adolescents are particularly vulnerable to the effects of air pollution, as they have a higher intake of contaminants relative to their body weight compared to adults, spend more time outdoors than

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adults, and their brains and bodies are still developing (Salvi, 2007). Although more pediatric studies are needed to fully characterize the mechanisms by which air pollution impacts brain development, a number of biological pathways have been implicated thus far.

The effects of air pollution on brain development likely begin in utero, as maternal respiratory uptake of air pollutants has been linked to maternal inflammation, oxidative stress, and endocrine disruption, which can impair placental development and transport of oxygen and nutrients to the fetus (Ha, 2021). After birth, children's primary route of exposure to air pollution is via inhalation, which allows pollutants to reach the airways, the lungs, and from the lungs the bloodstream and the brain, but fine and ultrafine pollutants also reach the brain more directly via the olfactory epithelium and olfactory bulb (Calderón-Garcidueñas et al., 2015a; Costa et al., 2019). Throughout development, pollutants can induce endocrine disruption, as well as inflammation and oxidative stress in both the central nervous system (CNS) and in the periphery (Costa et al., 2020), with peripheral inflammation increasing the permeability of the blood-brain-barrier and the brain's exposure to multiple harmful influences (Costa et al., 2019). Autopsy studies also reveal precursors of Alzheimer's and Parkinson's diseases in postmortem brain samples, including hyperphosphorylated tau, amyloid plaques, and misfolded α-synuclein (Calderón-Garcidueñas et al., 2015a). Air pollution is also a risk factor for the onset and exacerbation of asthma and wheezing (Chatkin et al., 2022), which could impact brain and cognitive development by affecting cerebral availability of oxygen and through the impact of pharmacological treatments for asthma (e.g., corticosteroids) on brain and behavior (Irani et al., 2017). Air pollution exposure has also been linked to alterations in autonomic nervous system functioning in children and adolescents (Parenteau et al., 2022; Ugarte et al., 2022), such as lower cardiac autonomic regulation, a measure of overall parasympathetic and sympathetic influence over cardiac activity (Parenteau et al., 2022). These findings suggest the plausibility of autonomic and cardiovascular mechanisms impacting brain development. While mechanisms underlying the effects of air pollution on child brain development are still being investigated, animal studies support many of the same pathways implicated in humans and provide additional insights into mechanisms. For instance, there is evidence revealing neuronal cell loss and markers of Alzheimer's disease in the brains of rodents experimentally exposed to traffic-related air pollution (TRAP), as well as behavioral and cognitive alterations (Berg et al., 2020; Patten et al., 2021).

The objective of this systematic review was to address a gap in the literature regarding links between outdoor air pollution and brain outcomes in human pediatric populations, as most previous reviews of the literature have focused on adults or animal models. The exceptions include three reviews focused on child neurodevelopment and air pollution. One review focused on studies published up to 2020 linking prenatal air pollution exposure with child cognitive and clinical outcomes (e.g., ADHD, autism spectrum disorder, cognition, mood), as well as brain outcomes from two imaging studies (Volk et al., 2021). A second review (Xie et al., 2023) focused on affective symptoms and neuroimaging outcomes, reporting links between air pollution and increased risk of depression, suicidality, and brain alterations (e.g., decreased gray matter volume in the cortico-striato-thalamo-cortical neurocircuitry in five studies and white matter hyperintensities in prefrontal regions in two studies). The third review by Herting et al. (2019) reviewed six studies that used magnetic resonance imaging (MRI) to examine the association between air pollution exposure and brain structure and function in the developing brain. The studies reviewed by Herting and colleagues suggest associations between air pollution and alterations in white matter, gray matter, and brain function; however, the findings were not conclusive (Herting et al., 2019). The current synthesis builds on these foundational reviews by including additional brain measures and more recent literature, as this field has been rapidly expanding.

This review synthesized available peer-reviewed published evidence examining associations between outdoor air pollution exposure and brain outcomes (e.g., brain function using functional MRI (fMRI), brain structure using MRI and diffusion tensor imaging (DTI), brainstem auditory evoked potentials, and CNS-related tumors) in children ages 0–18 years old, including prenatal effects on the fetus via maternal exposure to air pollution. Air pollution measures included particulate matter (PM, including PM10, defined as particulate matter that is less than 10 microns in diameter, PM2.5, fine particulate matter that is less than 2.5 microns in diameter, and PM0.1, ultrafine particulate matter that is less than 0.1 microns in diameter), as well as gasses including carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3), as these are common indices of outdoor air pollution monitored by governmental agencies (Costa et al., 2020). However, we considered additional key terms related to air pollution to capture a broad literature (please see the full list of terms in the Search Strategy section). Because causes of and policy solutions for outdoor and indoor air pollution may differ, we restricted the scope of the current review to outdoor sources of air pollution, though future research should examine the evidence linking neurodevelopmental outcomes to indoor air pollution (e.g., from cigarette smoking). Our search included five neuroimaging studies captured by a previous review (Herting et al., 2019), and provided an updated search of studies to date, resulting in 40 studies being eligible for inclusion. We report associations of brain outcomes with cognitive or behavioral indices whenever possible, if studies tested these additional associations. We also review methodologies that developmental cognitive neuroscientists can use to incorporate measures of outdoor air pollution exposure in their analyses and conclude by providing policy recommendations for reducing children's exposure to air pollution.

1. Methods

This review was preregistered on the Open Science Framework (OSF) platform: https://osf.io/cn25z.

2. Eligibility Criteria

The present review focused on studies that included a measure of air pollution in association with brain outcomes in developmental samples (up to and including 18 years of age). The following inclusion criteria informed our search: articles needed to include a measure of outdoor air pollution or air quality, a brain outcome, and be conducted with children (0–18 years old); articles needed to include human participants and be published in English. Articles had to be empirical studies, not reviews. This review focused on outdoor air pollution and air pollution measures that can be linked to an individual's location, such as by residential address or an individual's census tract (rather than broad statewide levels, for example).

3. Information Sources

We completed a search of the PubMed and Web of Science Core Collection databases. The search was conducted on August 14, 2023 and was not repeated.

4. Search Strategy

Full search terms and filters for the two database searches can be found in the OSF pre-registration. The following search terms and filters were used: ("air quality" OR "air monitoring" OR "air pollution" OR "air pollutant" OR "air pollutants" OR "particulate matter" OR "PM2.5" OR "PM10" OR "ozone" OR "nitrogen dioxide" OR "nitrogen oxides" OR "sulfur dioxide" OR "black carbon" OR "elemental carbon" OR "vehicle emission" OR "vehicle emissions" OR "diesel" OR "diesel exhaust" OR "diesel exhausts" OR "vehicle exhaust" OR "vehicle exhausts" OR "vehicular exhaust" OR "vehicular exhausts" OR "road traffic" OR "traffic-related air pollution" OR "TRAP" OR "coarse particle" OR

"coarse particles" OR "ultrafine particle" OR "ultrafine particles" OR "polycyclic aromatic hydrocarbon" OR "polycyclic aromatic hydrocarbons" OR "combustion and friction derived nanoparticles" OR "combustion derived nanoparticles" OR "ultrafine particulate matter") AND ("brain" OR "neuroimaging" OR "neuroimage" OR "neuroimages" OR "magnetic resonance image" OR "magnetic resonance images" OR "magnetic resonance imaging" OR "MRI" OR "fMRI" OR "neuroinflammation" OR "functional connectivity" OR "NIRS" OR "near-infrared spectroscopy" OR "computerized tomography" OR "CT scan" OR "computerized axial tomography" OR "CAT scan" OR "EEG" OR "ERP" OR "electroencephalography" OR "neurobehavioral" OR "brain imaging") AND ("child or "children" or "adolescent" or "youth" or "teenager" or "pediatric" or "infant" or "toddler"); filters applied: Humans, English, Child: birth-18 years. For the Web of Science database, "article" was selected as the "document type."

5. Selection Process

The files obtained from the database search were imported into the Covidence systematic review software (Covidence.org). The database search resulted in 1422 articles, after removing 234 duplicates. There were two screening stages (an initial screening of the titles and abstracts and a secondary screening of the full-text articles). In both screening stages, two reviewers (AP and SH) independently reviewed each article for inclusion. Conflicts (i.e., one reviewer voting "Yes" and one voting "No" for inclusion) were resolved through a vote by a third reviewer (CH). In the first stage (title and abstract screening), reviewers assessed the article title and abstract for inclusion criteria. In the second stage (full-text screening), reviewers assessed the full-text record of the article for inclusion criteria. 75 articles were assessed in the full-text screening stage. The two reviewers screened the entire paper to ensure each contained, at minimum, the following three components: a child sample (0–18 years old), a metric of outdoor air pollution linked to individual participants, and a brain outcome measure. Through these two screening phases, the final number of articles to be included was determined (40 articles in total). The article selection process is illustrated in the PRISMA Chart (Fig. 1).

6. Data Collection Process, Data Items, and Synthesis Methods

Of the 40 included articles, full-text PDFs were stored in the Covidence systematic review tool. Two reviewers divided the articles and

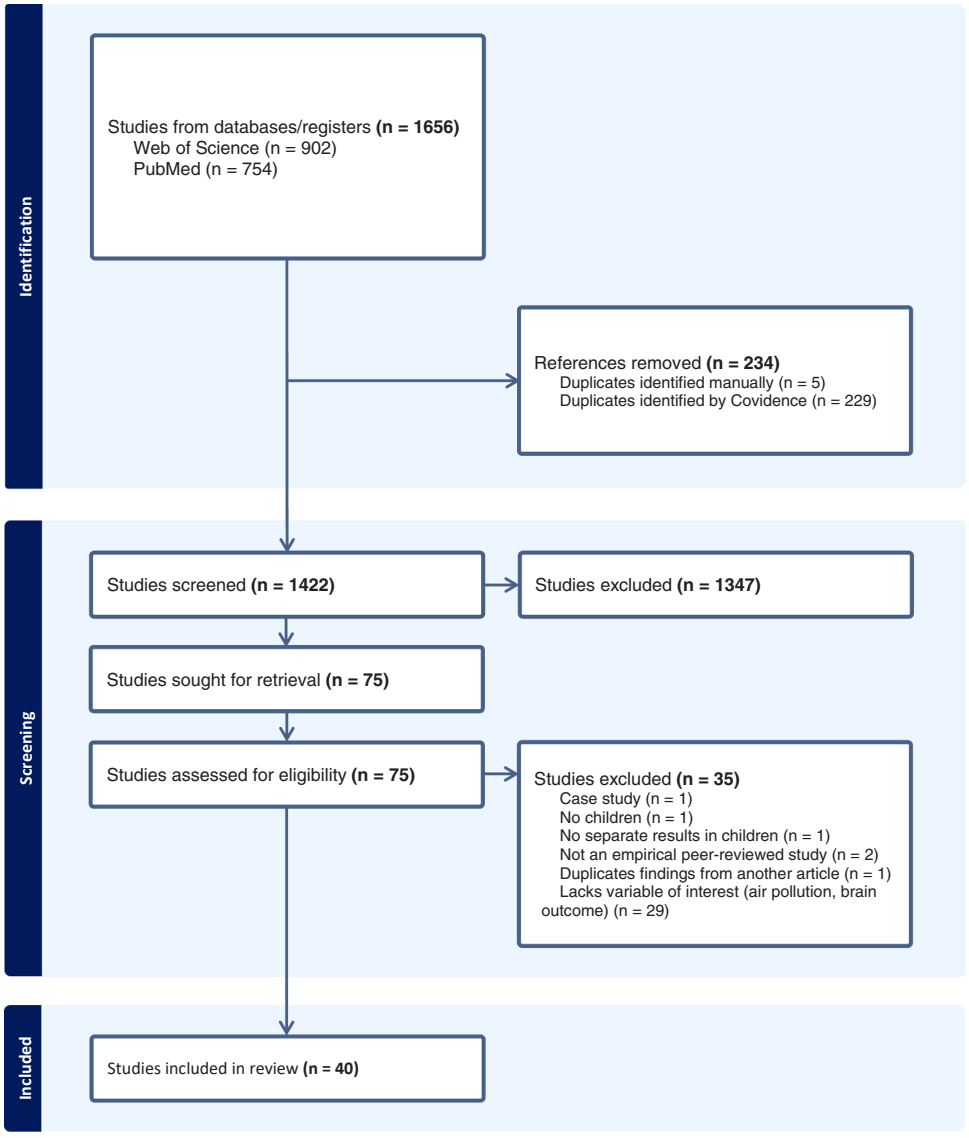

Fig. 1. PRISMA Flow Chart. *Note.* Figure represents the article selection and screening process for the current review, following PRISMA guidelines. The PRISMA flow diagram was generated using the Covidence systematic review tool.

