Published in final edited form as:

Neurotoxicology. 2022 December ; 93: 272–300. doi:10.1016/j.neuro.2022.10.011.

Air Pollution, Depressive and Anxiety Disorders, and Brain Effects: A Systematic Review

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Abstract

Accumulating data suggest that air pollution increases the risk of internalizing psychopathology, including anxiety and depressive disorders. Moreover, the link between air pollution and poor mental health may relate to neurostructural and neurofunctional changes. We systematically reviewed the MEDLINE database in September 2021 for original articles reporting effects of air pollution on 1) internalizing symptoms and behaviors (anxiety or depression) and 2) frontolimbic brain regions (i.e., hippocampus, amygdala, prefrontal cortex). One hundred and eleven articles on mental health (76% human, 24% animals) and 92 on brain structure and function (11% human, 86% animals) were identified. For literature search 1, the most common pollutants examined were $PM_{2.5}$ (64.9%), NO_2 (37.8%), and PM_{10} (33.3%). For literature search 2, the most common pollutants examined were $PM_{2.5}$ (32.6%), O_3 (26.1%) and Diesel Exhaust Particles (DEP) (26.1%). The majority of studies (73%) reported higher internalizing symptoms and behaviors with higher air pollution exposure. Air pollution was consistently associated (95% of articles reported significant findings) with neurostructural and neurofunctional effects (e.g., increased inflammation and oxidative stress, changes to neurotransmitters and neuromodulators and their metabolites) within multiple brain regions (24% of articles), or within the hippocampus (66%), PFC (7%), and amygdala (1%). For both literature searches, the most studied exposure

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time frames were adulthood (48% and 59% for literature searches 1 and 2, respectively) and the prenatal period (26% and 27% for literature searches 1 and 2, respectively). Forty-three percent and 29% of studies assessed more than one exposure window in literature search 1 and 2, respectively. The extant literature suggests that air pollution is associated with increased depressive and anxiety symptoms and behaviors, and alterations in brain regions implicated in risk of psychopathology. However, there are several gaps in the literature, including: limited studies examining the neural consequences of air pollution in humans. Further, a comprehensive developmental approach is needed to examine windows of susceptibility to exposure and track the emergence of psychopathology following air pollution exposure.

Keywords

Air pollution; mental health; frontolimbic; brain; anxiety; depression

1. BACKGROUND/INTRODUCTION

Emerging research links exposure to environmental pollutants, including sources from air pollution, to increased prevalence and/or severity of mental disorders (Braithwaite et al., 2019; Zhao et al., 2018). Understanding the potential role of air pollution in risk of psychiatric disease is a major public health concern given that 99% of the world's population live in environments that do not meet World Health Organization air quality guidelines (Ambient (Outdoor) Air Pollution Fact Sheet, 2021). Further, in 2019, more than one in ten people globally lived with a mental health disorder (Dattani et al., 2021). Exposure to air pollution is consistently linked to increased risk of internalizing disorders, such as anxiety and depression (Borroni et al., 2022; Trushna et al., 2021). Anxiety and depression are the most common mental disorders across the globe (Dattani et al., 2021) and can increase an individual's risk of suicide attempts and completion (Soto-Sanz et al., 2019), adversely affect family and social relationships, and are associated with substantial individual and societal economic burden. Indeed, these disorders cost the global economy approximately 1 trillion US dollars each year in lost productivity (The Lancet Global, 2020). Despite the emerging evidence that environmental pollutants play a role in mental health, the biological mechanisms underlying environmental risk of psychiatric disorders (e.g., central nervous system (CNS) disruptions) are unknown.

Atmospheric composition from air pollution is a complex mixture of particulate matter and gases including particulate matter (PM) of varying sizes, nitrogen oxides, ozone (O_3), volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs) and others (Hahad et al., 2020; Huang et al., 2020; Huang et al., 2017). Anthropogenic sources of air pollution includes both mobile (e.g., motor vehicles) and stationary (e.g., factories, power plants) sources (EPA, 2018). There is substantial regional variability in air pollution levels, with urban areas responsible for nearly 78% of emissions that affect over 50% of the world's population (Bereitschaft & Debbage, 2013; Liang & Gong, 2020). Additionally, there is substantial spatiotemporal variation in air pollution concentrations, and up to half of the variation is attributed to meteorological conditions (e.g., temperature, humidity, precipitation, wind) (Tai et al., 2010). With climate change concerns on the rise, including

increased temperatures and adverse weather events, changes in these meteorological parameters can adversely affect air quality, by changing atmospheric ventilation and dilution, precipitation, and other removal processes (Fiore et al., 2015; Kinney, 2008). Thus, continued research on the health consequences of air pollution is of utmost importance. Air pollution is considered a major environmental health threat and is associated with a range of health outcomes, including adverse birth outcomes, obesity, cancer, and respiratory and cardiovascular disease (see Manisalidis et al. (2020) for a review). Growing evidence indicates that exposure to air pollution can also impact the CNS (Babadjouni et al., 2017; Costa et al., 2020; Kim, Kim, et al., 2020), with studies showing adverse effects on cognitive and behavioral functioning, poor attention, decreased intelligence quotient (IQ), memory, and academic performance (Cipriani et al., 2018; Clifford et al., 2016; Stenson et al., 2021). Recent studies have also identified air pollution as a major risk factor of internalizing psychopathology. For example, a recent meta-analysis found that an increase in ambient PM ($PM_{2.5}$ and PM_{10}) concentration was strongly associated with increased risk of depression, as well as suicide (Q. Liu et al., 2021). However*, the mechanism(s)* by which pollutants, such as PM, affect the CNS and contribute to risk of internalizing psychopathology remains unclear.

A growing body of preclinical and human neuroimaging studies indicates that air pollution exposure may increase risk of internalizing psychopathology by altering frontolimbic brain regions, including the hippocampus, amygdala, and prefrontal cortex (PFC) (Ehsanifar, Montazeri, et al., 2021; Salvi et al., 2020; Yao et al., 2015). These regions play a key role in stress responding and emotion regulation and are implicated in the pathophysiology of internalizing disorders (Espinoza Oyarce et al., 2020; Janiri et al., 2020; Kolesar et al., 2019). Preclinical studies suggest that ultrafine particles (UFP) and nanosized particulate matter (nPM) may affect the nervous system directly through crossing the olfactory bulb and blood brain barrier and other air pollutants ($PM_{2.5}$, PM_{10}, O_3, etc.) may indirectly affect the CNS through neuroimmune or neuroinflammatory reactions (Costa et al., 2020; Genc et al., 2012). Indeed, animal studies frequently report an increase in inflammatory and oxidative stress reactions, and changes in neurotransmitter receptor gene expression in frontolimbic brain regions, particularly the hippocampus, amygdala, and PFC following air pollution exposure (Ehsanifar, Montazeri, et al., 2021; Salvi et al., 2020; Yao et al., 2015). Consistent with these findings, human neuroimaging studies show that air pollution exposure is associated with lower frontolimbic gray matter volumes (e.g., PFC, medial temporal regions), and altered microstructure of white matter tracts that connect frontolimbic brain regions (e.g., cingulum bundle) (Herting et al., 2019; Lubczynska et al., 2020). Thus, air pollution exposure may impact the frontolimbic brain regions and pathways associated with stress and emotion regulation, which then may lead to increased risk of internalizing symptomatology.

Several recent systematic reviews have been conducted on the impact of air pollution on mental health (Borroni et al., 2022; Braithwaite et al., 2019; Fan et al., 2020; Q. Liu et al., 2021; Margolis et al., 2022; Trushna et al., 2021; Zeng et al., 2019; Zhao et al., 2018). However, these reviews either focused on one specific air pollutant (e.g., PM) or on specific developmental periods (e.g., adults). Further, only one of these reviews included translational models of internalizing behaviors (e.g., open field test in rodent models);

the remainder included only human observational studies. More recently, Margolis et al. (Margolis et al., 2022) published an important review on animal models of prenatal air pollution exposure and internalizing and externalizing behaviors; however, no comparison was made between the animal models and the current human literature. Similarly, while recent systematic reviews have been conducted on air pollution and brain structure and function (Balboni et al., 2022; de Prado Bert et al., 2018; Herting et al., 2019), none have included preclinical studies, which account for most studies on this topic. Furthermore, only one review focused on frontolimbic brain regions, that are highly relevant to internalizing psychopathology (Balboni et al., 2022).

To address these gaps, we performed two systematic reviews to examine the literature, both human and animal studies, on the effects of air pollution on (1) anxiety and depressive symptoms and behaviors, and on (2) frontolimbic brain regions involved in internalizing psychopathology (i.e., PFC, amygdala, and hippocampus). We also explored the impact of exposure timing (e.g., prenatal/early-life, childhood, adolescent, adulthood), timing of outcome assessment, technique of exposure assessment, sex differences and age differences on psychopathology and neural outcomes. We synthesize the results, discuss potential neurobiological mechanisms (e.g., neuroinflammation), and highlight gaps in the literature. We end by discussing directions for future research and the implications of neurobehavioral alterations for the prevention and treatment of internalizing disorders in at-risk individuals, such as urban inhabitants.

2. METHODOLOGY

2.1 Search Strategy

On September 13, 2021, we performed two searches of the MEDLINE database through PubMed to identify publications linking outdoor air pollution with (1) internalizing psychopathology (anxiety or depression), and (2) outcomes in frontolimbic brain regions commonly implicated in the pathophysiology of these disorders. The literature search included both human and nonhuman animal studies, and English-language studies only. Figure 1 outlines the study selection process for searches 1 and 2. Each step of the review was informed by PRISMA guidelines (Page et al., 2021). Additional information on the search strategy and search terms used can be found in the Supplemental Material.

2.2 Study Screening

Titles and abstracts, and then full texts were subsequently screened to determine relevance to the review. Studies were included in both searches if they were a (i) full-length original research article, and (ii) reported on exposure to ambient air pollution, for animals – delivered via inhalation, intranasal, intratracheal, or oropharyngeal aspiration/instillation, and for humans – through fixed ground monitor stations, geospatial estimates, personal air monitoring, or targeted recruitment from highly polluted areas. Included studies examined air pollution exposure during the prenatal, early-life, childhood, adolescent, adult, and late-life periods. Studies were excluded from both searches if they were (i) out of scope, (ii) did not compare air pollution with anxiety/depression or brain outcomes, (iii) focused on indoor or occupational air pollutants (e.g., secondhand smoking, solvent exposure), (iv) conducted

in a clinical animal model or population (e.g., Alzheimer's phenotype), and (v) included additional interventions or exposures (e.g., air pollution + high fat diet). For search 2, we excluded *ex-vivo* studies and studies that did not report on our brain regions of interest (i.e., hippocampus, amygdala, (pre)frontal cortex). Although ventromedial prefrontal cortex (vmPFC) and adjacent ventral anterior cingulate cortex (vACC) are particularly implicated in emotion regulation and internalizing psychopathology (Hiser & Koenigs, 2018), most animal studies reported on frontal cortex or did not specify the cortical area. To limit our focus to *frontal* regions, we excluded studies that reported only on cortical regions or did not specify the location to be in the frontal cortex. Full texts were screened by CZ and HM, and uncertainty was discussed by both authors together.

2.3 Study classification

Articles were classified by (1) species (e.g., human, mice, rats), (2) pollutant (e.g., $PM_{2.5}$, PAHs), (3) exposure window (e.g., prenatal, early-life, adolescence, adulthood, and later life), (4), duration of exposure, (5) sample size, (6) gender or sex, (7) exposure assessment method (e.g., land-use regression, fixed site monitoring), (8) period of behavioral assessment (e.g., prenatal, early-life, adolescence, adulthood, and late-life) and (9) outcome measure, see Tables 1 and 2. For human studies, 0–5 years of age was considered 'early-life', 6–9 'childhood', 10–17 'adolescence', 18–64 years was considered 'adulthood', and ≥65 years was considered 'late-life'. For studies in rodents, we followed Semple et al. (2013)'s benchmarks of maturation and vulnerability to injury across species which considers post-natal day (PND) 1–21 to be 'early-life', PND 25–35 to be 'childhood', PND 35–49 as 'adolescence', and PND 60+ as 'adulthood'. To determine when rodents were considered senescent or the equivalent of human "late-life", we followed the Jackson Laboratory's established protocol of 18–24 months of age, when senescent changes in biomarkers can be detected (Flurkey et al., 2007; Life Span as a Biomarker, 2022). Thus, animal studies in which assessments were conducted during PND 540+ were considered "late-life". We also provide a brief overview of methodologically rigorous studies within each category.

3. RESULTS

3.1 Literature search 1: Effects of air pollution on internalizing psychopathology (i.e., anxiety and depression)

From an initial search that yielded 943 articles, 145 articles were eligible for full-text screening based on title and abstract review. Of these studies, 34 were excluded, leaving 111 articles for the review. See Figure 1 for a depiction of the review process for literature search 1. Much of the research on air pollution and internalizing symptom and behaviors included in the final systematic review was conducted within the past 3 years (see Figure 2, Panel A).