extracted the relevant study information into a secure spreadsheet. The relevant extracted data was then double-checked by an independent reviewer who did not initially input the study information.

From the list of included articles, reviewers recorded the following data items: Title, Author, Year, Age range, Sample size, Sample name (if applicable), Gender ratio, Race/ethnicity, SES of sample, Country, Air pollution measure, Air pollution methodology, Location specificity, Timing of air pollution exposure, Brain measure, Brain region(s), Timing between assessments, Results, Covariates, and Conclusions. If information was missing from the article, reviewers inputted "missing"; if not applicable, reviewers inputted "N/A". The reviewers summarized the relevant study information into a brief summary statement for each study, to be synthesized into the review.

Studies were grouped according to the brain outcome measurement method used in the study (e.g., MRI, DTI, fMRI, MRS, brain-derived neurotrophic factor [BDNF] levels, cancers, and autopsy results).

7. Results

7.1. Study Characteristics

Of the 40 studies included, 18 involved MRI structural brain measures, 7 included DTI methods, 4 included fMRI measures, and 4 included magnetic resonance spectroscopy (MRS) measures. Two additional studies examined brainstem auditory evoked potentials. One study measured DNA methylation of genes involved in neurodevelopment. One study examined BDNF, eight studies examined instances of brain and CNS tumors, and four studies examined brain outcomes assessed via autopsy methods.

Age ranges for most studies included participants as young as newborns (Bos et al., 2023), and adolescent samples up to age 18. Two studies included a child cohort with an age range of 0–19 years old (Amin et al., 2019) and 11–19 years old (Calderón-Garcidueñas et al., 2018). A majority of studies included brain imaging data in childhood and early adolescence, linked to early and concurrent air pollution exposure.

The included studies were conducted in several locations: the United States of America ($k = 14$), Mexico ($k = 10$), Europe ($k = 14$), Asia ($k = 1$), and Australia ($k = 1$). Several studies included large cohorts, such as the Adolescent Brain Cognitive Development (ABCD) Study, the BREATHE project, and Generation R.

8. Magnetic Resonance Imaging (MRI) Structural Measures

Several studies examined links between outdoor air pollution and measures of brain structure using MRI.

8.1. ABCD Study

Measures of outdoor air pollution and structural brain imaging were assessed in the Adolescent Brain Cognitive Development (ABCD) Study, a 21-site study of approximately 11,000 nine and ten-year-old participants from the U.S., with a focus on longitudinal measures of brain structure and function (Casey et al., 2018). With regard to structure, analyses of ABCD study data have shown associations between PM2.5 and variations in gray matter across various cortical and subcortical regions and the cerebellum (Cserbik et al., 2020). This study also found hemispheric-specific associations between PM2.5 and cortical surface area and cortical thickness, and volumes of the thalamus, pallidum, and nucleus accumbens (Cserbik et al., 2020), the direction of which differed by region. For example, increased PM2.5 exposure was associated with decreased cortical thickness in regions such as the left superior frontal, left orbital frontal, left cingulate, and right inferior temporal cortex, but was associated with increased cortical thickness in regions such as the right lateral orbital frontal, right paracentral, right caudal anterior and posterior cingulate, and left middle temporal cortex.

8.2. BREATHE Project

The BREATHE project, a cohort of school children in Barcelona, Spain, assessed measures of air pollution in children's school courtyards and linked these indices to brain outcomes and cognitive development. In the BREATHE project, air pollutants were measured in two one-week measurements, 6 months apart, and averaged to estimate yearly levels. In a sample of 163 children with imaging data, yearly estimates of traffic-related air pollution, including outdoor polycyclic aromatic hydrocarbons (PAHs), elemental carbon (EC), and NO_2, were found to be associated with smaller caudate volumes, but this effect was stronger in children carrying the e4 allele of the apolipoprotein E (APOE) gene compared to other children (Alemany et al., 2018). The APOE e4 allele has been linked to a higher risk of developing Alzheimer's disease (AD) compared to the e2 and e3 variants (Calderón-Garcidueñas et al., 2015a; Calderón-Garcidueñas et al., 2015b). Children who live in a polluted city and have the high-risk APOE e4 allele may be at greater risk of developing AD-related brain alterations compared to children with the APOE e3 allele (Calderón-Garcidueñas et al., 2015a).

Pujol and colleagues assessed exposure to airborne copper in the BREATHE cohort ($N = 263$), and found that airborne copper exposure was associated with higher gray matter concentration in the striatum (caudate nucleus), but had no effect on tissue volume or other significant alterations in structure, other than increased cortical thickness in the left hemisphere supplementary motor area (Pujol et al., 2016a). In the same sample ($N = 263$), Pujol and colleagues (Pujol et al., 2016b) also assessed traffic-related air pollution through a summary measure of elemental carbon and NO_2 exposure (including indoor and outdoor measures), which was not significantly related to any anatomical or structural measures in the study, though significant links with functional outcomes were reported (see Functional Measures section below). In another sample from the BREATHE study ($N = 242$), outdoor levels of a specific PAH, benzo[a]pyrene, were linked to decreases in caudate nucleus volume, and predicted these decreases more strongly than total PAHs (Mortamais et al., 2017). PAHs were not associated with other brain measures (putamen volume, globus pallidus volume, or brain parenchymal fraction in the BREATHE study, Mortamais et al., 2017). Considering retrospective estimates of prenatal exposure in the BREATHE study, exposure to air pollution (PM2.5) during the third trimester of pregnancy was linked to decreased corpus callosum volumes in children ages 8–12 (Mortamais et al., 2019). However, there were no significant associations between PM2.5 exposure and volumes of the lateral ventricles, gray matter, or white matter (Mortamais et al., 2019).

8.3. Generation R Study

The Generation R Study is a prospective cohort study conducted in Rotterdam, Netherlands with a focus on early environmental exposure, including air pollution exposure during pregnancy and childhood (White et al., 2013). A subgroup of Generation R, which was oversampled for fetal exposures and behavior problems, with MRI measures at ages 6–10 ($N = 783$), showed thinner cortices in various brain regions in both hemispheres for children who were exposed to higher particulate matter during gestation (Guxens et al., 2018). This study also found evidence of a partial mediation, such that reduced cortical thickness in the precuneus and rostral frontal regions partially mediated the association between fine particulate matter (PM2.5) and an increase of inhibition errors during a neuropsychological assessment. This study did not find links between prenatal air pollution exposure and global brain volume (Guxens et al., 2018). A sub-study of Generation R imaging results at ages 9–12 years old also found a lack of association between air pollution and global brain volume (Lubczyńska et al., 2021; $N = 3113$). Lubczyńska and colleagues report no significant associations between exposure to air pollution and total brain volume, cortical and subcortical gray matter, cerebral white matter, and basal ganglia-related structures (Lubczyńska et al., 2021). However, exposure to pollutants during

Table 1
Summaries of findings from eligible articles.

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
Alemany et al., (2018)	$M = 9.3$ years ($SD = 0.82$), range 7–11 years	163	BREATHE	Barcelona, Spain	PAHs, EC, NO_2; measured in school courtyards	MRI	Recruited in 2012, MRI collected 2012–14; AP measured 6 months apart in 2012 and early 2013	PAHs and NO_2 exposure was associated with smaller caudate volume for all children; the effect was stronger in carriers of the APOE e4 allele.	Yes
Amin et al., (2019)	0–19 years	Population data from Census	US Census and Census American Community Survey	Florida, USA	EPA National Air Toxics Assessment; linked via ZIP Code Tabulation Areas Census tract	Brain and CNS Cancers	Cancer incidence during childhood (2000–2015); National Air Toxics Assessment from 2011	No statistically significant link between clusters of childhood cancers and air pollution were found in this Southeast region of the United States.	No (but controlled for age and sex)
Beckwith et al., (2020)	$M = 12.2$ years ($SD = 0.75$)	135	CCAAPS	Ohio, USA	ECAT; residentially linked	MRI	MRI collected in childhood at age 12; time-weighted estimates of AP assessed throughout childhood	Children with high ECAT exposure showed decreased cortical thickness in a bilateral medial region of posterior frontal and anterior parietal lobes compared to the children from low ECAT exposure. High ECAT exposure group had reduced gray matter volume observed in the cerebellum and pre- and postcentral gyri. There were no differences in the white matter volumes in either group.	Yes
Binter et al., (2022)	$M = 10.1$ years ($SD = 0.6$), range 9–12 years	3515	Generation R	Netherlands and Belgium	NO_2, PM2.5 and PM2.5 absorbance; residentially linked	MRI, DTI	MRI collected at age 9–12; AP from conception until MRI scan	Link between PM2.5 exposure and larger putamen volume, particularly if air pollution exposure was during gestation up to 2 years old. Higher levels of NO_2, PM2.5, and PM2.5 absorbance were associated with lower global FA and higher MD, although the window of susceptibility varied. The vulnerable periods identified for significant changes in individual white matter tracts were between 0 and 6 years.	Yes

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
Bos et al., (2023)	Approximately one week after birth	469	dHCP	Greater London, UK	PM2.5, PM10, and NO_2; home, postcode unit linked	MRI	MRI during infancy; AP measured over gestational period	Higher prenatal exposure to PM10 and lower exposures to NO_2 were linked to relatively larger cerebellar and ventricular volume. These exposures were also modestly associated with smaller cortical grey matter, amygdala, hippocampal volumes, and larger volumes of brainstem and CSF.	Yes
Brunst et al., (2019)	$M = 12.2$ years	145	CCAAPS	Ohio, USA	ECAT; residentially linked	MRS	AP in early life (at birth), 12 months before visit, average childhood ECAT; linked to MRS at age 12	ECAT exposure in the previous 12 months before scan was related to altered brain metabolism with increased myo-inositol concentrations measured within the ACC; also related to glutamate (in supplemental materials).	No (but controlled for age and SES)
Burnor et al., (2021)	$M = 119$ months ($SD = 7.4$), range 107–133 months	7602	ABCD	USA	PM2.5, residentially linked	DTI, RSI	Annual mean AP values at time of baseline visit, imaging collected at age 9–10	Higher PM2.5 exposure was linked to increases in cellular barriers in white matter (reflected by decreases in MD, increases in restricted isotropic intracellular diffusion), which may indicate changes to the cellular composition of key white matter tracts, including microstructure of frontoparietal and limbic white matter circuitry.	Yes
Calderón-Garcidueñas et al., (2008a)	Mexico City (M =10.7 years, $SD = 2.7$); Polotitlán ($M = 10.69$ years, $SD = 2.1$)	36	MC	Mexico	Air pollution assessed via selecting a historically highly polluted city (Mexico City) and a lower-polluted city (Polotitlán)	MRI	MRI conducted at baseline and at 1 year follow up in childhood ($n = 3$); chronic exposure to air pollution	Children from Mexico City (13 of 23) had white matter lesions, whereas only 1 child out of 13 from a low-pollution control city exhibited white matter lesions.	Yes
Calderón-Garcidueñas et al., (2008b)	2–17 years	12	MC	Mexico	Presents O_3 and PM data from Mexico City Ambient Air Monitoring Network, compared to two	Autopsy, immunohistochemistry	Chronic exposure and brain outcomes at autopsy neuropathological examinations	Of the 12 children in the sample (age 17 and under), 7 of 8 MC children had disruption of the BBB,	N/A

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
					control cities (Tlaxcala and Veracruz)			0 out of 4 controls had disruption of the BBB.	
Calderón-Garcidueñas et al. (2011a)	M = 96.3 months (SD = 8.5); additional autopsy sample M = 14.4 years (SD = 2.96)	51; Additional 10 in autopsy sample	SWMC	Mexico	Lifelong exposure to O_3 and PM in SWMC, examined pollutant levels in 2008–2009 compared to levels in Polotitlán from 2004	BAEPs and brainstem neuropathology	Air pollution exposure in 2008–2009 (2004 in Control), BAEPs collected in 2009; autopsy samples from separate group	This study found that compared to control children, MC children, who were exposed to urban air pollution, exhibited delays in BAEP waves III and V and significantly longer latencies for interwave intervals, potentially consistent with delayed central conduction time in the brainstem. Waves III, IV, and V involve the cochlear nuclei, SOC, and lateral lemniscus, indicating that these pathways may be abnormal in MC children. In a separate autopsy sample of 5 MC and 5 control children, there were alterations in SOC architecture and significant differences in morphometry in MC children.	No (but matched groups by age and SES)
Calderón-Garcidueñas et al., (2011b)	Mexico City (M = 7.1 years, SD = 0.69); Polotitlán (M = 6.8 years, SD = 0.66)	30	SWMC	Mexico	A historically highly polluted city (SWMC) and a lower-polluted city (Polotitlán)	MRI	MRI conducted at baseline and at 1 year follow up in childhood; chronic AP exposure	Children living in a historically polluted city with or without white matter hyperintensities exhibited white matter volume differences in the temporal and parietal regions, compared to a control group of children from a less-polluted city.	No (but matched groups for SES)
Calderón-Garcidueñas et al., (2012)	Mexico City with WMH+ (M = 7.28 years, SD = .47); Mexico City without WMH (M = 7.04 years, SD = .51); Polotitlán (M = 7.06 years, SD = .45)	30	SWMC	Mexico	A historically highly polluted city (SWMC) and a lower-polluted city (Polotitlán)	MRI	MRI conducted at baseline and at 1 year follow up in childhood; chronic AP exposure	Children from highly polluted Mexico City with WMH+ showed significantly more growth in brain volume (both gray and white matter) than their MC WMH- counterparts in temporal,	No (but controlled for gender)

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
								parietal, and frontal cortical regions.	
Calderón-Garcidueñas et al., (2015b)	$M = 12.45$ years ($SD = 3.4$)	57	MCMA	Mexico	A historically highly polluted city (Mexico City) and a lower-polluted city (Polotitlán)	MRS	Brain scan in childhood; AP estimated from prenatal stage through age at scan	Prenatal and childhood exposure to PM 2.5 and chronically poor air quality (higher than U.S. standards) were linked to an observed difference between groups such as right frontal hippocampus NAA/Cr ratio in APOE e4 MC children compared to controls.	Yes
Calderón-Garcidueñas et al., (2016a)	Mexico City ($M = 11.2$ years, $SD = 5.5$); Control ($M = 12.7$ years, $SD = 4.2$)	73	MC Pediatric cohort	Mexico	A historically highly polluted city (MCMA), and several lower-pollution control cities	CSF Spinal Tap	Spinal tap during childhood; AP estimated from prenatal stage through age at assessment	BDNF concentrations in CSF were significantly lower in MCMA children compared to controls.	Yes
Calderón-Garcidueñas et al., (2016b)	Mexico City ($M = 12.67$, $SD = 4.9$); Control ($M = 12.62$, $SD = 3.5$)	34	MCMA	Mexico	Inhalable coarse PM; from a historically highly polluted city (MC) and several lower-polluted control cities	Autopsy; Transmission Electron Microscopy (TEM)	Post-mortem analysis of residents from a highly polluted city vs. a lower-polluted city	Post-mortem analysis showed that children living in a highly polluted urban environment exhibited a more compromised NVU, compared to children from a nearby, less polluted city in the same region.	No (but controlled for age)
Calderón-Garcidueñas et al., (2018)	$M = 16.16$ years ($SD = 2.92$)	6	N/A	Mexico	A historically highly polluted city (MMC), and several control cities	Postmortem ACC tissue	Lifetime exposure postmortem tissue (from four teens and young adults, average age 16.16, and two controls)	Differences were in ACC white matter axonal diameter, where MMC teens had smaller axonal diameters compared to controls, and differences in maximal and minimal diameter sizes (MMC had lower values).	Yes
Calderón-Garcidueñas et al., (2019)	MMC ($M = 8.52$ years, $SD = 3.3$); Control ($M = 6.53$ years, $SD = 0.072$)	69	MMC	Mexico	A historically, highly polluted city (MMC), marked by O_3 and PM; and a lower-polluted city (Polotitlán)	BAEPs	Lifetime exposure and BAEP collected in childhood	MMC children exhibited a delay in wave III and V latency intervals and a delay in interpeak latency intervals I-III and III-V, indicating a central conduction delay.	Yes
Cotter et al., (2023)	Baseline ($M = 119$ months, $SD = 7.52$), Year 2 ($M = 143$ months, $SD = 7.68$) range 9–10 years at	9497	ABCD	USA	PM2.5, O_3, & NO_2; residentially linked	fMRI	MRI collected (9/2016 – 2/2020); AP exposure was averaged from year 2016	PM2.5 was found to relate to a greater number of changes in FC (i.e., 2 inter-network and 10 subcortical-to-cortical	Yes

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
	baseline; 11–13 years at year 2							changes) over the transition from late childhood into early adolescence as compared to O_3 (i.e., 1 intra-network and 5 subcortical-to-cortical changes) and NO_2 (i.e., 2 inter-network and 4 subcortical-to-cortical changes).	
Cserbik et al., (2020)	*M* = 119 months (*SD* = 7.7), range 108 to 131 months	10,343	ABCD	USA	PM2.5; residentially linked	MRI	MRI collected at baseline, 2016–2018 (age 9–10); AP exposure was averaged from 2016	Yearly averaged residential PM2.5 concentrations were associated with differences in surface area and cortical thickness in regions of the frontal, parietal, temporal, occipital, and cingulate cortex and with differences in subcortical and cerebellum volumes.	Yes
Danysh et al., (2015)	< 15 years	1949	Texas Cancer Registry 2001–2009	Texas, USA	HAPs: ambient 1,3-butadiene, benzene, and diesel particulate matter (DPM); census tract linked	CNS Tumors	CNS Tumors diagnosis in children <15; annual air pollution concentration at time of tumor diagnosis linked to census tract	Traffic-related HAPs are positively linked to the occurrence of astrocytoma and medulloblastoma diagnoses. Residing in census tracts with elevated concentrations of traffic-related HAPs was linked with higher risk of certain central nervous system (CNS) tumor types compared to those living in census tracts with lower HAP levels.	Yes
Essers et al., (2023)	9 –12 years	1186	Generation R	The Netherlands and Belgium	Several pollutants; NO_2, NO_x, PM, OP, PAHs, and others; residentially linked	MRI	MRI conducted in childhood; AP estimated during pregnancy to age at MRI scan	Air pollution exposure at different time points was associated with different structural brain morphology. Prenatal exposure to PMcoarse was linked to greater cerebral white matter volumes in APOE e4 carriers compared to non-APOE e4 carriers. Childhood exposure to PAHs was associated with larger	Yes

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
								cerebral white matter volume in APOE e4 carriers. Children with a higher polygenic risk score for Alzheimer's Disease who had prenatal PMcoarse exposure showed larger cortical gray matter volumes.	
Guxens et al., (2018)	6 –10 years	783	Generation R	The Netherlands and Belgium	NO_2, fine particles, coarse particles, absorbance of fine particles; residentially linked	MRI	MRI collected in childhood; AP exposure was averaged for entire fetal period	Children who were exposed to higher particulate matter prenatally showed thinner cortices in various brain regions in both of the hemispheres, though no global brain volume differences were observed.	Yes
Konstantinoudis et al., (2020)	0 –15 years	1290 with CNS tumors	SCCR	Switzer-land	NO_2; residentially linked via Swiss grid coordinate system	CNS tumors	Residential address and birth address	There was evidence of regional clusters of CNS tumors, but clusters were not linked to air pollution levels. NO_2 was analyzed as a covariate in the model, but the association was weak.	No (but controlled for SES)
Lubczyńska et al., (2020)	M = 10.1 years (SD = 0.6), range 9–12 years	2954	Generation R	The Netherlands and Belgium	17 air pollutants including NO_X, particulate matter (PM), and components of PM; residentially linked	DTI	DTI conducted in childhood; AP estimated for pregnancy and childhood	Higher exposure to multiple air pollutants during gestation or childhood was linked with significantly lower levels of fractional anisotropy and higher mean diffusivity.	Yes
Lubczyńska et al., (2021)	9 –12 years	3133	Generation R	The Netherlands and Belgium	NO_X, NO_2, coarse, fine, and ultrafine particles, and composition of fine particles; residentially linked	MRI	MRI conducted in childhood at age 9–12; AP estimated for pregnancy and childhood	No significant associations were identified between exposure to air pollution and the overall volumes of the entire brain, encompassing both cortical and subcortical gray matter. Prenatal air pollution exposure was linked to a reduction in cortical thickness; high exposure during childhood was linked to higher cortical surface area.	Yes