Of the 111 articles reviewed, 81 (73%) reported increased internalizing symptoms or behaviors with air pollution exposure, 16 articles (14%) did not observe any significant effects of air pollution on internalization, 12 articles (11%) reported mixed effects (non-significant for depression, but significant for anxiety, or vice-versa), and only 2 articles (2%) reported associations between air pollution exposure and decreased internalizing symptoms and behaviors. Of the internalizing symptoms and behaviors assessed in this review, 47%

assessed depression alone, 38% assessed both anxiety and depression, and 15% assessed anxiety alone. Eighty-four studies (76%) reported findings in humans and 27 (24%) in animal models. Most studies examined more than one pollutant (46%). Across all studies, the most examined pollutants were $PM_{2.5}$ (64.9%), NO_2 (37.8%), and PM_{10} (33.3%). See Table 3 for all pollutants examined by studies within literature search 1. Eighty articles (72%) utilized air pollution estimates (e.g., land-use regression, chemical transport models). Of those, 61 (76%) controlled for meteorological conditions (e.g., temperature, wind, humidity), while 19 (24%) did not. Thirty-one articles (28%) did not utilize specific air pollutant estimates (e.g., animal studies using direct exposures, human studies using indirect estimates such as nearest roadway, etc.). Forty-three percent of studies examined exposures that spanned more than one developmental window and 8% of studies did not specify the exposure window. Adulthood (48%) was the most commonly examined exposure window across studies, followed by prenatal (26%), late-life (13%), adolescence (7%), early-life (4%), and childhood (2%). The results for literature search 1 are graphically represented in Figure 3.

3.1.1. Literature search 1 – Animal studies—Of the 27 nonhuman animal model studies, 70% were conducted in mice, 26% in rats, and 1 article (4%) used both a mouse and rat model. The majority of studies (59%) were conducted in males only and 41% included both male and female animals. The exposure methods used were whole body inhalation (78% of articles), intratracheal instillation (15%), intranasal instillation (4%), and nose-only inhalation (4%). The most common behavioral assessments in animal studies included the elevated plus maze (37%), open field test (37%), forced swim test (33%), and running wheel – voluntary activity (15%); see Table 4 for description of all behavioral assessments.

A recent example of one of the animal studies included in literature search 1 examined whether exposure to air pollutants was associated with increased anxiety-like behaviors (Ehsanifar, Jafari, et al., 2021). Ehsanifar, Jafari and colleagues exposed male NMRI mice to 300–350 $\mu g/m^3$ nanoscale diesel exhaust particles (DEPs) via whole-body inhalation for 2, 5, and 7 hours. Anxiety-like behavior was measured using the elevated plus maze. The results showed that exposed mice (2, 5, and 7 hours) demonstrated a significantly decreased ability to enter the open arms and a shorter elapsed time as compared to control mice, both indicators of increased anxiety-like behaviors.

3.1.2 Literature search 1 – Human studies—Of the 84 human studies, most (81%) included both men and women in their study design, 15% of studies assessed women only, and 3% did not report or did not specify. For the exposure methods utilized, 42% used measurements from fixed ground monitoring stations, 18% used land-use regression models, 7% used a combination of modeling techniques (e.g., ground monitoring measurements and land-use regression models), 6% used chemical transport models, 5% used general additive mixed models, 5% kriging models, and 4% dispersion models. Other assessment methods included collecting measurements during both heavy and light pollution time points, biological markers of exposure (e.g., DNA adducts), land use random forest models, personal air monitoring, kernel models, distance to major roadway, Bayesian maximum entropy models, and satellite-based measurements (each making up less than 2% of

articles). Internalizing outcomes varied widely, and the most common measures included the Center for Epidemiological Studies Depression Scale (CES-D) (21% of articles), emergency department visits (10%), hospital admissions for depression (10%), and the Patient Health Questionaire-9 (PHQ-9) (7%); see Table 4 for description of all outcomes assessed. Most of the observational studies were conducted in the United States (29%), China (27%), and South Korea (11%). See Figure 4, Panel A for a map of locations of the human observational studies included in literature search 1.

A recent example of one of the human studies included in literature search 1 examined whether air pollution exposure during childhood and adolescence was associated with increased depression and anxiety symptoms at age 18 (Reuben et al., 2021). Reuben and colleagues estimated childhood (past year at age 10) and late-adolescence (past year at age 18) air pollution based on participant's residential address using a combination of the U.S. Environmental Protect Agency's Community Multiscale Air Quality Modeling System and atmospheric dispersion model. Anxiety and depression symptoms were measured using a structured interview designed to assess internalizing-spectrum disorder symptoms from DSM-IV symptoms of Depression and Generalized Anxiety Disorder. Covariates included in the analyses were sex, family socioeconomic status, family psychiatric history, participant history of emotional and behavioral problems in early childhood, and tobacco smoking up to 18 years of age. Importantly, Reuben and colleagues also controlled for several disadvantageous neighborhood characteristics such as deprivation, dilapidation, disconnection, and dangerousness. The results showed that increased NOx exposure during childhood and late adolescence was associated with increased internalizing symptoms at age 18 and adjusting for the neighborhood characteristics did not change the results.

3.1.3 Literature search 1 – Sex-specific effects—Sixteen articles (12 human, 4 animal) were identified that reported on sex or gender specific effects in the impact of air pollution exposure on internalizing outcomes. The results from these studies were mixed. In the human studies, 6 studies reported findings in which women were more susceptible to the effects of air pollution than men (H. Gu et al., 2020; Szyszkowicz, 2007; Szyszkowicz et al., 2016; F. Wang, H. Liu, et al., 2018; Wei et al., 2020; Yue et al., 2020), 3 studies reported that men were more susceptible than women (Kim, Cho, et al., 2020; Pun et al., 2019; Shin et al., 2018), and 3 studies had mixed findings in which effects were observed for both sexes but had differential outcomes (e.g., differential lag times, different pollutants) (Lu et al., 2020; Zhang et al., 2017). In the animal studies, 3 studies reported that males were more susceptible to internalizing behaviors following air pollution exposure than females (Davis et al., 2013; Haghani, Johnson, Safi, et al., 2020; Haghani, Johnson, Woodward, et al., 2020), while 1 study reported that females were more susceptible than males (Miller et al., 2016).

3.1.4 Literature search 1 – Age effects—Twelve articles (11 human, 1 animal) were identified that reported age effects in the impact of air pollution exposure on internalizing outcomes. The results from these studies were mixed. For example, in the human studies, following recent air pollution exposure (up to 3 years before outcome assessed), five studies found that older adults (≥65) were more vulnerable to internalizing symptoms compared

to younger age groups (<65 yrstd) (Kim et al., 2016; Pun et al., 2019; Szyszkowicz et al., 2009; F. Wang, H. Liu, et al., 2018; Wei et al., 2020), 2 found that those who were middle-aged (35–64 years) were more vulnerable to developing internalizing symptoms following recent air pollution exposure, compared to those <35 as well as those >64 years of age (Muhsin et al., 2022; Xue et al., 2021), and one found effects on internalizing symptoms for differing pollutants for middle-aged versus older adults following recent air pollution exposure (e.g., middle adults were sensitive to $PM_{2.5}$, PM_{10}, NO_2, and SO_2, while older adults were sensitive to $PM_{2.5}$, NO_2, and O_3) (Lu et al., 2020). Two studies found that children and adolescents were more vulnerable to internalizing symptoms following air pollution exposure (Nguyen et al., 2021; Rasnick et al., 2021). Nguyen et al. (2021) found that children and adolescents (0–18 years) were more vulnerable to internalizing symptoms following recent (up to 7 days prior to outcome assessed) air pollution exposure than individuals ages 19–34 years. Rasnick et al. (2021) investigated sensitive exposure windows for 12-year-old adolescents. They found that the most sensitive time for air pollution exposure on anxiety, was in early childhood, between four years and four months and five years and eleven months, compared to all other timepoints from birth through 12 years. Interestingly, two studies (1 human, 1 animal) found that internalizing symptoms and behaviors developed later (into adolescence and adulthood) following prenatal and early-life exposure to air pollution, suggesting that these effects may be delayed (Liu et al., 2019; Margolis et al., 2016).

3.2 Literature search 2: Effects of air pollution on frontolimbic brain regions

From an initial search that yielded 371 articles, 119 articles were eligible for full-text screening. Of these studies, 27 were excluded, leaving 92 articles for the review. See Figure 1 for a depiction of the review process for literature search 2. Much of the research (49%) on air pollution and frontolimbic brain regions included in the final systematic review was conducted within the past 4 years (see Figure 2, Panel B).

Of the 92 articles reviewed, 87 (95%) reported significant effects of air pollution on frontolimbic brain regions. Seventy-nine articles (86%) were conducted in animal models (mice, rat, dogs), and ten articles (11%) assessed humans only. A small number (~3%) of studies included both human and animal models. A large portion of studies examined more than one pollutant (22%). Across all studies, the most examined pollutants were $PM_{2,5}$ (32.6%), O_3 (26.1%), and Diesel Exhaust Particles (DEP) (26.1%). See Table 3 for all pollutants examined by studies within literature search 2. Of the brain regions assessed in this review, 66% of articles assessed the hippocampus alone, 7% PFC, and 1% each the amygdala, anterior cingulate cortex, and frontal cortex. Twenty-two articles (24%) assessed more than one of our brain regions of interest. The measured neurobiological outcomes varied; the most common measured outcomes included inflammatory reactions (39% of articles) and neurite changes (21%), followed by changes to neurotransmitter metabolites or receptors (20%) and oxidative stress markers (17%); see Table 5 for description of all outcomes assessed.

Of the 33 studies (32 preclinical, 1 postmortem human study) evaluating inflammatory reactions, all but one reported significant increase in inflammation following air pollution

exposure. Inflammatory reactions were most studied in the hippocampus (73% or studies), followed by PFC (6%), or in multiple frontolimbic brain regions (21% of studies). Of the 19 studies (all preclinical), that evaluated neurite changes (e.g., dendritic spine lengths, neuronal degeneration), all studies reported significant findings including decreases in the hippocampus (79% of studies), PFC (11%), or in multiple frontolimbic brain regions (11%), following air pollution exposure. While 17 studies (all preclinical) investigated changes to neurotransmitter or neuromodulator systems, the directionality of results were mixed (i.e., increases vs. decreases); however, 100% of studies reported significant effects air pollution exposure. Studies on neurotransmitters were commonly focused on the glutamatergic system only (50% of studies), and half of the studies investigated multiple systems, e.g., dopaminergic, serotonin, gamma-aminobutyric acid (GABA). Changes to neurotransmitter systems were reported primarily in the hippocampus (71% of studies), PFC (6%), and in multiple frontolimbic brain areas (18%). Fifteen studies (all preclinical) reported significant increases in oxidative stress markers (e.g., MnSOD, GSH, MDA) following exposure to air pollution. Studies reporting increases in oxidative stress makers focused primarily on the hippocampus only (60% of studies), 7% PFC only, and 33% in multiple frontolimbic brain regions. Seven articles (8%) utilized air pollution estimates. Of those seven articles, only one controlled for meteorological conditions. Eighty-five articles (92%) did not utilize estimates (e.g., animal studies). Adulthood (59%) was the most frequently examined exposure window across studies, followed by prenatal (27%), early-life (5%), adolescence (5%), childhood (2%), and late-life (2%). The results for literature search 2 are graphically represented in Figure 3.

3.2.1. Literature search 2 – Animal studies—Of the nonhuman animal model studies, 51% were in mice, 44% in rats, 4% in both mice and rats within the same study, and 1% in dogs. Most studies (66%) were conducted in males only, 6% in females only, 24% included both male and female animals, and 3% did not specify. The exposure methods used were whole body inhalation (81% of articles), intratracheal instillation (6%), intranasal instillation (6%), oropharyngeal aspiration (3%), combination whole body inhalation and nose-only inhalation (1%), tracheal drip (1%), endotracheal nebulization (1%), and one study did not specify.

A recent example of one of the animal studies included in literature search 2 examined the developmental neurotoxicity of traffic-related air pollution (TRAP) exposure (Patten et al., 2020). Sprague-Dawley rats were exposed to TRAP 24 hours/day via whole-body inhalation, from gestational day (GD) 14 to PND 47–51. Both male and female rats were included in this study. Animals were sacrificed 2–4 days after final exposure. Exposed rats had increased levels of microglia and astrocyte activity within the hippocampus, compared to control rats. Regarding cellular neuroinflammatory responses, exposed female rats have significantly higher levels of an anti-inflammatory cytokine (IL-10) and more mature neurons in the hippocampus compared to control female rats. Additionally, exposed male rats had increased neurogenesis, cell proliferation, and expression of a growth factor implicated in autism spectrum disorder (Igf1) in the hippocampus, compared to control rats.

3.2.2. Literature search 2 – Human studies—Most studies (92%) included both men and women, and 1 study (7%) included women only. Recruitment from high-polluted vs. low-polluted areas was used as the exposure method for four of the ten studies. Three of the human studies used land-use regression models to estimate exposures, one used a Bayesian maximum entropy (BME) model, one used a universal kriging model, and one used a combination of personal air monitoring and urinary metabolites. Most observational studies were conducted in Mexico (50%), followed by the United States (22%), the United Kingdom (14%), the Netherlands (7%) and South Korea (7%), See Figure 4, Panel B for a map of locations of the human observational studies included in literature search 2. Of the 13 studies that included humans, 3 conducted brain assessments post-mortem and 10 utilized *in vivo* neuroimaging approaches. Of the studies that were conducted post-mortem, outcomes examined included altered DNA expression and damage, amyloid and tau-related pathologies, cerebrovascular changes, inflammatory reactions, and heavy metal deposits, within hippocampal and frontal cortex tissues. Of the studies that utilized neuroimaging, two studies examined alterations in neurochemistry though magnetic resonance spectroscopy (MRS), two studies examined white matter hyperintensities or lesions using T2 or FLAIR MRI scans, and the remaining 6 studies examined brain volumes and morphology using structural T1 MRI scans.