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
Mazzei et al., (2022)	0 –15 years	1290 cases of CNS tumors (10 controls matched to each case)	SCCR, Swiss National Cohort	Switzerland	AP exposure to petrol station; linked from Swiss Business Census	CNS tumors	Exposure at year of diagnosis and at birth; linked to age at diagnosis	Cancer rate was higher for children exposed to petrol stations compared to non-exposed children (odds ratio of 1.47 for CNS tumors). In the whole study, the observed associations between cancer diagnosis and petrol station exposure appeared to be stronger for CNS tumors, but only a small number of CNS cases were among children living in close proximity to a petrol station.	Yes
Miller et al., (2022a)	T1: $M = 11.38$ years ($SD = 1.04$), T2: $M = 13.35$ years ($SD = 1.05$)	184	Longitudinal study of early life stress and neurodevelopment	San Francisco Bay Area, CA, USA	Pollution burden linked at census tract level (CalEnviroScreen 3.0)	MRI	Pollution burden in neighborhood and MRI data at T1 and T2 (ages 11 and 13)	Pollution was linked to shorter telomere length at average and large levels of hippocampal volume. Bivariate correlations between pollution burden and hippocampal volume at T1 or T2 were not significant.	Yes
Miller et al., (2022b)	T1: $M = 11.51$ years ($SD = 1.08$), T2: $M = 13.47$ years ($SD = 1.16$)	115	Longitudinal study of early life stress and neurodevelopment	San Francisco and San Jose, CA, USA	PM2.5; residentially linked	MRI; tensor-based morphometry	MRI conducted at T1 and T2 (ages 11 and 13); AP estimated for 2 years prior to T1 assessment	PM2.5 was linked to changes in the volume of multiple gray and white matter regions over a two-year period and interacted with ELS. In youth who experienced milder ELS, PM2.5 was linked to contractions in multiple frontal, parietal, and temporal gray matter clusters, and in white matter clusters in the cerebellum; white matter in the left superior corona radiata was expanded. Those with more severe ELS exposure showed fewer effects of PM2.5 exposure, and some effects were in the opposite direction compared to low ELS exposure.	Yes

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
Mortamais et al., (2017)	Mdn = 9.7 years, range 8–12 years	242	BREATHE	Barcelona, Spain	Total PAHs; BAP; linked to school courtyards	MRI	Recruited in 2012, MRI collected 2012–14; AP measured 6 months apart in 2012 and early 2013	BAP levels were linked to decreases in CNV, independent of covariates. The effects of outdoor total PAHs on CNV were similar but to a lesser extent than for BAP outdoor levels. No other significant associations were found between total PAHs (outdoor or indoor) and the other brain measures (putamen volume, globus pallidus volume, or BPF).	Yes
Mortamais et al., (2019)	Mdn = 9.7 years, range 8–12 years	186	BREATHE	Barcelona, Spain	PM2.5; residentially linked	MRI	MRI conducted in childhood; air pollution estimated for pregnancy	Prenatal PM2.5 exposure, particularly during the third trimester, was linked with decreased corpus callosum volume in pre-adolescent children.	Yes
Park et al., (2017)	< 6 years old	13,636 cases and 270,673 controls	California Cancer Registry	California, USA	Exposure to ambient dichloromethane; linked to individual addresses	CNS tumors	Exposures based on birth addresses (over the course of pregnancy/birth year), and age of child in dataset	Across all models examining exposure and CNS tumors, odds ratios were close to 1.00 and did not show significantly elevated risk. Exposure was related to increased risk of other types of tumors.	Yes
Pérez-Crespo et al., (2022)	*M* = 10.2 years (*SD* = 0.6), range 9–12 years	2197	Generation R	The Netherlands and Belgium	NO_2, NO_x, and PM2.5; residentially linked	rs-fMRI	rs-fMRI conducted in childhood (age 9–12); AP estimated from pregnancy to childhood	Air pollution during the first six years of life was associated with greater brain functional connectivity in several brain regions; associations were strongest between brain regions of the task positive and task negative networks and were mainly inter-network.	Yes
Peters et al., (2013)	Cases (*M* = 7 years); Controls (*M* = 6.2 years), range 0–14 years	306 cases, 950 controls	Aus-CBT and Aus-ALL	Australia	Parental occupational exposure to engine exhaust (via survey)	Brain tumor diagnosis	AP exposure before and after birth measured through parental job history.	Maternal exposure to diesel exhaust any time before the child's birth and paternal exposure to diesel exhaust around conception were independently associated with childhood brain tumors.	No (but controlled for sex and age)

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
Peterson et al., (2022)	$M = 10.8$ years ($SD = 1.38$), range 6–14 years	332	Prospective cohort study of the CCCEH	Northern Manhattan, New York, USA	PM2.5; residentially linked via address of mother during pregnancy	MRI, DTI, MRS, ASL	Exposure during pregnancy and brain outcomes in childhood	PM2.5 exposures were associated with thinning of dorsal parietal cortices and thickening of temporal, posterior–inferior and mesial wall cortices. Exposure was also associated with region-specific increases and decreases in white matter volumes, higher FA in basal ganglia, thalamus, and anterior cingulate gyrus, greater diffusivity in posterior white matter tracts, anterior corpus callosum, and anterior corona radiata, higher metabolite concentrations in the ACC, and reduced regional cerebral blood flow in several regions.	Yes
Pujol et al., (2016a)	$M = 9.7$ years ($SD = 0.9$), range 8–12 years	263	BREATHE	Barcelona, Spain	Airborne copper exposure; measured in school courtyards	MRI, DTI, fMRI	Recruited in 2012, MRI collected 2012–14; AP measured 6 months apart in 2012 and early 2013	Copper exposure was significantly related to higher gray matter concentration in the caudate nucleus, higher FA in the caudate nucleus, and reduced caudate-to-frontal operculum functional connectivity.	Yes
Pujol et al., (2016b)	$M = 9.7$ years ($SD = 0.9$), range 8–12 years	263	BREATHE	Barcelona, Spain	Elemental carbon and NO; measured in school courtyards	MRI, DTI, MRS, fMRI	Recruited in 2012, MRI collected 2012–14; AP measured 6 months apart in 2012 and early 2013	Traffic-related air pollution was not related to anatomical, structural, or metabolic brain measures. Traffic-related air pollution (summary of elemental carbon and NO_2 exposure) was related to weaker functional connectivity between DMN regions (medial frontal cortex and angular gyrus bilaterally), and stronger functional connectivity between medial frontal cortex and frontal operculum at the lateral	Yes

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
								boundary of the DMN. Exposure to pollutants was significantly associated with lower deactivation in task activation measures, in supplementary motor area and somatosensory cortex. Age showed an opposite effect on functional connectivity within elements of the DMN, showing the potential maturational effects (slower brain maturation) of pollution on the brain.	
Reynolds et al., (2003)	< 15 years	1351 for gliomas, 6989 for all types of cancer	California Cancer Registry	California, USA	HAP; 25 pollutants; census tract linked	Cancers	Population-based cancer incidence rates; AP was a calculated exposure score by census tract	No significant increased risk (rate ratio) or distinct trend for gliomas across exposure categories, but childhood leukemia incidence was linked to tracts with the highest combined exposure to the 25 pollutants.	No (but adjusted for age, sex, and race/ ethnicity)
Sukumaran et al., (2023)	M = 119 months (SD = 7.52), range 9–10.99 years	8796	ABCD	USA	PM2.5, NO_2 and O_3, residentially linked	DTI, RSI	Averaged over the 2016 calendar year, corresponding with ABCD baseline data collection.	Air pollution exposure was significantly related to subcortical gray matter microstructure, specifically PM2.5 was positively associated with restricted isotropic diffusion in both right and left nucleus accumbens, the right thalamus, and the brainstem. Restricted isotropic diffusion in these regions was linked to cognitive performance. NO_2 and O_3 were not significantly associated with gray matter microstructure.	Yes
Von Ehrenstein et al. (2016)	< 6 years old, PNET (M = 2.5 years, SD = 1.6); Medulloblastoma (M = 2.0 years, SD =	183 with cancer and 30,569 no-cancer controls	California Cancer Registry	California, USA	42 substances; residentially linked	Brain tumors: medulloblastoma, CNS PNET, and astrocytoma	Brain tumors diagnosed < age 6; air pollution estimated across pregnancy and the first year after birth	Exposure to industrial and traffic air pollutants were shown to increase risks for PNET and medulloblastoma for	Yes

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Table 1 (*continued*)

Article	Age	Sample Size	Study Cohort	Geographic Location	Air Pollution (Measures, Location Linked)	Brain Outcomes	Timing of Assessments	Main Findings	Reported findings adjusted for or matched groups by child age, sex, and SES?*
	1.5); Astrocytoma (M = 2.5 years, *SD* = 1.8)							children up to 6 years of age. Specifically, exposure to butadiene, BTEX, selenium, acetaldehyde, perchlorethylene, trichloroethylene, chloroform increased the PNET risk. Medulloblastoma risk increased with higher prenatal exposure to PAHs and trichloroethylene. Astrocytoma risk was estimated to increase with exposure to lead and some PAHs within the first year of life.	
Zeng et al., (2022)	0 (birth measure)	204	N/A	Haojiang and Guiyu (e-waste recycling area), China	PM2.5, maternal exposure during pregnancy; linked via two study locations	Birth head circumference, DNA methylation of genes involved in neurodevelopment	Exposure during pregnancy, assessment of head circumference and DNA methylation in genes involved in neurodevelopment at birth	Maternal PM2.5 chronic daily intake during pregnancy, which was higher in those in an exposed (e-waste) city, was negatively associated with child birth head circumference. A mediation model found that this association may be partially mediated through DNA methylation in genes involved in neurodevelopment. Birth head circumference was lower in the exposed city. In addition, a linear regression model revealed a negative association between chronic daily intake of PM2.5 and birth head circumference.	No (but included gender as covariate & groups did not differ by age; groups differed by parental education)

Note. This table summarizes the 40 included studies. Whenever possible, we standardized terms. *ABCD* = Adolescent Brain Cognitive Development Study; *AUS-ALL* = Australian childhood acute lymphoblastic leukemia study; *AUS-CBT* = Australian case–control study of childhood brain tumors; *CCAAPS* = Cincinnati Childhood Allergy and Air Pollution Study; *CCCEH* = Columbia Center for Children's Environmental Health; *dHCP* = Developing Human Connectome Project; *MC* = Mexico City; *MCMA* = Mexico City Metropolitan Area; *MMC* = Metropolitan Mexico City; *SCCR* = Swiss Childhood Cancer Registry; *SWMC* = Southwest Mexico City. Air pollution acronyms: *AP* = air pollution; *BAP* = benzo[*a*]pyrene; *BTEX* = benzene, toluene, ethylbenzene, and xylene; *EC* = elemental carbon; *ECAT* = elemental carbon attributable to traffic; *HAPs* = hazardous air pollution; NO_2 = nitrogen dioxide; NO_X = nitrogen oxides; O_3 = Ozone; *OP* = oxidative potential of PM2.5; *PAHs* = Polycyclic Aromatic Hydrocarbons; *PM* = particulate matter. Brain-related acronyms: *ACC* = anterior cingulate cortex; *APOE* = Apolipoprotein E; *ASL* = arterial spin labeling; *BAEP* = brainstem auditory evoked potential; *BBB* = blood-brain barrier; *BDNF* = brain-derived neurotrophic factor; *CC* = corpus callosum; *CNV* = caudate nucleus volume; *CNS* = central nervous system; *CSF* = cerebrospinal fluid; *DMN* = default mode network; *DTI* = diffusion tensor imaging; *ELS* = early-life stress, *FA* = fractional anisotropy; *FC* = functional connectivity; *fMRI* = functional magnetic resonance imaging; *MD* = mean diffusivity; *MRS* = magnetic resonance spectroscopy; *MRI* = magnetic resonance imaging; NVU = neurovascular unit; *PNET* = primitive neuroectodermal tumor; *SOC* = superior olivary complex; *WMH* = white matter hyperintensities. *Socioeconomic Status (SES) broadly defined. A full list of covariates for each study is available upon request.

gestation was associated with a larger volume of specific structures including the cerebellum, putamen, pallidum, and amygdala, and a smaller corpus callosum and hippocampal volume (Lubczyńska et al., 2021). Generation R findings may point to sensitive periods of exposure, as air pollutant exposure during pregnancy was associated with lower cortical volume and exposure during childhood was associated with more pronounced cortical surface area (Lubczyńska et al., 2021). In another Generation R study, there was a significant link between higher PM2.5 exposure and a larger putamen volume, specifically when exposure was during gestation up to 2 years old (Binter et al., 2022).