A recent example of one of the human studies included in literature search 2 examined whether prenatal or childhood exposure to air pollution was associated with changes in brain morphology in pre-adolescence (Lubczynska et al., 2021). Lubczyńska and colleagues estimated air pollution exposure based on participants' residential addresses using well-validated land-use regression models. The specific pollutants examined included PM_{10}, $PM_{2.5}$, absorbance of $PM_{2.5}$ fraction, composition of $PM_{2.5}$ consisting of polycyclic aromatic hydrocarbons (PAH), benzo[a]pyrene, organic carbon, copper, iron, potassium, silicon (Si), zinc, and oxidative potential of $PM_{2.5}$ (OP). Brain morphology was measured using structural magnetic resonance imaging (MRI) on a 3T scanner. Regional gray matter volumes of subcortical brain regions, including the hippocampus and amygdala, were computed. Covariates included in the analyses were parental education, household income, country of birth, parental age, maternal smoking and alcohol consumption during pregnancy, parity, marital status, parental psychological distress, pre-pregnancy BMI, maternal IQ at child's age 6, child sex, and child current age. Results showed that prenatal exposure to PAH was associated with smaller hippocampal volumes, and higher prenatal exposure to Si was associated with larger amygdala volume. Higher exposure to OP during childhood was associated with smaller hippocampal volumes. No associations were observed between childhood exposures and amygdala volumes.

3.2.3 Literature search 2 – Sex-specific effects—Nine articles (3 human, 6 animal) were identified that reported on sex- or gender- specific effects in the impact of air pollution exposure on frontolimbic brain outcomes. The results from these studies were mixed. For example, in the animal studies, 4 studies reported that the effects on frontolimbic brain regions following air pollution exposure were stronger in males as compared to females (Cole et al., 2016; Ehsanifar, Montazeri, et al., 2021; Haghani, Johnson, Woodward, et al., 2020; Nway et al., 2017), while 2 studies reported mixed findings (e.g., the effects of

air pollution on certain brain outcomes were stronger in males and others were stronger in females) (Custodio et al., 2019; Patten et al., 2020). In the human studies, two studies reported that females were more susceptible to the effects of air pollution on frontolimbic brain regions than males (Hedges et al., 2019; Peterson et al., 2015), and one study reported that males were more susceptible than females (Cho et al., 2020).

3.2.4 Literature search 2 – Age effects—Three articles (all animal) were identified that reported on age effects. The results from these studies were mixed. One study found differential effects in both young and aged rats following exposure to air pollution in adulthood and late-life (e.g., both young and aged exposed rats demonstrated oxidative damage in frontolimbic brain regions, however only the young exposed rats had effects observed in the frontal cortex) (Kodavanti et al., 2021). One study found that effects of air pollution exposure (i.e., altered cell proliferation, increased oxidative stress, cerebrovascular changes, amyloid deposits) on frontolimbic brain regions were more pronounced in exposed aged mice as compared to exposed young mice (Armstrong et al., 2020). In contrast, one study reported that effects of exposure (i.e., myelin alterations, changes to microglia, dendritic spine length or neurite changes, neurotransmitter or neuromodulator changes, increase inflammation) on frontolimbic brain regions were diminished in older mice and did not exacerbate effects associated with normal aging; young mice, in contrast, displayed significant effects on frontolimbic brain regions following exposure (Woodward, Pakbin, et al., 2017).

4. DISCUSSION

This paper is the first, to the best of our knowledge, to systematically review the literature on the effects of air pollution on (1) both internalizing symptoms and behaviors in humans and animal models, and (2) the impact on underlying frontolimbic brain regions. An overall conceptual model of neurobehavioral mechanisms by which exposure to air pollution increases risk of internalizing symptoms and behavior is provided in Figure 5. Here, we summarize results of our systematic reviews, discuss gaps in the literature, and identify future directions for research.

4.1 Summary of systematic reviews

In summary, our first systematic review on air pollution and internalizing symptoms and behaviors revealed that air pollution exposure is consistently associated with increased anxiety and depression across different exposure windows and in both human and animal models. We found that most research focused specifically on depression outcomes, while only 15% of articles focused on anxiety alone. Most studies examined multiple pollutants, while studies that focused on one pollutant primarily assessed $PM_{2.5}$ and DEPs — two pollutants that have been shown to directly affect the CNS (Ehsanifar, Tameh, et al., 2019; Ferreira et al., 2022; Hartz et al., 2008; Kang et al., 2021). Most articles included in literature review 1 examined exposures that spanned multiple developmental windows, with less attention given to exposure windows specifically within childhood and adolescence, a period of dramatic neurodevelopment (Arain et al., 2013). Within the human studies, most

obtained air pollution estimates from fixed ground monitoring stations, rather than using modeling techniques that incorporate land-use and meteorological variables.

Our second systematic review, which focused on air pollution exposure and frontolimbic brain regions, revealed that air pollution exposure is associated with several neurobiological changes, predominantly increased inflammation, neuronal degeneration, and oxidative stress. The hippocampus was the most commonly assessed brain region with less attention given to the PFC and the amygdala. In contrast to the first systematic review on internalizing symptoms and behaviors, most studies included in this review on frontolimbic brain regions were conducted predominantly in animal models, with only 10 articles that assessed humans. Of note, the majority of the animal model studies (66%) focused exclusively on males, which is a significant gap given that internalizing disorders are more prevalent among females than males (Dattani et al., 2021). Similar to the first systematic review, the majority of studies examined multiple pollutants, with studies that focused on one pollutant primarily assessing $PM_{2.5}$ and DEPs. Additionally, most articles examined exposures that spanned more than one developmental window, with childhood and adolescence less studied.

Both systematic reviews identified several studies that reported on sex effects following air pollution exposure; however, the results from these studies were mixed, and thus no conclusion can be drawn. Sex effects were reported in both the neurotoxic effects on frontolimbic brain regions as well in the internalizing symptoms and behaviors observed following air pollution exposure. Future studies should take a more targeted approach at investigating the differential sex effects and their potential mechanisms (e.g., menstrual cycle fluctuations, changes in estrogen/testosterone), and how these changes may influence vulnerability.

Additionally, both systematic reviews identified studies that reported on age effects following air pollution exposure. While findings were mostly mixed, a large portion of studies suggested that children and adolescents and older adults were more vulnerable to both the neurotoxic effects on frontolimbic brain regions and internalizing symptoms and behaviors following air pollution exposure, as compared to young and middle adults. While these studies indicated increased vulnerability for these specific age groups, the exposure windows within these studies were extremely variable (i.e., recent exposures versus prenatal or early-life) and thus it is difficult to conclude at what point in the life cycle individuals are associated with enhanced vulnerability to the negative effects of air pollution exposure. For example, most studies examined *recent* exposures, which for children would impact their developing brains, but for older adults would impact fully developed or aging brains. Thus, future studies are needed that address all developmental windows or exposures and subsequent timepoints in which assessments occur (i.e., in childhood or decades later). In fact, accelerated longitudinal study designs would be most equipped to help further elucidate age effects, including delayed effects, following air pollution exposure.

4.2 Gaps in the literature

For both literature search 1 and 2 the most assessed exposure window was adulthood followed by the prenatal period. Early-life, childhood, and adolescence exposure windows were rarely assessed (accounting for 1–4% of studies in each search). This is especially

concerning when evaluating neurobehavioral outcomes as the brain continues to develop until young adulthood and may therefore be particularly sensitive to neurotoxic effects of air pollution during development (Arain et al., 2013). While prenatal exposure may have a substantial impact on development, less is known about post-natal exposures and how those may affect brain neural circuity, which undergoes dramatic development and refinement throughout adolescence (Gogtay et al., 2004). For example, the neural circuity underlying PFC-hippocampal interactions, a system that is implicated in emotion regulation and internalizing psychopathology, develops throughout adolescence (Calabro et al., 2020). Thus, more preclinical, and clinical studies specifically assessing frontolimbic or internalizing outcomes in childhood and adolescence are sorely needed.

Within literature search 2, a majority of studies focused on the hippocampus, when examining effects of air pollution exposure on frontolimbic brain regions. While the hippocampus is an essential part of the frontolimbic neural circuity, the PFC and amygdala — and interactions within these structures — are also important for internalizing psychopathology. For example, meta-analyses on brain function and structure within anxiety disorders have consistently revealed hyperactivation in the amygdala and hypoactivation and decreased volume within the PFC relative to healthy controls (Etkin & Wager, 2007; Janiri et al., 2020; Kolesar et al., 2019). Meta-analyses on brain function and structure within depressive disorders have revealed hyperactivation within the PFC relative to healthy controls (Espinoza Oyarce et al., 2020; Miller et al., 2015; Wang et al., 2012). Studies that have correlated these neural differences to internalizing symptoms have found that greater resting state functional connectivity between the amygdala and PFC is associated with increased rumination and worry (Feurer et al., 2021). Thus, future studies should investigate changes associated with air pollution in both the PFC and amygdala in addition to the hippocampus, and interactions between these regions.

Additionally, within literature search 2, only 10 studies were conducted in humans, three of which were post-mortem assessments. While the animal literature has extensively shown that air pollution can induce a multitude of changes to frontolimbic brain regions, including inflammatory and oxidative stress reactions, the replication of these studies within humans is lacking. The 7 neuroimaging studies examining the effects of air pollution primarily assessed brain volumetrics through T1 MRI, white matter hyperintensities or lesions via T2 or FLAIR MRI, and alterations in neurochemistry assessed by MR spectroscopy imaging. While the majority of studies assessed total brain volumes (e.g., total volume of the frontal lobe), future studies should incorporate region-of-interest analyses to identify regional changes in the hippocampus, PFC, and amygdala, and their associations to internalizing symptoms and behaviors. No studies included in this review assessed functional MRI outcomes (either resting-state or task-based). While structural imaging is useful for detecting brain damage and abnormalities, functional imaging can often detect changes that precede structural changes or subtle changes in cerebral blood flow or activation) as opposed to brain atrophy (Gore, 2003; Grajski et al., 2019). Additionally, functional imaging can identify changes in activity that occur during specific behavioral tasks, allowing for the potential identification of neurobehavioral mechanisms linking air pollution exposure and internalizing psychopathology. Thus, future studies are needed to examine the effect of

air pollution on neuroimaging outcomes, specifically functional neuroimaging techniques, within humans.

Finally, only 13 articles were identified in *both* literature search 1 and literature search 2 that examined internalizing symptomology and frontolimbic brain regions within the same study. To elucidate the neurobehavioral mechanisms underlying the associations between air pollution exposure and mental health, additional studies, both preclinical and clinical, are needed that assess these outcomes within the same study design, and to evaluate these associations through a mediation design (see conceptual model in Figure 5). For example, does air pollution affect internalizing symptomology through changes in frontolimbic brain regions? This question could be more readily answered in studies that analyze both brain and behavioral outcomes.

4.3 Directions for future research

While the epidemiological evidence associating air pollution exposure with increased internalizing symptoms and behaviors continues to be replicated in different populations and with differing exposure windows, less is known concerning the neurobiological underpinnings. Preclinical studies have shown that air pollution affects frontolimbic brain regions involved in internalizing symptoms and behaviors in a multitude of ways, however human neuroimaging studies have been less prevalent and have focused more on global measures, rather than region-of-interest-based approaches. In fact, literature search 1, on internalizing symptoms and behaviors, was disproportionally composed of human studies (76%), whereas literature search 2, on neurobiological effects on frontolimbic brain regions, was composed primarily of animal models (86%). Thus, future human neuroimaging studies are sorely needed and should target their investigations on emotion-regulation brain regions, such as the hippocampus, amygdala, and PFC, and should incorporate emotion-based functional tasks into their studies.

One of the most prevalent gaps in the literature is the lack of knowledge surrounding windows of susceptibility of air pollution exposure and subsequent mental health and brain outcomes. A developmental approach to these associations is warranted, as many mental health disorders develop during adolescence in concordance with the development of emotion-regulation neural circuits (Calabro et al., 2020; Kessler et al., 2005). Preclinical studies that clearly state the age of the animal at exposure and during behavioral and brain assessments are also critical for elucidating critical periods of exposure. Further, while only two studies were identified that reported *delayed* internalizing symptoms and behaviors following air pollution exposure in youth (Liu et al., 2019; Margolis et al., 2016), more longitudinal human neuroimaging studies are critical to forming the trajectory of air pollution-based changes in mental health and frontolimbic structure and function. In fact, the Adolescent Brain Cognitive Development (ABCD) study (https://abcdstudy.org/), the largest long-term study of brain development and child health in the United States, has begun to look at the effects of air pollution (Burnor et al., 2021; Cserbik et al., 2020). As the ABCD study continues with yearly follow-ups, the effects of air pollution on brain development as well as neuropsychiatric outcomes will be explored.

Additionally, only three studies were identified in our literature searches that used a pre- and post-exposure study design that allows for individuals to serve as their own control, thus reducing between-subject variability. For example, Chen and colleagues examined mood symptoms in the same participants once during a week that had low levels of air pollution and again during a week that had extremely high levels of air pollution, and found that depression symptoms were significantly higher on the day with extreme air pollution levels(S. Chen et al., 2017). Additionally, Roe and colleagues measured mood symptoms immediately following two different walking routes, one with high air pollution exposure (e.g., near highway) and one with low air pollution exposure (e.g., more greenspace). They found that hedonic depression symptoms decreased significantly following the low air pollution exposure route, while no significant change in symptoms was observed after the high air pollution route (Roe et al., 2020). Further, Brokamp and colleagues used a time-stratified case-crossover study to examine the associations between $PM_{2.5}$ exposure and psychiatry pediatric emergency department visits. This design that allows each participant to serve as their own control (Brokamp, Strawn, et al., 2019). While these studies are rare and often difficult to conduct, future studies may benefit from designs that incorporate participants as their own controls so that the specific effects of air pollution exposure — independent of the effects of potential confounders (e.g., interindividual variability) — can continue to be identified.