Incorporating existing genetic data in the Generation R cohort, Essers et al. (2023) found differential associations with structural brain measures, depending on APOE gene status. Exposure to several air pollution measures during pregnancy was associated with larger volumes for cerebral white matter, cortical gray matter, and corpus callosum in APOE e4 carriers compared to non-carriers. Further, exposure was linked to smaller volumes across subcortical gray matter, putamen, thalamus, and nucleus accumbens in carriers compared to non-carriers (Essers et al., 2023). Compared to other pollutants, coarse PM (between 10 and 2.5 microns in diameter) during the prenatal period and PAHs during childhood were both linked to greater cerebral white matter volumes in carriers. Lastly, children with a higher polygenic risk score for Alzheimer's Disease and exposure to coarse PM prenatally showed larger cortical gray matter volumes (Essers et al., 2023).

8.4. Mexico City Studies

Studies by Calderón-Garcidueñas and colleagues have examined exposure to high levels of air pollution in the Mexico City Metropolitan Area and associations with various brain outcomes, ranging from molecular to structural measures. In a study comparing 20 seven- to eight-year-old children from Mexico City, an area characterized by high levels of air pollution, with ten children from a control city in the same region with lower levels of air pollution, Mexico City children showed significant white matter volumetric differences (Calderón-Garcidueñas et al., 2011b). Children from Mexico City had smaller white matter volume in temporal and parietal regions compared to children in the control, low-pollution city, although some differences depended on the presence or absence of white matter hyperintensities (Calderón-Garcidueñas et al., 2011b). Further, the children in this sample with white matter hyperintensities showed differences in gray and white matter volumes in temporal, parietal, and frontal cortical regions compared to those without white matter hyperintensities, but not compared to children in the control group (Calderón-Garcidueñas et al., 2012). Another sample of children from Mexico City showed white matter lesions were present for 13 of 23 children compared to one child out of 13 from a low-pollution control city, a result that was significantly different from chance (Calderón-Garcidueñas et al., 2008a).

8.5. Other Structural Studies

Additional studies have examined brain structure and volume in association with prenatal air pollution exposure. Through the Developing Human Connectome Project (dHCP) in London ($N = 469$), higher prenatal exposure to PM10 and lower exposure to NO_2 was positively associated with larger ventricle and cerebellum volume, smaller cortical gray matter, amygdala, and hippocampus volume, and larger brainstem and extracellular cerebrospinal fluid (CSF) volumes (Bos et al., 2023). In this study, prenatal PM2.5 exposure was not associated with any brain volume measure.

In a prospective cohort study of 12-year-old children from Ohio, U.S., children with exposure to traffic-related air pollution in their first year of life were found to have decreased frontal and parietal cortical thickness compared to children with lower exposure (Beckwith et al., 2020). Further, children with higher exposure also had reduced gray matter volumes compared to those with lower exposure, primarily in the cerebellum; yet there were no significant findings with white matter volumes (Beckwith et al., 2020). Another study examined exposure to PM2.5 during pregnancy, which was associated with later cortical thickening in lateral temporal, postero-inferior, and mesial wall surfaces and thinning in dorsoparietal and orbitofrontal cortices in childhood (Peterson et al., 2022). Exposure to higher levels of PM2.5 was associated with smaller local white matter volumes in some regions, including the lateral temporal, inferoparietal, and mesial cingulate surfaces, and larger white matter volumes in dorsal convexity, mesial superior frontal gyrus, and postero-inferior surface (Peterson et al., 2022). In this study, boys were at a greater risk for the effects of PM2.5 on the brain (Peterson et al., 2022).

In a study of adolescents, although there were no significant bivariate associations between pollution burden (including air pollution) and hippocampal volumes at the two time points (Miller et al., 2022a), there was a significant interaction effect on telomere length, such that hippocampal volume and pollution burden predicted telomere length. In adolescents with average and larger (+1 *SD*) hippocampal volumes, pollution burden was negatively associated with telomere length, a marker of biological aging (Miller et al., 2022a). In the same sample, using tensor-based morphology, residential levels of PM2.5 were positively associated with changes in brain volume in several gray and white matter regions over a two-year period (Miller et al., 2022b). Further, air pollution may be differentially associated with brain outcomes depending on early-life experiences. In this study, PM2.5 was linked to these volumetric changes in children who experienced mild levels of early life stress (ELS) compared to those who experienced more severe ELS, indicating differences in sensitivity to PM2.5 (Miller et al., 2022b). These results highlight possible interactions between exposure to pollutants and experiences of early-life adversity.

8.6. Summary of structural MRI studies

Overall, studies have identified several associations between air pollution exposure and altered brain structure, including measures of cortical structure, white matter structure, and subcortical volume. Focusing first on studies that have identified altered cortical structure, findings have been mixed depending on brain region, the pollutant examined, and the timing of the air pollution assessment. For example, several studies have found that exposure to pollutants is associated with decreased cortical thickness. Guxens et al. (2018) found that higher prenatal exposure to particulate matter was associated with decreased cortical thickness measured in childhood in several regions, including dorsal and ventral frontal regions, the cuneus, and precuneus. Beckwith et al. (2020) found that exposure to traffic-related air pollution during infancy was associated with decreased cortical thickness in several regions, including frontal and parietal regions, in childhood. Other studies have found both increases and decreases in measures of cortical structure depending on the region examined. For example, Cserbik et al. (2020) found that PM2.5 concentrations measured in childhood were associated with altered cortical thickness and surface area, but the direction of effects depended on the region, with higher PM2.5 exposure being associated with both increases and decreases in cortical surface area and thickness in frontal, cingulate, occipital, and temporal cortex. Peterson et al. (2022) found that prenatal exposure to PM2.5 was associated with both increased and decreased cortical thickness, with higher PM2.5 exposure generally associated with increased cortical thickness in frontal, temporal, parietal and occipital regions. Other research has found no significant association between childhood air pollution exposure and cortical thickness (Pujol et al., 2016b). In sum, studies suggest that air pollution exposure is associated with altered cortical thickness and surface area, but the direction of effects has been mixed, and likely depends on a variety of factors including the type of pollutant, the timing of exposure (e.g., prenatal vs. during childhood), exposure location (e.g., at home vs. city-wide), and the region of cortex. Brain region-specific effects of pollutants may also explain why several

studies have found no associations between air pollution exposure and global measures of gray matter volume (Guxens et al., 2018; Mortamais et al., 2019; Lubczyńska et al., 2021).

Similar to the findings for cortical structure, associations between air pollution exposure and white matter structure have also been mixed and varied depending on factors such as the white matter tract and the timing of pollution exposure. For instance, some studies have found that prenatal or childhood exposure to different pollutants is associated with decreased corpus callosum volume (Mortamais et al., 2019, Lubczyńska et al., 2021). Other research has shown that children living in Mexico City have decreased white matter volume in temporal and parietal regions (Calderón-Garcidueñas et al., 2011b) and more white matter lesions (Calderón-Garcidueñas et al., 2008a) compared to children living in a less-polluted control city. Miller et al. (2022b) found tract-specific associations, with higher PM2.5 exposure in childhood associated with larger white matter volume in the corpus callosum, cingulum, inferior fronto-occipital fasciculus, splenium, and temporal and frontal regions but smaller white matter volume in the inferior temporal gyrus, angular gyrus, thalamic radiation, and other regions. Other studies have found no association between traffic-related air pollution exposure in childhood and white matter volume (Beckwith et al., 2020). In sum, similar to findings for cortical structure, the associations between air pollution exposure and white matter structure appear to vary depending on the white matter tract, the type of exposure, and the timing of exposure.

Focusing on studies that have identified associations with subcortical gray matter volume, again results have been mixed. Several studies have found associations with basal ganglia structures, although sometimes in opposing directions. For example, studies have found that childhood exposure to PAHs and NO_2 was associated with smaller caudate volume (Alemany et al., 2018), childhood copper exposure was associated with higher gray matter concentration in the caudate (Pujol et al., 2016a), childhood exposure to PAHs was associated with smaller caudate volume (Mortamais et al., 2017), increased childhood PM2.5 exposure was associated with increased left accumbens and right pallidum volume but decreased left putamen and left pallidum volume (Cserbik et al., 2020), prenatal exposure to pollutants was associated with larger putamen and pallidum volumes and childhood exposure to pollutants was associated with larger nucleus accumbens volume in childhood (Lubczyńska et al., 2021), and higher PM2.5 exposure in the first 2 years of life was associated with larger putamen volume (Binter et al., 2022). Studies have also found associations between pollutants and the volume of other subcortical regions including the thalamus, amygdala, and hippocampus (e.g., Cserbik et al., 2020; Lubczyńska et al., 2021; Bos et al., 2023). Overall, associations between pollution exposure and structural MRI measures appear to be specific to the region examined, type of pollutant, and timing of exposure.

9. Diffusion Tensor Imaging (DTI) and Restricted Spectrum Imaging (RSI)

9.1. ABCD Study

Studies using ABCD data have examined associations of air pollution with DTI measures as well as restricted spectrum imaging (RSI) microstructure measures. Specifically, in one study, higher PM2.5 exposure was linked to increases in cellular barriers in white matter (Burnor et al., 2021). This was reflected by decreases in mean diffusivity (MD) and increases in restricted isotropic intracellular diffusion, which may indicate cellular changes to key white matter tracts (Burnor et al., 2021). Sukumaran and colleagues found that exposure to air pollution was significantly related to subcortical gray matter microstructure in ABCD participants (Sukumaran et al., 2023). Specifically, PM2.5 was positively associated with restricted isotropic intracellular diffusion in both left and right nucleus accumbens, the right thalamus, and the brainstem (Sukumaran et al., 2023).