Future research should also incorporate more advanced modeling of air pollution estimates or the use of personal air monitors. In both literature searches, most human studies relied on measurements from fixed ground monitoring stations, often using a single monitor or several monitors averaged while weighted by distance. Monitoring is prohibitively expensive (most counties in the US do not have a regulatory air pollution monitor) and cannot fully capture the complex spatiotemporal variations in air pollution. Alternatives are to utilize personal sampling, whereby individuals use personal monitors to better capture variability in air pollution due to time-behavior patterns, or to use exposure assessment models, which use spatiotemporal features (e.g., meteorological data, satellite-based measures, land characteristics, and measures of air pollution sources like vehicles and industrial activity) to predict air pollution concentrations in locations and times that measurements were unavailable. Additionally, these two exposure techniques (i.e., fixed ground modeling and personal monitoring) are utilized to answer *different* scientific questions. For example, fixed air monitoring can help examine the effects of ambient air pollution concentrations at the neighborhood level, while personal monitoring can examine the effects of an individual's personal concentration of air pollutants. While these two types of exposures (i.e., community and personal) may synergistically contribute to health effects, they are studied using different methods. For a more detailed discussion on the advantages and disadvantages of model-based and personal sample strategies, see Brokamp, Brandt, et al. (2019).

Further, most human studies examine the *average* air pollution estimates across time periods, and do not necessarily evaluate the *cumulative* air pollution an individual may be exposed to, which contrasts with preclinical/animal studies. This discrepancy has led to calls by the Office of Research and Development of the United States Environmental Protection Agency for further research into cumulative impacts, as the "single pollutant/single exposure" paradigm is not well suited to the reality that individuals are exposed to several pollutants

over time (EPA, 2022). Lastly, future studies should investigate independent contributions of indoor and outdoor air pollution to internalizing symptoms and behaviors and changes in frontolimbic brain regions.

4.4 Limitations and conclusions

The systematic review performed in this paper is not without limitations. First, potentially eligible studies may have been missed. To minimize this risk, a wide search was performed on one of the best tools for biomedical electronic research, MEDLINE. While this review focused on a comprehensive report on all air pollutants, future reviews may take a pollutant-specific approach to examine if there are differential effects of different types of pollutants on both internalizing symptoms and behaviors and frontolimbic brain regions. Further, while our review on internalizing symptoms and behaviors following air pollution exposure encompassed many definitions and measurements of anxiety and depression, the observed pattern (i.e., increased symptoms post-exposure) appears to be consistent across measurement types. Next, we focused our search on frontolimbic brain regions, given their key role in emotion regulation and internalizing psychopathology (Espinoza Oyarce et al., 2020; Janiri et al., 2020; Kolesar et al., 2019). However, future studies should consider other brain regions and white matter pathways that may be involved in emotional regulation and their susceptibility to air pollutant exposures.

In conclusion, air pollution exposure is associated with increased internalizing symptoms and behaviors as well as structural and functional changes to frontolimbic brain regions across the lifespan. Further investigation with improvements in design and reporting would fill the following key gaps in literature: First, more assessments of the brain and behavioral effects of air pollution are needed during childhood and adolescence, and longitudinal evaluations would be a welcome addition. Next, more human neuroimaging assessments are needed to replicate or compare the effects of air pollution on frontolimbic brain regions that have been reported in the nonhuman animal literature. Lastly, more comprehensive studies are needed that examine *both* internalizing symptoms and frontolimbic brain outcomes within the same study design, which will allow for mediation analyses to be explored. The identification of the neurobiological mechanisms underlying the associations between air pollution exposure and increased mental health issues is imperative. This research would identify biological targets for intervention to stem the pathophysiology of internalizing disorders. While air pollution exposure may not be decreased as quickly and effectively as needed, additional research will aid in the development of appropriate interventions that will mediate air pollution's negative effects on the brain and subsequent mental health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

HM is supported by the National Institute of Mental Health (K01MH119241) and Eunice Kennedy Shriver National Institute of Child Health and Human Development (R21HD105882). HM, CZ, and YH acknowledge funding support from the Center for Urban Responses to Environmental Stressors (CURES) (P30ES020957). PR and CB are supported by the National Institute of Environmental Health Sciences (R01ES031621). JRS is supported by

the National Institute of Child Health and Human Development (R01HD099775, R01HD09875) and the Yung Family Foundation. YH acknowledges funding support from the Faculty Competition for Postdoctoral Fellows of the Office of Vice President for Research at Wayne State University. The grant providers had no influence on study design, the collection, analyses and interpretation of data, report writing nor decision of submission for publication

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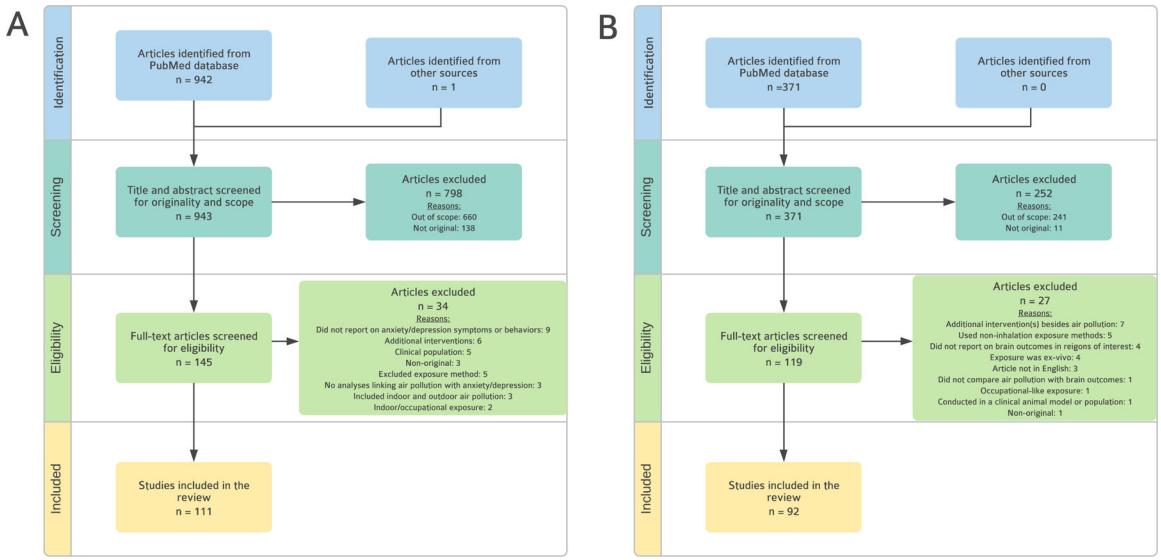

Figure 1.

Flowchart for Literature Search 1 and 2.

Panel A describes Literature Search 1: Air Pollution and Internalizing Behaviors and Symptoms. Panel B describes Literature Search 2: Air Pollution and Frontolimbic Brain Regions Each step of the reviews was informed by PRISMA guidelines (Page et al., 2021).

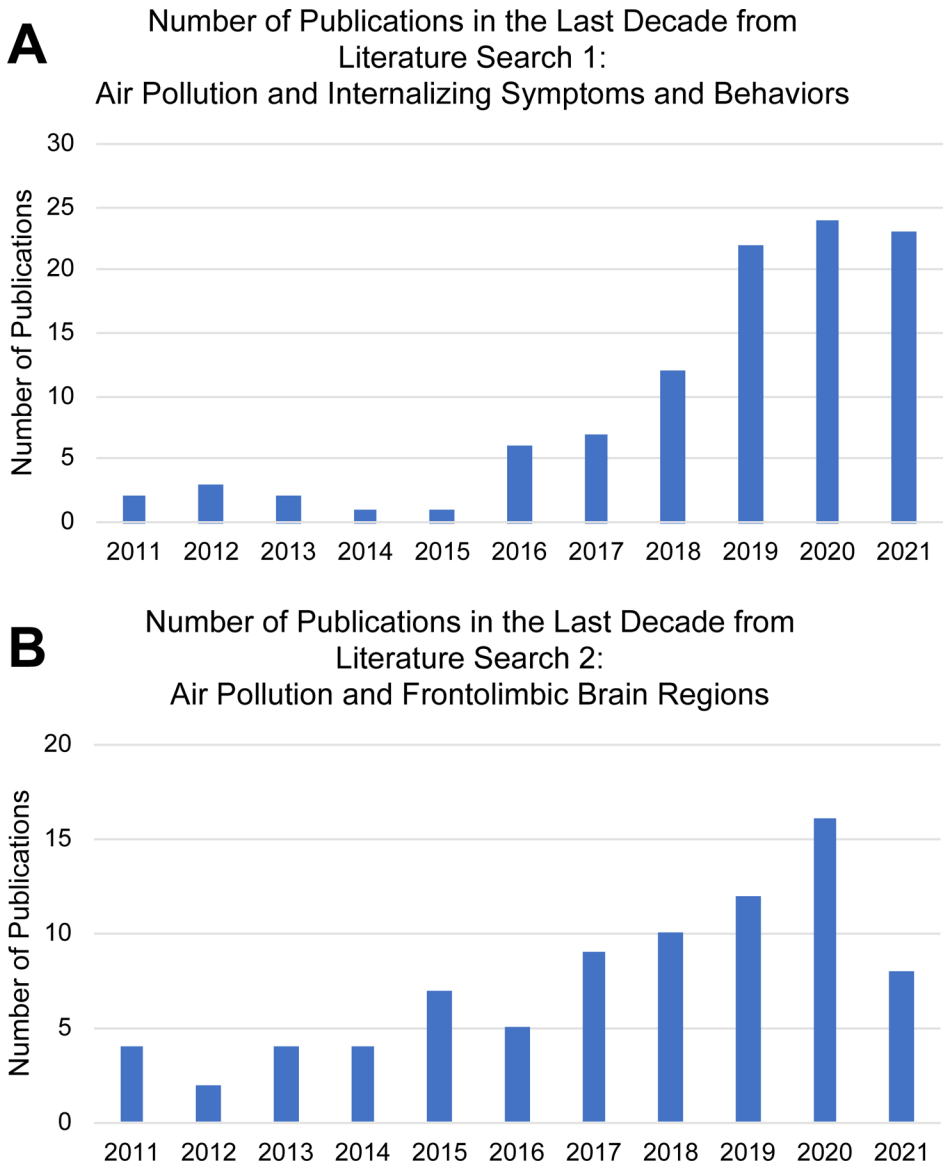

Figure 2.
Publications by Year for Literature Searches 1 (A) and 2 (B).

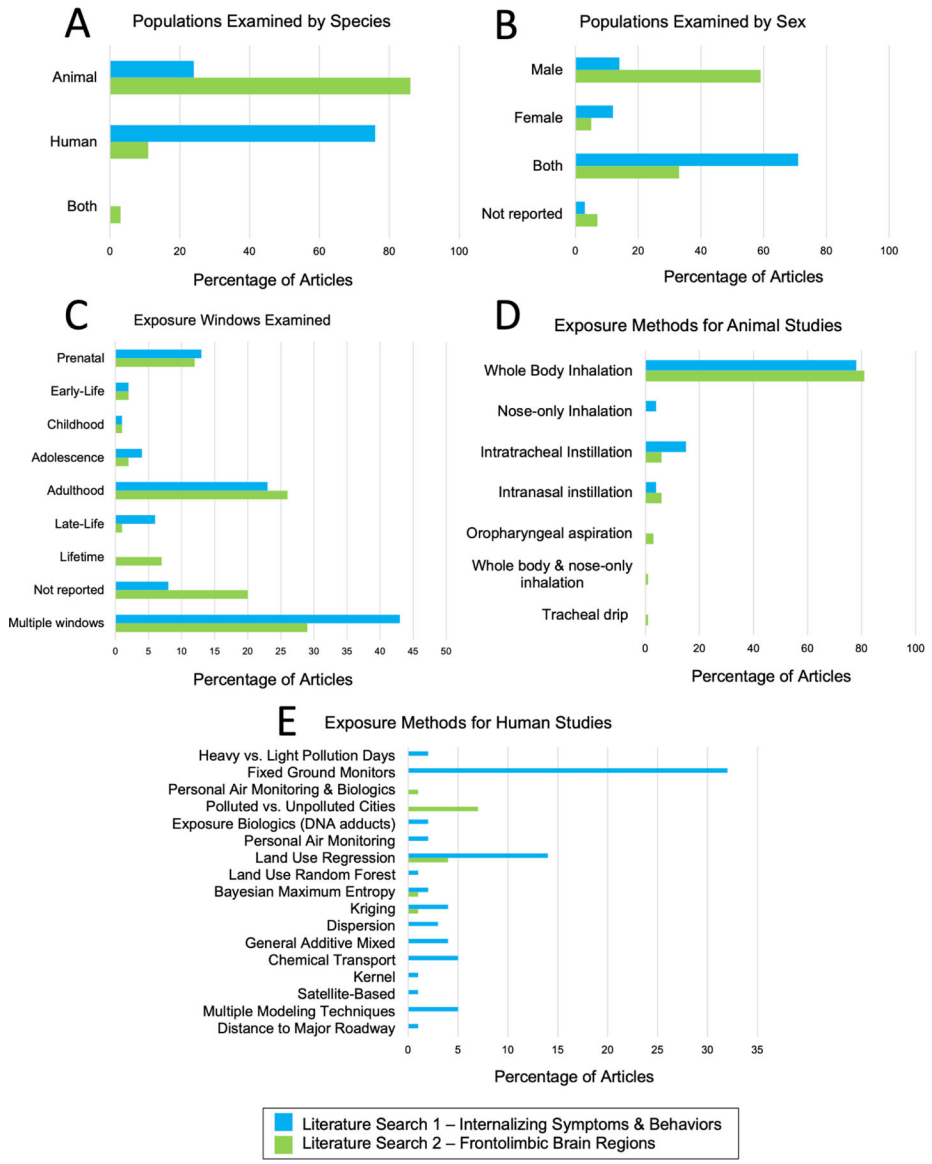

Figure 3.