9.2. BREATHE Study

Two studies from the BREATHE project assessed DTI measures in association with air pollution exposure across schoolyards in Barcelona. One found that airborne copper exposure was associated with increased fractional anisotropy (FA) in white matter surrounding and in the caudate nucleus (Pujol et al., 2016a). Higher copper exposure was also associated with a combination of diffusion changes in the caudate nucleus (Pujol et al., 2016a). In contrast, Pujol and colleagues found that traffic-related air pollution, a summary of elemental carbon and NO_2 exposure, was not associated with FA measures in the same sample (Pujol et al., 2016b).

9.3. Generation R

In a study of the Generation R sample ($N = 3515$), higher exposure to NO_2 and PM2.5 during the prenatal period and early childhood was associated with lower global FA and higher global brain MD at ages 9–12 (Binter et al., 2022). The authors observed potential vulnerable periods of exposure between 0 and 6 years, for which they found an association between air pollutants and individual white matter tracts (Binter et al., 2022). These findings built upon an earlier study in the Generation R cohort ($N = 2954$) that examined exposure to air pollutants during gestation and childhood, but with less temporal specificity in exposure (Lubczyńska et al., 2020). Indeed, Lubczyńska and colleagues found that higher exposure was linked to lower levels of FA and higher MD compared to those with lower exposure during gestation or childhood (Lubczyńska et al., 2020). Specifically, higher exposure to fine particulate matter during pregnancy was related to lower FA and specific pollutant exposure during pregnancy and childhood was associated with higher MD (Lubczyńska et al., 2020). However, Binter and colleagues expanded on these findings by using novel modeling techniques (distributed lag non-linear models) to identify more specific periods of susceptibility (Binter et al., 2022).

9.4. Other Cohorts

Further, results from the Columbia Center for Children's Environmental Health cohort ($N = 332$) showed that exposure to PM2.5 during pregnancy was associated with higher FA values in subcortical gray matter nuclei and the anterior cingulate gyrus in childhood (Peterson et al., 2022). Higher PM2.5 was also associated with higher Average Diffusion Coefficient (ADC) diffusivity in large white matter bundles in posterior brain regions and anterior corona radiata (Peterson et al., 2022). Taken together, these studies highlight brain alterations due to air pollutant exposure.

9.5. Summary of DTI studies

Similar to results for structural MRI, associations between air pollution measures and DTI measures depend on the region examined, the timing of exposure, and the type of exposure. For example, Binter et al. (2022) found that NO_2 and PM2.5 exposure was associated with lower FA and higher MD in white matter tracts, but the susceptibility of different tracts depended on the timing of the exposure. In contrast, Burnor et al. (2021) found no association between PM2.5 exposure and FA of white matter tracts but did find that higher PM2.5 exposure was associated with decreased MD in a number of different white matter tracts. Peterson et al. (2022) found that PM2.5 exposure was associated with higher diffusivity in posterior white matter tracts, the anterior corpus callosum, and anterior corona radiata. In sum, air pollution exposure has been associated with altered properties of white matter microstructure, but the associations vary by study.

10. Functional Measures

10.1. Functional Magnetic Resonance Imaging (fMRI)

Resting-state, functional brain imaging techniques have revealed additional links between air pollution and brain development. A study by Cotter et al. (2023) found that higher PM2.5 exposure was associated with changes in inter-network cortical functional connectivity (FC) as well as subcortical network functional connectivity over a two-year follow-up period. In contrast, elevated O_3 concentrations were associated with heightened intra-network FC of the default mode network but a simultaneous reduction in subcortical-to-network FC over time. Moreover, greater NO_2 exposure during this follow-up period resulted in a marked decrease in both inter-network and subcortical-to-network FC. In conclusion, the cumulative effects of childhood exposure to PM2.5, O_3, and NO_2 are intricately linked to specific alterations in the maturation patterns of neural networks over time.

A study by Pujol and colleagues with the BREATHE cohort found that airborne copper was associated with reduced caudate-to-frontal operculum connectivity (Pujol et al., 2016a). Pujol and colleagues also found that traffic-related air pollution was related to weaker functional connectivity between default mode network (DMN) regions (medial frontal cortex and angular gyrus bilaterally) and stronger functional connectivity between the medial frontal cortex and frontal operculum at the lateral boundary of the DMN (Pujol et al., 2016b). Both of these measures suggest lower network integration and segregation, respectively (Fair et al., 2009; Pujol et al., 2016b). In the Generation R study, 31 brain regions were examined and children exposed to higher levels of air pollution during the first six years of life showed greater resting state functional connectivity between several regions at ages 9–12 (Pérez-Crespo et al., 2022). The authors examined specific periods of exposure. NO_2, nitrogen oxides (NO_x), and PM2.5 absorbance were associated with functional connectivity, but PM10 and PM2.5 were not. Specifically, higher exposure to NO_2 and PM2.5 absorbance (a marker for black carbon) from 0 to 3 years old was associated with greater functional connectivity between cortical regions and regions in the task positive and task negative networks. NO_x exposure from ages 3–6 years old was associated with increased functional connectivity between visual regions and regions of the task positive network. Most associations were identified as inter-network, between brain regions of the task positive and task negative networks. This suggests lower network segregation and higher within-network integration. Additionally, more than half of these connections were intra-hemisphere and were primarily in the right hemisphere (Pérez-Crespo et al., 2022).

10.2. Summary of fMRI studies

Across these fMRI studies, there is mixed evidence of decreased and increased functional connectivity between some regions, lower between-network segregation, and both lower and higher within-network integration, with Cotter and colleagues presenting longitudinal data indicating dynamic changes in connectivity (2023). Again, the results appear to vary depending on the type of exposure, timing of exposure, and networks examined. Two studies found that higher pollutant exposure was associated with increased between-network connectivity (Pujol et al., 2016b; Pérez-Crespo et al., 2022), possibly suggesting decreased segregation of the networks. However, Cotter et al. (2023) found that associations between air pollution exposure and network connectivity differed depending on the type of pollutant examined. In this study, higher PM2.5 exposure was associated with greater between-network connectivity of multiple networks, O_3 exposure was associated with greater within-network connectivity of the default mode network, and NO_2 exposure was associated with decreased within-network connectivity of the frontoparietal network and decreased between-network connectivity of multiple networks. Thus, results appear to be network- and pollutant-specific.

10.3. Arterial Spin Labeling

The study by Peterson and colleagues (2022) also included a measure of Arterial Spin Labeling (ASL), which measures regional cerebral blood flow (rCBF). PM2.5 exposure was associated with lower rCBF in lingual and fusiform gyri, the hippocampus, internal capsule, and dorsal parietal cortex (Peterson et al., 2022). The authors speculate that these findings may be reflective of the effect of pollutant exposure on mitochondrial dysfunction, since rCBF is associated with cellular energy expenditure and lower rCBF may reflect reduced energy expenditure in these regions.

10.4. Auditory Evoked Potentials

Auditory processing in children has also been used to investigate the impact of urban air pollution on children's brain health. Specifically, children from Mexico City, an area characterized by a history of chronic air pollution exposure, exhibited delays in brain auditory evoked potentials (BAEPs) waves III and V and showed significantly longer latencies for interwave intervals (Calderón-Garcidueñas et al., 2011a). It is worth noting that waves III through V involve the cochlear nuclei, superior olivary complex (SOC), and lateral lemniscus. These delays can indicate potential abnormalities within these neural pathways among the affected children. In a more recent study, Mexico City children exhibited a delay in wave III and V latency intervals and delayed interpeak latency intervals I-III and III-V, indicating a central conduction delay (Calderón-Garcidueñas et al., 2019). The authors describe that these central delays are generated "rostral to the auditory nerve"; and these delays are likely associated with bilateral lesions in the auditory brainstem and other regions that have been shown to have inflammatory changes (Calderón-Garcidueñas et al., 2011a; Calderón-Garcidueñas et al., 2019).

11. MRS (Magnetic Resonance Spectroscopy)

Some studies have used magnetic resonance spectroscopy (MRS) to examine the concentrations of certain brain metabolites in association with air pollution exposure. Higher exposure to PM2.5 in pregnancy was associated with higher N-acetyl-L-aspartate (NAA) and choline concentrations in the dorsal anterior and midcingulate cortex of youth ages 6-14 years old (Peterson et al., 2022). This study also examined levels of PAHs via personal monitoring, and these findings are not included in this review, as they include both indoor and outdoor air pollution levels. Brunst and colleagues found that elemental carbon attributable to traffic (ECAT) exposure in the 12 months before a scan in early adolescence was related to altered brain metabolism, with increased myoinositol concentrations measured within the anterior cingulate cortex (ACC) compared to children with low ECAT exposure (Brunst et al., 2019). In a study of children in Mexico, chronic prenatal and lifetime exposure to poor air quality was linked to a decrease in hippocampal NAA/Cr (creatine) ratio (Calderón-Garcidueñas et al., 2015b).

12. Methylation of Genes Involved in Neurodevelopment

A study from China examining maternal exposure to PM2.5 and electronic waste (e-waste) during pregnancy found that higher maternal exposure to PM2.5 was associated with lower child birth head circumference. A mediation model suggested that this association may be partially mediated by neonatal DNA methylation of genes involved in neurodevelopment (Zeng et al., 2022).

13. Brain-Derived Neurotrophic Factor Levels

BDNF levels from CSF are important markers of brain health and plasticity. Understanding the disparities between regions with and without clean air is crucial, as living in disadvantaged neighborhoods

may shape these levels. For instance, children who grew up in highly polluted cities in Mexico show lower levels of BDNF in CSF compared to children from cities with lower pollution in the same region (Calderón-Garcidueñas et al., 2016a). While the exact cause of lower BDNF levels in these children is not fully understood, these findings shed light on the potential molecular-level effects from chronic air pollution exposure.

14. Brain Pathology

14.1. Cancers

In addition to studies that have found associations of air pollution with measures of brain structure and function, others have found it increases risk for brain pathology such as cancers. For example, a large U. S. study from Texas showed that children living in census tracts exposed to higher levels of air pollution such as ambient 1,3-butadiene, benzene, and diesel particulate matter (DPM) have been found to have higher incidence of tumors such as astrocytomas and medulloblastomas compared to those who had lower exposure (Danysh et al., 2015). However, one study from Florida could not link geographic clusters with high pediatric cancer incidence to air pollution (Amin et al., 2019). In the western region of the United States, prenatal exposure to PAHs elevate medulloblastoma risk in children (Von Ehrenstein et al., 2016), while other studies in this same region show no significantly elevated risk of central nervous system tumors (Park et al., 2017) or gliomas (Reynolds et al., 2003) in high-exposure areas, though these studies linked high pollution exposure to leukemia incidence (Park et al., 2017; Reynolds et al., 2003). A study conducted in Switzerland (Mazzei et al., 2022) found that children exposed to emissions from petrol stations had significantly increased odds of developing central nervous system (CNS) tumors when compared to children who were not exposed to such pollutants. However, regional CNS tumor clusters there were not always associated with air pollution exposure (Konstantinoudis et al., 2020).