Summary of Study Types for Literature Searches 1 (blue) and 2 (green). Panel A – Populations Examined by Species, Panel B – Populations Examined by Sex, Panel C – Exposure Windows Examined Panel D – Exposure Methods for Animal Studies, Panel E – Exposure Methods for Human Studies

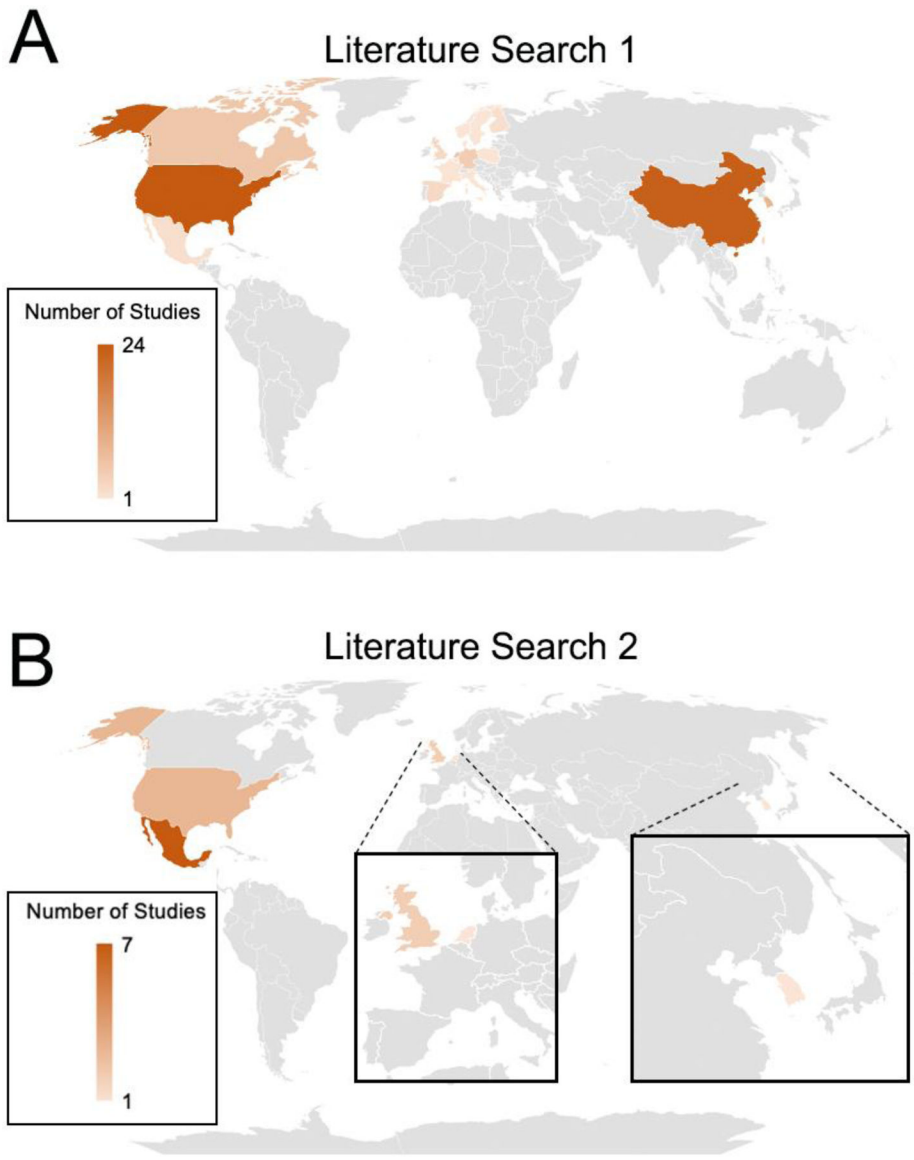

Figure 4.

Map of Locations of Human Observations Studies for each Literature Search. Panel A – Literature Search 1 – Internalizing Symptoms & Behaviors, Panel B – Literature Search 2 – Frontolimbic Brain Regions

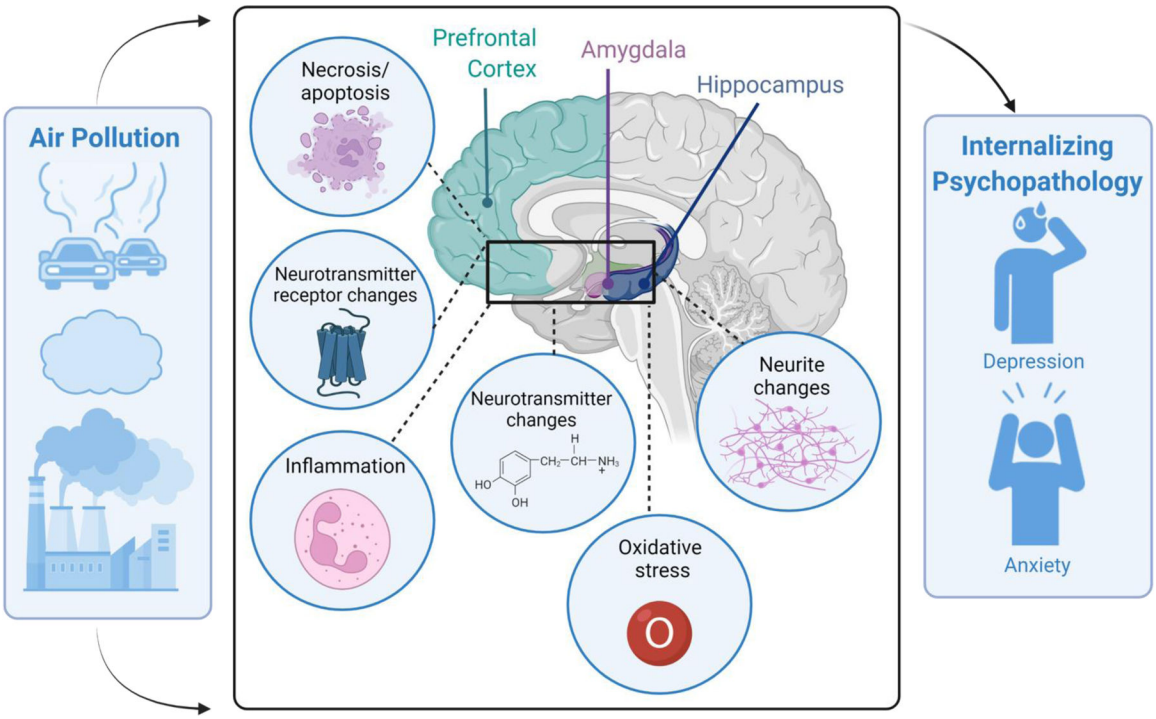

Figure 5.

A conceptual model of neurobehavioral mechanisms by which air pollution exposure increases risk of internalizing psychopathology through structural and functional changes in frontolimbic brain regions. This figure was created with BioRender.com.

Neurotoxicology. Author manuscript; available in PMC 2023 December 01.

Table 1.

Final Included Articles from Literature Search 1: Air Pollution and Internalizing Symptoms and Behaviors

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
Emik and Plata (1969)	Mice (C57 BL)	Multiple Pollutants	Adulthood	Continuously for 8 weeks	24	Male	Whole Body Inhalation	Late-life	Depression	Increased
Campbell et al. (1970)	Mice (C57BL)	Peroxyacetyl nitrate (PAN)	Adulthood	224 days, 7–8 months	9–12/group	Male	Whole Body Inhalation	Adulthood	Depression	Increased
Tepper et al. (1982)	Rats (Long-Evans)	Ozone	Adulthood	6 hours	16	Male	Whole Body Inhalation	Adulthood	Depression	Increased
Evans et al. (1988)	Human	Ozone	Adulthood	Not reported	1,002	Both	Conducted during a heavy and light polluted seasons	Adulthood	Both	Mixed
Musi et al. (1994)	Mice (CD-1)	Ozone	Not reported	13 days	10/group	Both	Whole Body Inhalation	Not reported	Both	Increased
Szyszkowicz (2007)	Human	Multiple Pollutants	Early-life through Late-life	0–2 days	15,556	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Both	Mixed
Szyszkowicz et al. (2009)	Human	Multiple Pollutants	Early-life through Late-life	0–2 days	27,047	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Depression	Increased
Szyszkowicz et al. (2010)	Human	Multiple Pollutants	Early-life through Late-life	0–2 days	9,358	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Depression	Increased
Fonken et al. (2011)	Mice (C57BL/6)	PM2.5	From Childhood through Adulthood	10 months	Not reported	Male	Whole Body Inhalation	Adulthood	Both	Increased
Perera et al. (2011)	Human	PAH	Prenatal, Childhood	Biomarkers used, not specified	215	Both	Biological markers	Childhood	Both	Increased
(Bowler et al., 2012)	Human	Manganese	Adulthood	Estimated off of years of residence, mean was 36.1 + 15.8 years.	190, 100 exposed, 90 controls	Both	Dispersion modeling	Adulthood	Anxiety	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
Lim et al. (2012)	Human	Multiple Pollutants	Adulthood to Late-life	0–28 days	537	Both	Used measurements from fixed ground monitoring stations	Adulthood and Late-life	Depression	Increased
Perera et al. (2012)	Human	PAH	Prenatal	3 months	253	Both	Personal air monitoring	Childhood	Both	Increased
Davis et al. (2013)	Mice (C57BL/6J)	nPM	Prenatal	10 weeks	5–10/group	Both	Whole Body Inhalation	Adulthood	Both	Mixed
Peiffer et al. (2013)	Rats (Wistar Han)	PAH	Adulthood	14 days	18/group	Male	Nose-only inhalation	Adulthood	Anxiety	Decreased
Y. Wang et al. (2014)	Human	Multiple Pollutants	Late-life	1–14 days, 1 year	765	Both	Combination	Late-life	Depression	No effects observed
Power et al. (2015)	Human	Multiple Pollutants	Adulthood and Late-life	1, 3, 6, months, 1 year, 15 years	71,271	Female	General additive mixed models	Adulthood & Late-life	Anxiety	Increased
Kim et al. (2016)	Human	PM2.5	Adolescence, Adulthood, Late-life	1 year, 3 years	27,270	Both	Used measurements from fixed ground monitoring stations	Adolescence, Adulthood, Late-life	Depression	Increased
Margolis et al. (2016)	Human	PAH	Prenatal	3–4 months	462	Both	Biological markers	Early-life, childhood, adolescence	Both	Increased
Miller et al. (2016)	Mice (BALB/cByj)	PAH	Prenatal	3 weeks	14–18/group	Both	Whole Body Inhalation	Adulthood	Anxiety	Mixed
Szyszkowicz et al. (2016)	Human	Multiple Pollutants	Early-life through Late-life	0–8 days	118,602	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Depression	Increased
Yokota, Oshio and Takeda (2016)	Mice (ICR)	DEP	Prenatal	5 days	30/group	Male	Intratracheal Administration	Adulthood	Anxiety	Increased
Zijlema et al. (2016)	Human	Multiple Pollutants	Adulthood and Late-life	3 years	70,928	Both	Land use regression models	Adulthood & Late-life	Depression	No effects observed
S. Chen et al. (2017)	Human	PM2.5	Adolescence, Adulthood	1 week	102	Both	Conducted during a heavy and light polluted week	Adolescence and Adulthood	Both	Mixed

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
Kim and Kim (2017)	Human	PM10	Adolescence through Late-life	9 years	23,139	Both	Used measurements from fixed ground monitoring stations	Adulthood & Late-life	Depression	No effects observed
Kioumourtzoglou et al. (2017)	Human	Multiple Pollutants	Adulthood and Late-life	1, 2, 5 years	41,844	Female	Generalized additive models	Adulthood & Late-life	Depression	Increased
Lin et al. (2017)	Human	Multiple Pollutants	Adulthood	0–15 days	1,931	Female	Used measurements from fixed ground monitoring stations	Adulthood	Both	Increased
Pun et al. (2017)	Human	PM2.5	Adulthood and Late-life	7, 30, 180 days, 1, 4 years	Wave 1 – 3,005, Wave 2 – 3,377	Both	Generalized additive mixed models	Adulthood & Late-life	Both	Increased
Salvi et al. (2017)	Rats (Sprague-Dawley)	DEP	Adulthood	2 weeks	13/group	Male	Whole Body Inhalation	Adulthood	Both	Increased
Vert et al. (2017)	Human	Multiple Pollutants	Adulthood and Late-life	4–5 years	958	Both	Land use regression models	Adulthood & Late-life	Both	Increased
Zhang et al. (2017)	Human	Multiple Pollutants	Adulthood	1 day	23,259	Both	Used measurements from fixed ground monitoring stations	Adulthood	Depression	Increased
Kulas et al. (2018)	Mice (FVB)	PM2.5	Prenatal	3 weeks	10/group	Male	Whole Body Inhalation	Adulthood	Anxiety	No effects observed
Liu et al. (2018)	Mice (C57BL/6)	PM2.5	Adulthood	4, 8, 12 weeks	12/group	Male	Whole Body Inhalation	Adulthood	Depression	Increased
Sheffield et al. (2018)	Human	PM2.5	Prenatal	9 months	557	Female	General additive mixed models	Adulthood	Both	Increased
Shin et al. (2018)	Human	Multiple Pollutants	Adulthood	1 year	124,205	Both	Used measurements from fixed ground monitoring stations	Adulthood	Depression	Increased
Umezawa et al. (2018)	Mice (NMRI)	PM2.5	Prenatal	14 days	10/group	Both	Whole Body Inhalation	Adulthood	Anxiety	Decreased
F. Wang, H. Liu, et al. (2018)	Human	Multiple Pollutants	Early-life through late-life	0–7 days	19,646	Both	Used measurements from fixed ground	Early-life through late-life	Depression	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
							monitoring stations			
R. Wang et al. (2018)	Human	PM2.5	Adulthood	1 year	20,861	Both	Kriging model	Adulthood	Depression	Increased
Wang and Yang (2018)	Human	Multiple Pollutants	Adulthood and Late-life	2 years	11,634	Both	Used measurements from fixed ground monitoring stations	Adulthood & Late-life	Depression	Increased
Woodward et al. (2018)	Rats (Sprague-Dawley)	nPM	Prenatal through Adulthood	28 weeks	15–17	Male	Whole Body Inhalation	Adulthood	Both	Mixed
Zhang et al. (2018)	Mice (SPF Kunming)	PM2.5	Prenatal	7 days	6/group	Both	Intratracheal Instillation	Adolescence	Both	Increased
Zock et al. (2018)	Human	Multiple Pollutants	Early-life through Late-life	1 year	4,450	Both	Land use regression models	Early-life through late-life	Both	Mixed
Brokamp, Strawn, et al. (2019)	Human	PM2.5	Adolescence	0–3 days	6,812	Both	Combination	Adolescence	Both	Increased
Brunst et al. (2019)	Human	TRAP	Prenatal/Early-life through Adolescence	1 year, 12 years	145	Both	Land use regression models	Adolescence	Anxiety	Increased
Chu et al. (2019)	Rats (Sprague-Dawley) and Mice (Wild Type)	PM2.5	Rats - Adulthood, Mice - Adolescence through Adulthood	Rats - 12 weeks, Mice - 9 weeks	8/group	Male	Whole Body Inhalation	Adulthood	Both	Increased
Generaal, Hoogendijk, et al. (2019)	Human	PM2.5	Adulthood	1 year	32,487	Both	Land use regression models	Adulthood	Depression	Increased
Generaal, Timmermans, et al. (2019)	Human	PM2.5	Adulthood	1 year	2,980	Both	Land use regression models	Adulthood	Both	Mixed
Ehsanifar, Jafari, et al. (2019)	Mice (NMRI)	DEP	Adulthood	2, 5, 7 hrs	12/group	Male	Whole Body Inhalation	Adulthood	Anxiety	Increased
Ehsanifar, Tameh, et al. (2019)	Mice (NMRI)	DEP	Adulthood	12 weeks	12/treatment/time, 48 total	Male	Whole Body Inhalation	Adulthood	Both	Increased
Fan et al. (2019)	Human	PM2.5	Adolescence	3 years	21,780	Both	Land use regression models	Adolescence	Depression	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
Jorcano et al. (2019)	Human	Multiple Pollutants	Prenatal through Adolescence	1 year, 7 years	13,182	Both	Land use regression models	Childhood, adolescence	Both	No effects observed
Khan et al. (2019)	Human	Multiple Pollutants	For the U.S.: Early-life through Late-life. For Denmark - Early-life through Childhood	U.S. - Not reported, Denmark - 10 years	For U.S.: 151,104,811. For Denmark: 1,435,074	Both	Combination	For the U.S.: early-life through late-life, for Denmark: not reported	Depression	Increased
Lee et al. (2019)	Human	PM10	Early-life through Late-life	0–5 days	30,704	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Depression	Increased
Liu et al. (2019)	Rats (Sprague-Dawley)	PM2.5	Early-life	12 days	20/group	Both	Intranasal instillation	Childhood, Adulthood	Both	Increased
Morris-Schaffer et al. (2019)	Mice (C57BL/6J)	UFP	Early-life	6 days	Not reported	Both	Whole Body Inhalation	Not reported	Anxiety	No effects observed
Motesaddi Zarandi et al. (2019)	Rats (Wistar)	PM2.5	Adolescence through Adulthood	3 months, 6 months	96, 32/group	Both	Whole Body Inhalation	Adulthood	Depression	No effects observed
Petkus et al. (2019)	Human	PM2.5	Late-life	3 years	1,989	Female	Bayesian Maximum Entropy	Late-life	Depression	Increased
Pun et al. (2019)	Human	Multiple Pollutants	Late-life	1 year	4118	Both	Distance to major roadway	Late-life	Both	Increased
Qiu et al. (2019)	Human	Multiple Pollutants	Early-life through Late-life	0–7 days	10,947	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Depression	Increased
Roberts et al. (2019)	Human	Multiple Pollutants	Adolescence	1 year	284	Both	KCLurban model - kernel modeling approach	Adolescence and Adulthood	Both	Mixed
Wang et al. (2019)	Human	PM2.5	Adulthood	1 year	20,861	Both	Used measurements from fixed ground monitoring stations	Adulthood	Depression	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
Yolton et al. (2019)	Human	TRAP	Prenatal/Early-life through Adolescence	1 year, 12 years	344	Both	Land use regression models	Adolescence	Both	Increased
Yue et al. (2020)	Human	Multiple Pollutants	Early-life through Late-life	0–7 days	16,601	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Anxiety	Increased
Zhang et al. (2019)	Human	Multiple Pollutants	Adulthood	1, 5 years	123,045	Both	Land use regression models	Adulthood	Depression	Increased
Zhao et al. (2019)	Human	Multiple Pollutants	Adolescence	0–7 days, 1 year	2827	Both	Combination	Adolescence	Depression	No effects observed
Altug et al. (2020)	Human	Multiple Pollutants	Late-life	Not reported	821	Female	Land use regression models	Late-life	Depression	Increased
Diaz et al. (2020)	Human	Multiple Pollutants	Not reported	0–8 days	1,461	Both	Used measurements from fixed ground monitoring stations	Not reported	Both	No effects observed
H. Gu et al. (2020)	Human	PM2.5	Adulthood	1 year	14,772	Both	Satellite-based measurements	Adulthood	Both	Increased
X. Gu et al. (2020)	Human	Multiple Pollutants	Early-life through Late-life	0–7 days	111,620	Both	Used measurements from fixed ground monitoring stations	Early-life through Late-life	Depression	Increased
Haghani, Johnson, Safi, et al. (2020)	Mice (C57BL/6NJ)	nPM	Prenatal	3 weeks	5–16/group	Both	Whole Body Inhalation	Adulthood	Depression	Increased
Haghani, Johnson, Woodward, et al. (2020)	Mice (C57BL/6J)	nPM	Prenatal	3 weeks	Not reported	Both	Whole Body Inhalation	Adulthood	Depression	Increased
Kim, Cho, et al. (2020)	Human	Multiple Pollutants	Adulthood and Late-life	5 years	2,729	Both	Kriging model	Adulthood & Late-life	Depression	Increased
Li and Zhou (2020)	Human	Multiple Pollutants	Adulthood	1 year	11,908	Both	Used measurements from fixed ground monitoring stations	Adulthood	Depression	Increased
Lu et al. (2020)	Human	Multiple Pollutants	Early-life, Childhood, Adolescence,	0–5 days	111,842	Both	Used measurements from fixed ground	Early-life, childhood, adolescence,	Both	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
			Adulthood, Late-life				monitoring stations	adulthood, late-life		
McGuinn et al. (2020)	Human	PM2.5	Prenatal	Up to 39 weeks	539	Both	Combination	Childhood	Both	No effects observed
Nephew et al. (2020)	Rats (Sprague-Dawley)	PM2.5	Prenatal through Early-life	29 days	18/group	Male	Whole Body Inhalation	Childhood, Adolescence	Anxiety	Increased
Niedzwiecki et al. (2020)	Human	PM2.5	Adulthood	Up to 39 weeks	509	Female	Land use regression models	Adulthood	Both	Mixed
Nishimura et al. (2020)	Human	Multiple Pollutants	Not reported	1 month	Not reported	Both	Used measurements from fixed ground monitoring stations	Not reported	Depression	No effects observed
Petkus et al. (2020)	Human	PM2.5	Late-life	3 years	2,202	Female	Bayesian Maximum Entropy	Late-life	Depression	No effects observed
Pinault et al. (2020)	Human	Multiple Pollutants	Adulthood and Late-life	1 year	84,800	Both	Chemical transport	Adulthood & Late-life	Both	Increased
Roe et al. (2020)	Human	PM2.5	Adulthood, Late-life	15–20 mins	11	Both	Personal air monitoring	Adulthood & Late-life	Both	Mixed
Shi et al. (2020)	Human	Multiple Pollutants	Adulthood and Late-life	2 weeks	1,811	Both	Used measurements from fixed ground monitoring stations	Adulthood & Late-life	Both	Increased
Tsai et al. (2020)	Human	Ozone	Not reported	0–2 days	80,813	Not reported	Used measurements from fixed ground monitoring stations	Not reported	Depression	Increased
Wang et al. (2020)	Human	PM2.5	Adulthood and Late-life	1 year	24,623	Both	Chemical transport	Adulthood and Late-life	Depression	Increased
Wei et al. (2020)	Human	Multiple Pollutants	Adolescence, Adulthood, Late-life	0–7 days	16,225	Both	Used measurements from fixed ground monitoring stations	Adolescence, Adulthood, Late-life	Depression	Increased
Zhao et al. (2020)	Human	Multiple Pollutants	Childhood, Adolescence, Adulthood, Late-life	10 years	1,126,014	Both	Used measurements from fixed ground	Adolescence, Adulthood, Late-life	Both	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
							monitoring stations			
Zu et al. (2020)	Human	Multiple Pollutants	Not reported	Not reported	4,721	Both	Used measurements from fixed ground monitoring stations	Adulthood	Depression	Increased
Ahlers and Weiss (2021)	Human	PM2.5	Adulthood	3 months, 9 months	50	Female	Used measurements from fixed ground monitoring stations	Adulthood	Depression	Increased
Allaouat et al. (2021)	Human	PM2.5	Adulthood, Late-life	4 years	5,895	Both	Dispersion modeling	Adulthood, Late-life	Depression	No effects observed
Chen et al. (2021)	Human	PM2.5	Not reported	1 year	1,782	Not reported	Used measurements from fixed ground monitoring stations	Not reported	Anxiety	Increased
Dores et al. (2021)	Human	Multiple Pollutants	Adolescence, Adulthood	1–3 years	55,650	Both	Chemical transport	Adolescence and Adulthood	Depression	No effects observed
Ehsanifar, Jafari, et al. (2021)	Mice (NMRI)	DEP	Adulthood	12 weeks	12/group	Male	Whole Body Inhalation	Adulthood	Anxiety	Increased
Jeong et al. (2021)	Mice (C57BL/6nCrlOri)	DEP	Adulthood	7 days	8/group	Male	Intratracheal Instillation	Adulthood	Anxiety	Increased
Joo et al. (2021)	Human	PM2.5	Adolescence, Adulthood	1 year	1,484	Both	Used measurements from fixed ground monitoring stations	Adolescence, Adulthood	Both	Increased
Kanner et al. (2021)	Human	Multiple Pollutants	Adolescence through Adulthood	15 months	11,173	Female	Chemical transport	Adolescence and Adulthood	Depression	Increased
Lamichhane et al. (2021)	Human	Multiple Pollutants	Adulthood	3 months	1,481	Female	Land use regression models	Adulthood	Both	Increased
Latham et al. (2021)	Human	Multiple Pollutants	Childhood	1 year	2,066	Both	Chemical transport model	Adulthood	Depression	No effects observed
Muhsin et al. (2022)	Human	Multiple Pollutants	Adulthood, Late-life	0–7 days	81,548	Both	Used measurements from fixed ground	Adulthood, late-life	Both	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
							monitoring stations			
Nguyen et al. (2021)	Human	Multiple Pollutants	Early-life through Late-life	0–29 days	1,997,992	Both	Used measurements from fixed ground monitoring stations	Early-life through late-life	Depression	Increased
Pelgrims et al. (2021)	Human	Multiple Pollutants	Adulthood	1 year	1,325	Both	Dispersion modeling	Adulthood	Both	Mixed
Petkus, Wang, et al. (2021)	Human	Multiple Pollutants	Late-life	3 years	6,118	Female	Kriging model	Late-life	Both	Increased
Petkus, Younan, et al. (2021)	Human	Multiple Pollutants	Late-life	3 years	1,583	Female	Kriging model	Late-life	Depression	Increased
Rasnick et al. (2021)	Human	PM2.5	Early-life through Early-adolescence	12 years	263	Both	Land use random forest model	Adolescence	Both	Increased
Reuben et al. (2021)	Human	Multiple Pollutants	Adolescence, Adulthood	1 year	2,039	Both	combination	Adolescence and Adulthood	Both	Increased
Roberts and Helbich (2021)	Human	PM2.5	Adulthood	1 year	393	Both	Land use regression models	Adulthood	Depression	No effects observed
Tsai et al. (2021)	Human	Multiple Pollutants	Not reported	0–3 days	80,813	Not reported	Used measurements from fixed ground monitoring stations	Not reported	Depression	Increased
Wen et al. (2021)	Mice (C57BL/6)	Multiple Pollutants	Prenatal	3 weeks	8/group	Both	Intratracheal Instillation	Adolescence	Anxiety	Increased
Xue et al. (2021)	Human	PM2.5	Adulthood and Late-life	1 year	15,954	Both	Chemical transport model	Adulthood & Late-life	Depression	Increased
Yao et al. (2022)	Human	PM2.5	Adulthood and Late-life	1 month - 2 years	15,105	Both	Used measurements from fixed ground monitoring stations	Adulthood & Late-life	Depression	Increased
Zhou, An, et al. (2021)	Human	Multiple Pollutants	Not reported	0–5 days	92,387	Both	Used measurements from fixed ground monitoring stations	Not reported	Depression	Increased
Zhou, Fan, et al. (2021)	Human	Multiple Pollutants	Not reported	0–3 days	23,773	Both	Used measurements from fixed ground	Not reported	Anxiety	Increased

First author & Year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Internalizing outcome assessed	Internalizing increased or decreased
							monitoring stations			

*0 days refers to pollution estimates that occurred on the same day as the outcome

Neurotoxicology. Author manuscript; available in PMC 2023 December 01.