Furthermore, a separate study in Australia (Peters et al., 2013) has illuminated the risks of pollutant exposure during early development. Specifically, maternal exposure to diesel exhaust fumes, extending from preconception to the year after giving birth, was associated with a heightened risk of child brain tumors. This risk appeared to escalate when the exposure occurred within the two years preceding the child's birth and during their first year of life. This observation underlines geographic variability in risk and the importance of considering early development as a potential period of vulnerability to the effects of air pollution.

14.2. Autopsy Results

Postmortem analyses of brain tissue samples from regions with significant air pollution have revealed additional insights. Signs of vascular damage in the prefrontal white matter region have been observed in post-mortem analyses of brain tissue samples of children who resided in a highly polluted urban environment in Mexico City. Specifically, children in Mexico City exhibited signs of a compromised neurovascular unit (NVU) compared to children from a nearby, less polluted control city (Calderón-Garcidueñas et al., 2016b). Morphologic alterations in the brainstem, such as architecture differences in the superior olivary complex, have also been observed in children from this highly-polluted region (Calderón-Garcidueñas et al., 2011a) compared to children from a control city. In another autopsy sample, authors compared disruptions in the blood-brain barrier (BBB) by analyzing abnormal tight junctions in children from Mexico City, who had chronic exposure to air pollution, to a control city with low levels of air pollution. Of the 12 children in the sample (17 years old and younger), 7 of 8 Mexico City children exhibited disruptions of the BBB, whereas none of the four control participants had BBB disruptions (Calderón-Garcidueñas et al., 2008b). In post-mortem samples from older adolescents, differences were found in ACC white matter axonal diameter, such that the average diameter was smaller in four MC youth compared to two controls (Calderón-Garcidueñas et al., 2018). These findings reveal potential pathological brain outcomes due to chronic air pollution burden.

15. Summary

The majority of studies in this review examined the associations between exposure to air pollution and structural brain measures (k = 18). Many of these studies had a focus on basal ganglia structures, such as the caudate (Alemany et al., 2018; Pujol et al., 2016a; Mortamais et al., 2017). Other structural studies examined cortical thickness and found differences in cortical thickening and thinning related to air pollution exposure (e.g., Beckwith et al., 2020; Cserbik et al., 2020; Guxens et al., 2018; Peterson et al., 2022; Pujol et al., 2016a). Over a two-year period, residential air pollution was associated with changes in brain volume in several gray and white matter regions (Miller et al., 2022b). Early exposure to air pollution (such as during pregnancy and in the first year of life) was associated with reduced gray matter volumes in the cerebellum in adolescence (Beckwith et al., 2020) and smaller white matter volumes in several regions during childhood (Peterson et al., 2022). Prenatal exposure to air pollution was also linked to decreased corpus callosum volumes in childhood (Mortamais et al., 2019). Across these studies, several regions of the brain were found to have reduced gray and white matter volume and differences in cortical thickness. However, some findings are mixed (Pujol et al., 2016a).

DTI studies (k = 7) showed several associations between air pollution exposure and atypical white matter microstructure. Air pollutant exposure was associated with increases in cellular barriers in white matter, and positive associations with restricted isotropic intracellular diffusion in several regions in the ABCD study (Burnor et al., 2021; Sukumaran et al., 2023). Higher exposure to air pollutants prenatally and during early childhood was linked to lower global FA and higher MD later in childhood (Binter et al., 2022; Lubczyńska et al., 2020). However, school-based exposures to copper air pollution in Barcelona were linked to increased FA in white matter surrounding and in the caudate nucleus, and a combination of diffusion changes in the caudate nucleus (Pujol et al., 2016a); but exposure to different air pollutants was not associated with FA in the same sample (Pujol et al., 2016b).

Studies using fMRI (k = 4) highlighted changes in network integration and segregation (Cotter et al., 2023; Pérez-Crespo et al., 2022; Pujol et al., 2016a; Pujol et al., 2016b). A longitudinal study measuring the changes in FC using the ABCD study cohort found evidence of altered cortical and subcortical FC associated with air pollution exposure (Cotter et al., 2023). Yet, more longitudinal studies are needed with larger datasets (such as ABCD) and more longitudinal measures to assess changes across development. MRS studies (k = 4) indicated potential metabolic effects of pollutant exposure on brain health, with effects on brain metabolites being associated with air pollution. Findings from these studies suggest that air pollution is associated with altered levels of markers of neuronal integrity and metabolism.

One study revealed links between air pollution and DNA methylation of genes involved in neurodevelopment, which were related to birth head circumference (Zeng et al., 2022). These initial findings suggest possible mechanisms for prenatal effects of air pollution.

Tumor studies (k = 8) illuminated that there is spatial clustering of tumor incidence in areas with higher air pollution (Danysh et al., 2015; Mazzei et al., 2022; Peters et al., 2013; Von Ehrenstein et al., 2016). However, these findings were not always found consistently across studies (Amin et al., 2019; Konstantinoudis et al., 2020; Park et al., 2017; Reynolds et al., 2003). Lower BDNF levels (k = 1) have also been observed in children from highly polluted areas, which sheds light on potential molecular effects due to chronic pollutant exposure (Calderón-Garcidueñas et al., 2016a). Autopsy studies (k = 4) also revealed structural and vascular damage from air pollution exposure, particularly in geographical locations burdened with higher pollution

levels (Calderón-Garcidueñas et al., 2008b; Calderón-Garcidueñas et al., 2011a; Calderón-Garcidueñas et al., 2016b; Calderón-Garcidueñas et al., 2018), though sample sizes are small in these studies. As some of these findings show that the impact of air pollution exposure on child brain health is not uniform across geographic regions, they underscore the need for region-specific strategies to mitigate these risks and safeguard child brain development.

In sum, we draw preliminary conclusions from this review in Box 1.

16. Discussion

Increasing evidence supports the association between air pollution exposure and brain-related outcomes in developmental samples, suggesting the need for urgent policy actions. Examining these associations is imperative, as children are more susceptible to the effects of air pollution compared to adults (Salvi, 2007). Exposure to pollutants during periods of rapid brain development can increase susceptibility to adverse effects. This review included empirical studies of exposure to outdoor air pollution and brain outcomes in developmental samples (ages 0–18 years old). Studies examined air pollution exposure across a range of developmental periods, from the prenatal period to adolescence. Studies included measures of brain structure, function, and potential pathology, but additional research is needed to uncover longitudinal brain changes related to air pollution and potential sensitive periods of exposure. Additionally, more experimental data is needed in humans, given the predominance of correlational study designs in the current literature. Acknowledging the significance of air pollution exposure, developmental researchers may consider incorporating measures of air pollution in their studies.

We identified 40 studies linking air pollution exposure to brain outcomes in children and adolescents. The studies reviewed included various methodologies to assess brain outcomes. The majority of studies used brain imaging methods (MRI, DTI, fMRI, MRS) and others incorporated additional functional measures such as brain auditory evoked potentials. Other studies examined associations between spatial distribution patterns for air pollution and pathological outcomes, such as CNS tumors or autopsy tissue sample analysis.

Structural MRI studies were the most prevalent in our review and revealed associations between air pollution and differences in gray and white matter volumes, cortical thickness, and subcortical brain region volumes. While many studies showed reduced volumes, some findings were mixed and showed no volumetric differences (Pujol et al., 2016a) and larger volumes of specific brain regions (e.g., Binter et al., 2022; Bos et al., 2023). Studies that demonstrated decreases in gray matter volumes revealed that these decreases were not a function of brain maturation or pruning associated with age (Beckwith et al., 2020). Overall, effects in structural MRI studies appeared dependent on a variety of factors, including the brain region examined, the type of pollutant exposure, and the timing of exposure. Although there does not appear to be a consistent pattern of effects across all MRI studies, these studies do suggest that air pollution is associated with a range of structural alterations, including alterations in cortical thickness and surface area, white matter volume, and subcortical volume. However, more research is needed that systematically compares effects of pollution exposure at different developmental periods, effects of different types of pollutant exposure, and effects for specific brain regions in order to gain a more comprehensive understanding of associations between pollution exposure and brain structure.

DTI studies emphasized links between pollution and differences in white matter microstructure, including increases in cellular barriers and restricted intracellular isotropic diffusion, lower global FA, and higher MD (Binter et al., 2022; Burnor et al., 2021; Lubczyńska et al., 2020; Sukumaran et al., 2023). However, some findings were mixed, showing increases in FA in white matter (Pujol et al., 2016a) or decreased MD (Burnor et al., 2021). These studies point to potential effects of air pollution exposure on microstructure development. Similar to the findings for structural MRI, there was no consistent association between air pollution exposure and white matter structural properties across studies. Instead, the direction of associations differed depending on the type of pollutant, the timing of exposure, the white matter tracts examined, and the DTI methods and parameters assessed.

Studies using fMRI showed mixed evidence of decreased and increased FC, depending on the regions and networks examined. Additionally, fMRI findings demonstrate lower between-network segregation, and both lower and higher within-network integration. Only one study highlighted effects of air pollution exposure on longitudinal changes in connectivity (Cotter et al., 2023). However, this emerging literature seems to suggest that air pollution may be linked to alterations in the maturation of neural networks (Cotter et al., 2023), as network segregation and integration are important for brain maturation processes (Fair et al., 2007). Similar to the findings for structural MRI and DTI, the specific associations between pollution exposure and functional connectivity appear to depend on the type of exposure, timing of exposure, and the networks examined. More research is needed to systematically characterize the changes in functional connectivity associated with each of these factors.

Additional studies examined the potential pathological implications of air pollution exposure, linking air pollution to the prevalence of CNS tumors across geographic regions (Danysh et al., 2015; Mazzei et al., 2022; Von Ehrenstein et al., 2016) and BDNF concentrations (Calderón-Garcidueñas et al., 2016a). Other studies found that air pollution exposure was related to differences in key brain metabolites in childhood (Brunst et al., 2019; Peterson et al., 2022).

Importantly, many of the findings in this review were in countries, regions, or communities where the air pollution values were below US EPA recommended values and EU quality standards. Therefore, the associations were seen even in community samples of children not exposed to chronically high levels of air pollution. Across the studies, most samples were largely composed of healthy, typically-developing children. These results emphasize the magnitude of air pollution impacts on brain health in both typically-developing and clinical populations, and even at levels of air pollution that are below thresholds required by regulations.

17. Limitations and Future Directions

The current review is not without limitations. First, our review did not include gray literature (e.g., conference abstracts or dissertations). To maintain a focus on brain outcomes, we excluded studies that included only cognitive outcomes, such as cognitive task performance, without accompanying brain outcomes. Thus, the current review does not address associations between air pollution exposure and cognitive development, although such reviews exist (see Allen et al., 2017; Chandra et al., 2022; Clifford et al., 2016). However, a small number of included studies did reveal associations between air pollution, brain outcomes, and cognitive task performance (Guxens et al., 2018; Sukumaran et al., 2023). In addition, this review focused on outdoor air pollution and excluded studies of indoor air pollution. In studies that included both outdoor air pollution measures and personal air monitoring methods (e.g., Peterson et al., 2022), only findings related to outdoor air pollution were presented. We focused on outdoor air pollution measures due to the difference in the specific policy recommendations that can address outdoor versus indoor air pollution. These limitations present possible next steps for future research, including reviewing extant gray literature and incorporating studies with cognitive development outcomes. In addition, future research could incorporate measures of personal air monitoring for estimating precise individual-level exposure and associations with brain development.

Few studies in this review used longitudinal measures of neuroimaging or brain outcomes to assess changes in brain development over time. More longitudinal evidence on the association between air pollution exposure and developmental changes in brain structure and

function is needed. Additionally, more research is needed to investigate potential sensitive periods of air pollution exposure. While some of the included studies used measures and analyses that revealed vulnerable periods of exposure (e.g., Binter et al., 2022), other studies measured air pollution exposure at one time point or included measures of chronic exposure. Thus, future research is needed that measures air pollution at specific periods in association with brain measures across development, in order to better understand potential sensitive developmental periods of exposure. In addition to developmental timing of exposure, results of studies were highly varied depending on the types of pollutants examined and the measures of brain structure or function examined. This indicates an important need for more studies that comprehensively examine and compare the effects of exposure at different developmental periods, the effects of exposure to different types of pollutants, and that include more comprehensive measures of brain structure and function to allow comparisons across studies.

Although results from studies included in this review are compelling, most study designs are not experimental in nature, precluding causal inference. Furthermore, the possibility of unobserved confounders (e.g., SES, other toxicants) can make it difficult to attribute the totality of effects observed to air pollution. Animal studies provide initial proof-of-concept about the causal effects of air pollution on various neurodevelopmental outcomes (Berg et al., 2020; Patten et al., 2021), thus it is plausible the correlational findings reported in humans reflect causal associations. Nevertheless, experimental manipulations are needed in humans to advance this area of research (e.g., the introduction of air purification in schools or homes; retrospective studies examining outcomes before and after regulatory changes; studies capitalizing on changes in traffic flows or meteorological conditions).

Another limitation in the literature is the imprecise measurement of children's actual exposure in some studies. Future studies could consider protocols using personal air pollutant monitoring to enhance the precision of individualized exposure estimates. For instance, personal air monitoring has been used to assess prenatal exposure to PAHs during pregnancy (Pagliaccio et al., 2020). This approach could help complement outdoor exposure estimates and measure air pollution exposure more precisely.

Taken together, the reviewed articles point to a growing body of evidence emphasizing the impacts of outdoor air pollution exposure on the developing brain. As climate change-related disasters and disparities in air pollution exposure continue, there is a need for additional research and specific policy actions in this area. Exposure to air pollution early in life is linked to brain development outcomes starting in infancy (Bos et al., 2023; Zeng et al., 2022). Thus, a call to action for both research and policy is needed. To further this agenda, we review the various ways in which researchers can incorporate air pollution measures into their research designs next.

18. Incorporating Air Pollution Measures into Research Studies

These findings underscore the importance of understanding the broader implications of maternal and child exposure to air pollutants on child brain health. Future studies should examine spatial and temporal features of exposure to air pollution. First, it is imperative to narrow down the location of exposure (country of residence and locale of exposure, such as residential or school-based). This research will help illuminate how geographic locations pose differential risks due to the regional disparities of various pollutant exposures. Secondly, identifying vulnerable developmental periods will aid in assessing when air pollution exposure poses the most heightened risks. To facilitate future work, we review a variety of methods that can be used to incorporate measures of air pollution in studies of brain development and health in developmental samples, drawing from examples in this review.

18.1. Air Pollution Estimates at Various Scales

Air pollution can be assessed with a range of technologies, including remote sensors from satellite technology, recordings from regulatory-quality stationary monitors and other non-regulatory monitors, computational air quality modeling, and low-cost portable sensor systems (Cromar et al., 2019). These monitoring systems provide data across different time scales (real-time, daily, monthly, annual) and also at various spatial scales (street, city, regional, global) (Cromar et al., 2019). Developmental cognitive neuroscientists should carefully consider their research question when selecting the temporal and spatial scales to focus on (e.g., interest in characterizing acute versus chronic effects of air pollution would guide the choice of temporal scale, and interest in comparing high versus low air pollution areas versus obtaining precise estimates for each individual would guide the choice of spatial scale).

Researchers can link air pollution exposure to spatial locations such as residential homes (e.g., Essers et al., 2023; Miller et al., 2022; Mortamais et al., 2019; Pérez-Crespo et al., 2022; Von Ehrenstein et al., 2016), which can be obtained from residential address or zip code information. Of note, children spend the majority of their days in schools or educational settings, and air pollutant levels can be obtained from the geographic location of their schools or sensors placed in school areas (Pujol et al., 2016b,a). In studies with residential address or school location data, researchers can incorporate air pollutant levels from large, open datasets from organizations such as the EPA's Air Quality System Data Mart, which contains archives of various air pollutant measures across the United States.

Air pollution exposure has been assessed at various spatial scales: gross, intermediate, and granular. To understand how air pollution exposure impacts brain health outcomes at a gross scale, estimating air pollution at the regional, city or census tract level via publicly available

Box 1
Preliminary Conclusions from This Systematic Review

- Air pollution exposure is associated with a range of structural brain alterations in children, including alterations in cortical thickness and surface area, white matter volume, and subcortical volume.
- Associations between pollution exposure and structural MRI measures are specific to the region examined, the type of pollutant, and the timing of exposure.
- DTI and functional connectivity findings are mixed, and more research is needed.
- Air pollution exposure is associated with alterations in brain metabolites, although no consistent associations with certain metabolites have been detected.
- Large studies have linked air pollution exposure to childhood CNS tumor incidence.
- Autopsy studies indicate structural and vascular damage from air pollution exposure.
- Early development (e.g., prenatal period, early childhood) appears to be a vulnerable window of exposure.
- The pollutants of most concern seem to be PM2.5 and traffic-related pollutants.

records could be used to assign geographic air pollution estimates to participants within those spatial limits (Amin et al., 2019; Danysh et al., 2015; Miller et al., 2022b; Mazzei et al., 2022; Park et al., 2017; Reynolds et al., 2003).

To assess a more intermediate level of analysis, researchers may use spatial distances to highways and other geographic points such as monitoring and sampling sites to create individually-linked air pollution burden scores. Studies based in London have used a toolkit to assess air pollution by using both a modeling-measurement and kernel modeling approach (Bos et al., 2023). Land-use regression is also a commonly used method (Beckwith et al., 2020; Binter et al., 2022; Brunst et al., 2019; Essers et al., 2023; Guxens et al., 2018; Lubczyńska et al., 2020; Lubczyńska et al., 2021; Pérez-Crespo et al., 2022; Mortamais et al., 2019). These models help establish estimates of spatial concentrations of air pollutants in a particular area, by incorporating environmental characteristics, such as meteorological factors and land-use characteristics (e.g., road density). These models have been utilized to average air pollution exposure across a specified timeframe from infancy to childhood.

For a more granular and comprehensive assessment, geocoding techniques such as organizing a geographic information system (GIS) database and linking it to spatial coordinates via Application Programming Interface (API) keys have been employed to link detailed air pollution metrics to each participant's locale–as seen in the ABCD study's externally linked data (Fan et al., 2021). These methods employ a more precise linkage between the participants' relation to individual and community-level features in order to build a more comprehensive geo-coded air pollution measurement.

Using open-source geocoding techniques to link participant addresses with data from air monitoring boards (such as the California Air Resources Board) can produce more precise exposure estimates (von Ehrenstein et al., 2016). Throughout their efforts to incorporate air pollution data in their studies, researchers should ensure the protection of participant confidentiality when linking addresses to spatial coordinates through these methods (Fan et al., 2021; Rundle et al., 2022).

18.2. Timing of Air Pollution Exposure

Next, it is important to consider the timing of exposure, both in regard to the developmental stage and specificity of air pollutant exposure duration (e.g., daily, weekly, monthly, and per annum levels). These considerations are dependent on the research question and measures of interest. Highlighted in this review, extant research has linked air pollution exposure during various developmental periods to later brain development. This includes exposures in the prenatal period (Lubczyńska et al., 2020) and childhood (e.g., Cotter et al., 2023), with some studies examining potential vulnerable periods of exposure from gestation to early childhood (Binter et al., 2022). Prior research has examined air pollution levels using daily (Burnor et al., 2021; Cotter et al., 2023; Peterson et al., 2022), weekly (Alemany et al., 2018; Guxens et al., 2018; Lubczyńska et al., 2020; Lubczyńska et al., 2021; Mortamais et al., 2017; Pujol et al., 2016a), monthly (Miller et al., 2022b) or annual estimates (Cotter et al., 2023; Cserbik et al., 2020; Danysh et al., 2015; Mortamais et al., 2019; Pujol et al., 2016b; Peters et al., 2013; Sukumaran et al., 2023; Zeng et al., 2022). Through incorporating spatial pollution estimates and narrowing down the timing and extent of pollution exposure, researchers can contribute to a better understanding of sensitive periods of exposure. This nuanced approach can account for contextual and societal events that may be contributing to temporal variations in pollutant exposure, such as climate change (Trentacosta and Austin, 2022). This future research can inform policy recommendations and solutions.

19. Policy Recommendations

Clean air is essential for healthy brain development. Policies and regulations that reduce emissions of pollutants and their precursors will improve child wellbeing and brain development. Such policies include those that reduce pollutants and greenhouse emissions from vehicles, power plants, and many industrial sources. A number of policy recommendations have been suggested and many are currently being implemented (U. S. Global Change Research Program, 2023).

First, shifting to a renewable, electricity-based energy economy reduces greenhouse gas emissions and concomitantly reduces emissions of particulate matter, volatile organic compounds and nitrogen and sulfur oxides from fossil-fueled combustion sources such as vehicles, heating systems, power plants and refineries.

Second, government incentives to install air purifiers in homes, schools and workplaces, that were implemented in parts of Utah and California during the peak of the COVID pandemic, result in cleaner air and reduced exposure to air pollutants. Studies suggest that these measures also improve student cognitive performance (Gilraine, 2023).

Third, communities living close to air pollutant sources are exposed to higher pollutant concentrations and these communities are frequently of lower socioeconomic status and do not have the resources to purchase air cleaners or relocate farther from such sources. Policies that provide air purifiers in homes, schools and workplaces in these communities or enable relocation would reduce exposure and promote brain health.

Fourth, low-cost air pollution sensors are now available. Policies that enable communities to measure their own air pollution, such as California AB617, empower communities to advocate for cleaner air and also inform them when to take mitigating measures, such as turning on air purifiers.

We urge the adoption of these policies and others to reduce air pollution exposure and thereby promote healthy brain development.

CRediT authorship contribution statement

Camelia E. Hostinar: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Anthony S. Wexler:** Writing – review & editing, Writing – original draft. **Anna M. Parenteau:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Johnna R. Swartz:** Writing – review & editing, Writing – original draft, Supervision. **Sally Hang:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT for sections of the manuscript to help improve flow and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content.

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.

Data Availability

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