Table 2.

Final Included Articles from Literature Search 2: Air Pollution and Frontolimbic Brain Regions

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
Avila-Costa et al. (1999)	Rats (Wistar)	Ozone	Not reported	4 hours	24	Male	Whole Body Inhalation	Not reported	Hippocampus	Dendritic spine length or neurite changes
Avila-Costa et al. (2001)	Rats (Wistar)	Ozone	Not reported	4 hours	24	Male	Whole Body Inhalation	Not reported	Prefrontal Cortex	Dendritic spine length or neurite changes
Dorado-Martínez et al. (2001)	Rats (Wistar)	Ozone	Not reported	4 hours	136	Male	Whole Body Inhalation	Not reported	Hippocampus, Frontal Cortex	Lipid peroxidation
Niño-Cabrera (2002)	Rats (Wistar)	Ozone	Late-life	4 hours	7 (3 controls)	Male	Whole Body Inhalation	Late--ife	Hippocampus CA1 and Prefrontal Cortex	Necrotic processes, myelin alterations, altered astrocytes
Calderon-Garciduenas et al. (2003)	Dogs	Multiple pollutants	Lifetime	Dogs - 1 year, Humans - 2–10 years	40 (14 controls)	Both	Whole Body Inhalation	Adulthood	Hippocampus, Frontal Cortex	Altered DNA, amyloid, immune reactions, inflammatory reactions, altered astrocytes
Calderon-Garciduenas et al. (2004)	Humans	Multiple pollutants	Lifetime	34–83 years	19 (9 low pollution, 10 high pollution)	Both	Lived in polluted city versus unpolluted city	Adulthood & Late-life	Hippocampus, Frontal Cortex	Altered DNA, amyloid, inflammatory reactions
Santucci et al. (2006)	Mice (CD-1)	Ozone	Prenatal	47 days	8 (4 females, 4 males)	Both	Whole Body Inhalation	Adulthood	Hippocampus	Neurotrophins
Calderon-Garciduenas et al. (2008)	Humans, Dogs	Multiple pollutants	Lifetime	Humans - 9.2 + 2.3 years, Dogs - 12–19 months	73 children (55 high polluted, 18 low polluted), 12 dogs (7 high polluted, 5 low polluted)	Both	Lived in polluted city versus unpolluted city	Childhood	Subcortical prefrontal white matter	White matter lesions, inflammatory reactions
Gerlofs-Nijland et al. (2010)	Rats (Fischer F344/ DUCRL)	Multiple pollutants	Adulthood	4 weeks	15/group	Male	Combination of whole body inhalation and nose-only inhalation	Adulthood	Hippocampus	No effects observed (inflammatory reactions, immune reactions)
Rivas-Arancibia et al. (2010)	Rats (Wistar)	Ozone	Not reported	15–90 days	110 (22 in each group)	Male	Whole Body Inhalation	Not reported	Hippocampus	Microglia, altered neurogenesis, altered cell proliferation, lipid

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
										peroxidation, altered astrocytes,
Suzuki et al. (2010)	Mice (ICR)	DEP	Prenatal	2 weeks	272 (114 exposed, 161 control)	Male	Whole Body Inhalation	Childhood	Prefrontal Cortex, Hippocampus	Neurotransmitter or neuromodulator metabolites and receptors
Calderon-Garciduenas et al. (2011)	Humans	Multiple pollutants	Lifetime	7.1 + 0.69 years	30 (10 low polluted, 20 high polluted)	Both	Lived in polluted city versus unpolluted city	Childhood	Prefrontal white matter, temporal white matter, hippocampus, amygdala	Brain volumes, white matter lesions
Fonken et al. (2011)	Mice (C57BL/6)	PM2.5	Childhood through Adulthood	10 months	Not reported	Male	Whole Body Inhalation	Adulthood	Hippocampus	Dendritic spine length or neurite changes, inflammatory reactions
Gackiere et al. (2011)	Rats (Wistar)	Ozone	Adolescence	Up to 120 hours	Not reported	Male	Whole Body Inhalation	Adolescence	Amygdala	Activated neurons
Morgan et al. (2011)	Mice (C57BL/6J) and Rats (F344)	nPM	Adulthood	10 weeks	Not reported	Male	Whole Body Inhalation	Adulthood	Hippocampus	Microglia, neurotransmitter or neuromodulator metabolites and receptors, dendritic spine length or neurite changes, altered astrocytes, inflammatory reactions
Bos et al. (2012)	Mice (C57BL6)	PM2.5	Adolescence	5 days	20	Male	Whole Body Inhalation	Adulthood	Hippocampus	Inflammatory reactions, immune reactions
Hallberg et al. (2012)	Rats (Wistar Han) and Mice (C57BL/6)	DEP	Not reported	6 hours	5/group	Both	Whole Body Inhalation	Not reported	Hippocampus	No effects observed (inflammatory reactions)
Davis et al. (2013)	Mice (C57BL/6J)	nPM	Prenatal	10 weeks	4/group	Both	Whole Body Inhalation	Early-life	Hippocampus	Necrotic processes
Guerra et al. (2013)	Rats (Sprague-Dawley)	Multiple pollutants	Adolescence through Adulthood	8 weeks	Not reported	Male	Whole Body Inhalation	Adulthood	Frontal cortex, Hippocampus	Mitochondrial changes, misfolded proteins, inflammatory reactions
Rodriguez-Martinez et al. (2013)	Rats (Wistar)	Ozone	Not reported	Up to 60 days	180 (36/ group)	Male	Whole Body Inhalation	Not reported	Hippocampus	Oxidative stress markers, swollen and damaged cells, mitochondrial changes
Win-Shwe et al. (2013)	Mice (BALB/c)	Multiple pollutants	Adulthood	1 single intranasal	24, 8/group	Male	Intranasal instillation	Adulthood	Hippocampus	Inflammatory reactions

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
				instillation dose of 50 ul						
Gomez-Crisostomo et al. (2014)	Rats (Wistar)	Ozone	Not reported	Up to 90 days	72	Male	Whole Body Inhalation	Not reported	Hippocampus	Necrotic processes, altered cell proliferation, oxidative stress markers
Kinawy et al. (2014)	Rats (Wister)	DEP	Not reported	Single session - 30 mins, Chronic session - 8 weeks	90, 30/ group	Male	Whole Body Inhalation	Not reported	Hippocampus	Neurotransmitter or neuromodulator metabolites and receptors
F. Wang et al. (2014)	Mice (Kun Ming)	VOCs	Childhood through Adulthood	3 months	60	Male	Whole Body Inhalation	Adulthood	Hippocampus	Decreased number of neurons, altered cell proliferation, oxidative stress markers, lipid peroxidation, neurotransmitter or neuromodulator metabolites and receptors
Win-Shwe et al. (2014)	Mice (BALB/c)	DEP	Childhood through Adulthood	1–3 months	6/group	Both	Whole Body Inhalation	Adulthood	Hippocampus	Neurotransmitter or neuromodulator metabolites and receptors
Calderon-Garciduenas et al. (2015)	Humans	Multiple pollutants	Lifetime	Children - 12.45 + 3.4 years. Adults - 37.5 + 6.77	57 polluted children and 9 control children. 48 polluted adults, and 7 control adults.	Both	Lived in polluted city versus unpolluted city	Childhood and Adolescence, Adulthood	Hippocampus	MR Spectroscopy
Heidari Nejad et al. (2015)	Mice (BALB/c)	DEP	Adulthood	8 days	12/group	Both	Whole Body Inhalation	Adulthood	Hippocampus	Altered astrocytes, blood brain barrier integrity
Hallberg et al. (2015)	Rats (Wistar Han)	DEP	Not reported	Up to 24 months	10, 5/group	Both	Not reported	Not reported	Hippocampus	No effects observed (oxidative stress makers)
Hernandez-Zimbron and Rivas-Arancibia (2015)	Rats (Wistar)	Ozone	Not reported	Up to 90 days	72, 12/ group	Male	Whole Body Inhalation	Not reported	Hippocampus	Amyloid, mitochondrial changes

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
Kodavanti et al. (2015)	Rats (Long-Evans)	VOCs	Adulthood	Acute - 6 hours, Subchronic - 13 weeks	Not reported	Male	Whole Body Inhalation	Adulthood	Frontal Cortex, Hippocampus	Oxidative stress markers
Peterson et al. (2015)	Humans	PAH	Prenatal, Childhood	Prenatal - 48 hours, Postnatal 5 years	40	Both	Combination of personal air monitoring, and urinary metabolites	Childhood	Frontal lobe white matter, Temporal lobe white matter, dorsal prefrontal white matter	Brain volumes
Yao et al. (2015)	Rats (Wistar)	SO2	Not reported	90 days	20/group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Neurotransmitter or neuromodulator metabolites and receptors, inflammatory reactions, memory related kinases and genes
Calderon-Garciduenas et al. (2016)	Humans and Dogs	Multiple pollutants	Lifetime	Dogs - 3.11 + 0.67 years, Humans - 12.67 + 4.9 years	9 high polluted dogs, 6 control dogs	Both	Lived in polluted city versus unpolluted city	Not reported	Frontal white and gray matter in dogs. Prefrontal white and gray matter in children	Cerebrovascular changes
Cole et al. (2016)	Mice (C57BL/6)	DEP	Adulthood	6 hours	3–6/group	Both	Whole Body Inhalation	Adulthood	Hippocampus	Inflammatory reactions, microglia, lipid peroxidation
Hernandez-Zimbron and Rivas-Arancibia (2016)	Rats (Wistar)	Ozone	Not reported	Up to 90 days	72 (12/ group)	Male	Whole Body Inhalation	Not reported	Hippocampus	Endoplasmic reticulum changes, amyloid
Rodriguez-Martinez et al. (2016)	Rats (Wistar)	Ozone	Not reported	Up to 90 days	108	Male	Whole Body Inhalation	Not reported	Hippocampus	Endoplasmic reticulum changes, necrotic processes
Yokota, Oshio, Moriya, et al. (2016)	Mice (ICR)	DEP	Prenatal	2 weeks	15/group	Male	Whole Body Inhalation	Adulthood	Prefrontal cortex, amygdala	Neurotransmitter or neuromodulator metabolites and receptors
Chao et al. (2017)	Rats (Sprague-Dawley)	PM2.5	Prenatal	Up to 25 mg instillation intratracheal test	12	Not reported	Intratracheal instillation	Not reported	Hippocampus	Memory related kinases and genes, endoplasmic reticulum changes, altered cell proliferation

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
J. C. Chen et al. (2017)	Humans	Multiple pollutants	Adulthood, Late-life	9 years	1403	Female	Bayesian maximum entropy	Late-life	Hippocampus, Frontal and Temporal Gray and White Matter	Brain volumes
Cheng et al. (2017)	Rats (Sprague-Dawley)	PM2.5	Adulthood	28 days	20, 10/ group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Dendritic spine length or neurite changes
Ku et al. (2017)	Mice (C57BL/6)	PM2.5	Adulthood	4 weeks	Not reported	Male	Oropharyngeal aspiration	Adulthood	Hippocampus	Amyloid, neurotransmitter or neuromodulator metabolites and receptors, synaptic changes, altered cell proliferation
Nway et al. (2017)	Mice (C3H/ HeN)	DEP	Prenatal and Early-life	5 days	8/group	Both	Whole Body Inhalation	Early-life	Hippocampus	Neurotransmitter or neuromodulator metabolites and receptors, inflammatory reactions, microglia
Rivas-Arancibia et al. (2017)	Rats (Wistar)	Ozone	Not reported	Up to 90 days	72, 12/ group	Male	Whole Body Inhalation	Not reported	Hippocampus	Amyloid
Woodward, Levine, et al. (2017)	Mice (C57BL/6J)	nPM	Adulthood	10 weeks	Not reported	Female	Whole Body Inhalation	Adulthood	Hippocampus	Inflammatory reactions, immune reactions
Woodward, Pakbin, et al. (2017)	Mice (C67BL/6J)	nPM	Adulthood through Late-life	10 weeks	9/group	Female	Whole Body Inhalation	Adulthood and Late-life	Hippocampus	Microglia, dendritic spine length or neurite changes, neurotransmitter or neuromodulator metabolites and receptors, inflammatory reactions, myelin alterations
Yang et al. (2017)	Rats (Wistar)	Multiple pollutants	Not reported	10 days	6/group	Male	Intratracheal instillation	Not reported	Hippocampus	Inflammatory reactions, amyloid
Andrade-Oliva et al. (2018)	Rats (Sprague Dawley)	PM2.5	Adulthood	Acute - 3 days, Subchronic - 8 weeks	Not reported	Male	Whole Body Inhalation	Not reported	Prefrontal Cortex	No effects observed (Neurotransmitter or neuromodulator metabolites and receptors, altered astrocytes
Jia et al. (2018)	Mice (C57BL/6J)	PM2.5	Adulthood	20 weeks	10/group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Dendritic spine length or neurite changes,

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
										inflammatory reactions, glucocorticoid receptors,
Kim et al. (2018)	Mice (BALB/c)	DEP	Adolescence through Adulthood	4 weeks, 8 weeks	32, 8/group	Female	Whole Body Inhalation	Adulthood	Prefrontal Cortex, Temporal Cortex	Synaptic changes, neurotrophins, oxidative stress markers
Li et al. (2018)	Rats (Sprague-Dawley)	PM2.5	Early-life	2 weeks	Not reported	Male	Intranasal instillation	Early-life	Hippocampus, Prefrontal Cortex	Inflammatory reactions, autism genes expression, altered astrocytes, microglia
Liu et al. (2018)	Mice (C57BL/6)	Multiple pollutants	Adulthood through Late-life	Up to 12 weeks	Not reported	Male	Whole Body Inhalation	Not reported	Hippocampus	Neurotrophins, necrotic processes, dendritic spine length or neurite changes, inflammatory reactions
Ning et al. (2018)	Mice (C57BL/6)	PM2.5	Childhood through Adolescence	4 weeks	Not reported	Not reported	Oropharyngeal aspiration	Not reported	Hippocampus	Energy metabolites, cholesterol metabolites, arachidonic acid metabolites, inositol phosphate metabolites, aspartic acid metabolites
Shih et al. (2018)	Rats (Sprague Dawley)	TRAP	Adulthood	3 months, 6 months	9/group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Dendritic spine length or neurite changes, inflammatory reactions, brain volumes, arachidonic acid metabolites, necrotic processes
Valand et al. (2018)	Rats (Fisher344)	DEP	Not reported	28 days	7/group	Male	Whole Body Inhalation	Not reported	Hippocampus, Frontal Cortex	Genes involved in bronchial smooth muscle cells, genes associated with neuronal development, alterations in neuronal migration, swollen and damaged cells, synaptic changes, immune reactions, oxidative stress markers, dendritic spine length or neurite changes, inflammatory reactions
F. Wang, Z. Fangfang, et al. (2018)	Mice (Kunming)	VOCs	Childhood	10 days	10/group	Male	Whole Body Inhalation	Adolescence	Hippocampus	Dendritic spine length or neurite changes, neurotransmitter

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
										or neuromodulator metabolites and receptors, oxidative stress markers
Woodward et al. (2018)	Rats (Sprague-Dawley)	TRAP	Prenatal through Adulthood	28 weeks	Not reported	Male	Whole Body Inhalation	Adulthood	Hippocampus	Cerebral microbleeds, altered neurogenesis, blood brain barrier integrity, microglia
Zheng et al. (2018)	Mice (Kunming)	PM2.5	Prenatal	7 days	6/group	Not reported	Tracheal drip	Early-life	Hippocampus	Activated neurons, altered neurogenesis, mitochondrial changes, synaptic changes, immune reactions, altered cell proliferation, necrotic processes, dendritic spine length or neurite changes, inflammatory reactions
Bai et al. (2019)	Rats (Sprague Dawley)	TRAP	Adulthood	3 months, 6 months	Not reported	Male	Whole Body Inhalation	Adulthood	Hippocampus	Microglia
Bello-Medina et al. (2019)	Rats (Wistar)	Ozone	Not reported	Up to 90 days	80, 10/ group	Male	Whole Body Inhalation	Not reported	Hippocampus	Dendritic spine length or neurite changes
Brunst et al. (2019)	Humans	TRAP	Early-life, Childhood, Cumulative	1 year, 12 years	145	Both	Land use regression models	Adolescence	Anterior Cingulate Cortex (ACC)	MR Spectroscopy
Chu et al. (2019)	Rats (Sprague-Dawley) and Mice (WT and Nrfs−/− (KO))	PM2.5	Rats - Adulthood, Mice - Adolescence through Adulthood	Rats - 12 weeks, Mice - 9 weeks	24, 8/group	Male	Whole Body Inhalation	Adulthood	Prefrontal Cortex	Dendritic spine length or neurite changes, inflammatory reactions, heavy metal deposits, neurotrophins, altered astrocytes, necrotic processes, oxidative stress markers, neurotransmitter or neuromodulator metabolites and receptors
Custodio et al. (2019)	Rats (Wistar)	Ozone	Prenatal	20 days	18 exposed, 16 controls	Both	Whole Body Inhalation	Adulthood	Prefrontal Cortex, Hippocampus	Neurotransmitter or neuromodulator metabolites and receptors, altered cell proliferation

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
Ehsanifar, Jafari, et al. (2019)	Mice (NMRI)	DEP	Prenatal	3 weeks	10/group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Dendritic spine length or neurite changes, inflammatory reactions, neurotransmitter or neuromodulator metabolites and receptors
Ehsanifar, Tameh, et al. (2019)	Mice (NMRI)	DEP	Adulthood	12 weeks	48, 12/ group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Oxidative stress markers
Hedges et al. (2019)	Humans	Multiple pollutants	Adulthood and Late-life	1 year	18,278	Both	Land use regression models	Adulthood & Late-life	Hippocampus	Brain volumes
Kim et al. (2019)	Mice (BALB/c)	DEP	Adolescence into Adulthood	4 weeks, 8 weeks	32, 8/group	Female	Whole Body Inhalation	Adulthood	Prefrontal Cortex, Temporal Cortex	Immune reactions, synaptic changes, necrotic processes, neurotransmitter or neuromodulator metabolites and receptors, inflammatory reactions, neuronal plasticity measures, genes associated with neuronal development
Li et al. (2019)	Mice (C57BL/6J)	PM2.5	Adulthood	Acute - 24 hours, Chronic - up to 4.5 months	Acute - 10, Chronic - 6	Male	Whole Body Inhalation	Adulthood	Hippocampus	Altered DNA
Liu et al. (2019)	Rats (Sprague Dawley)	PM2.5	Early-life	12 days	8/group	Both	Intranasal instillation	Childhood or Adulthood	Hippocampus	Neurotrophins, synaptic changes
Armstrong et al. (2020)	Mice (C57/BL/6)	DEP	Adulthood and Late-life	50 days	16/group	Male	Whole Body Inhalation	Adulthood, Late-life	Hippocampus	Cerebrovascular changes, altered cell proliferation, amyloid, oxidative stress markers
Calderon-Garciduenas et al. (2020)	Humans and Mice (C57BL/6J)	Multiple pollutants	Humans - not reported, adulthood for animals	Humans - 29.8 years, Mice - 7 months	Humans (5 controls, 9 exposed). Mice - 4/ group	Humans - both. Mice - Female	Humans - Lived in polluted city versus unpolluted city, Mice - whole body inhalation	Humans- Adulthood Mice – Adulthood	Humans - Frontal white matter, Mice - Frontal Cortex	Tau-related pathology, heavy metal deposits, altered DNA
Cho et al. (2020)	Humans	Multiple pollutants	Adulthood and Late-life	1 year, 5 years	957	Both	Kriging model	Adulthood, Late-life	Frontal Cortex, Temporal Cortex,	Brain volumes

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
									Hippocampus, Amygdala	
Cole et al. (2020)	Mice (C57BL/6J)	DEP	Prenatal through Early-life	3 weeks	Not reported	Both	Whole Body Inhalation	Early-life, Adulthood	Hippocampus	Altered neurogenesis
Di Domenico et al. (2020)	Mice (Balb/C)	PM2.5	Prenatal, Childhood through Adulthood	85 days	Not reported	Male	Whole Body Inhalation	Adulthood	Hippocampus	Neurotrophins, altered astrocytes, microglia
Gale et al. (2020)	Humans	Multiple pollutants	Adulthood and Late-life	1 year, 4 years	18,288	Both	Land use regression models	Adulthood & Late-life	Prefrontal Cortex	Brain volumes
Greve et al. (2020)	Rats (Wistar Kyoto)	DEP	Adulthood	1 month	7–8/group	Male	Whole Body Inhalation	Adulthood	Hippocampus, Frontal Cortex	Microglia, inflammatory reactions
Haghani, Johnson, Woodward, et al. (2020)	Mice (C57BL/6J)	nPM	Prenatal	3 weeks	Not reported	Both	Whole Body Inhalation	Adulthood	Hippocampus	Neurotransmitter or neuromodulator metabolites and receptors, inflammatory reactions, altered neurogenesis, altered cell proliferation, immune reactions
Hajipour et al. (2020)	Rats (Wistar)	Dusty PM	Not reported	4 weeks	88, 22/ group	Male	Whole Body Inhalation	Not reported	Hippocampus	Synaptic changes
Li et al. (2020)	Mice (C57BL/6)	DEP	Adulthood	14 days	10/group	Male	Intranasal instillation	Adulthood	Hippocampus	Inflammatory reactions, mitochondrial changes, immune reactions, microglia
Liu et al. (2020)	Mice (C57BL/6)	Multiple pollutants	Adulthood	Up to 12 weeks	72, 12/ group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Necrotic processes, dendritic spine length or neurite changes, inflammatory reactions, heavy metal deposits
Milani et al. (2020)	Mice (BALB/ cOlaHsd)	DEP	Adolescence into Adulthood	Acute - single instillation, Subacute - 3 instillations	6/group	Male	Intratracheal instillation	Adulthood	Hippocampus	Amyloid, oxidative stress markers, inflammatory reactions
Nephew et al. (2020)	Rats (Sprague-Dawley)	TRAP	Prenatal through Early-life	6 weeks	6/group	Male	Whole Body Inhalation	Early-life	Hippocampus, Anterior Cingulate	Diffusion tensor imaging
Park et al. (2020)	Mice (C57Bl6/J)	UFP	Adulthood	3 weeks	10/group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Amyloid, oxidative stress markers, inflammatory reactions,

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
Patten et al. (2020)	Rats (Sprague Dawley)	TRAP	Prenatal to adulthood	11 days	15/group	Both	Whole Body Inhalation	Adulthood	Hippocampus	Necrotic processes, microglia, inflammatory reactions, alterations in neuronal migration, genes associated with neuronal development, altered neurogenesis, brain volumes, altered astrocytes
Zhou et al. (2020)	Mice (ICR)	PM2.5	Prenatal, Early-life	8 days	Not reported	Both	Intratracheal instillation	Childhood	Hippocampus	Altered DNA, neurotrophins
Ehsanifar, Jafari, et al. (2021)	Mice (NMRI)	DEP	Adulthood	12 weeks	48, 12/ group	Male	Whole Body Inhalation	Adulthood	Hippocampus	Lipid peroxidation, neurotransmitter or neuromodulator metabolites and receptors, dendritic spine length or neurite changes, inflammatory reactions
Ehsanifar, Montazeri, et al. (2021)	Mice (NMRI)	DEP	Adulthood	14 weeks	10/group	Both	Whole Body Inhalation	Adulthood	Hippocampus	Oxidative stress markers, neurotransmitter or neuromodulator metabolites and receptors, dendritic spine length or neurite changes, inflammatory reactions, lipid peroxidation
Kodavanti et al. (2021)	Rats (Brown Norway)	Ozone	Adulthood, Late-life	13 weeks	Not reported	Male	Whole Body Inhalation	Adulthood & Late-life	Frontal cortex, Hippocampus	Oxidative stress markers, mitochondrial changes
F. Liu et al. (2021)	Mice (ICR)	Multiple pollutants	Adulthood	4 weeks	6/group	Male	Intranasal instillation	Adulthood	Hippocampus, Frontal Cortex	Necrotic processes, oxidative stress markers, dendritic spine length or neurite changes, CA2+ signaling pathway-related genes, decreased number of neurons, heavy metal deposits, altered neurogenesis, neurotrophins, synaptic changes
Lubczynska et al. (2021)	Humans	Multiple pollutants	Prenatal through childhood	Prenatal - 9 months,	3133	Both	Land use regression models	Childhood	Hippocampus, Amygdala	Brain volumes

First author & year	Species	Pollutant	Exposure Window	Duration of Exposure	N	Gender or sex	Exposure Assessment Method	Period of Behavioral Assessment	Brain regions assessed	Brain outcome assessed
				Childhood - 9–12 years						
Sahu et al. (2021)	Mice (C57BL/6;C3H)	PM2.5	Adulthood	3 months	Not reported	Male	Whole Body Inhalation	Adulthood	Hippocampus	No effects observed (altered astrocytes, microglia, inflammatory reactions, amyloid)
Wen et al. (2021)	Mice (C57BL/6)	Multiple pollutants	Prenatal	3 months	6/group	Both	Intratracheal instillation	Adulthood	Hippocampus	Thyroid hormone signaling pathway genes
Zhang et al. (2021)	Mice (SPF ICR)	PM2.5	Prenatal	Not reported	Not reported	Both	Endotracheal nebulization	Early-life	Hippocampus	Inflammatory reactions, immune reactions

Table 3.

Pollutants Examined in Literature Searches 1 and 2

Type of Pollutant	Percentage of Articles for Literature Search 1	Percentage of Articles for Literature Search 2
Benzo[a]pyrene (B[a]P)	0.0	1.1
Black Carbon (BC)	1.8	0.0
CO	14.4	0.0
Diesel Exhaust Particles (DEP)	5.4	26.1
Distance from major roadway	0.9	0.0
Elemental carbon (EC)	0.9	0.0
Heavy Metals (Pb, Mn, Zn, etc.)	0.9	3.3
Methane (CH_4)	0.9	0.0
NO	3.6	1.1
NO_2	37.8	2.2
Non-methane hydrocarbons (NMHC)	0.9	0.0
NOx	7.2	2.2
Nanoscale Particulate Matter or Ultrafine Particulates (nPM/UFP)	5.4	8.7
O_2	0.9	0.0
Organic Carbon (OC)	0.9	1.1
O_3	27.0	26.1
Polycyclic Aromatic Hydrocarbons (PAHs)	5.4	2.2
Peroxyacetyle nitrate (PAN)	0.9	0.0
PM	0.9	8.7
PM_{10}	33.3	6.5
$PM_{2.5}$	64.9	32.6
$PM_{2.5absorbance}$	3.6	1.1
PM2.5–10	0.9	2.2
PM_{coarse}	1.8	1.1
SO_2	21.6	2.2
SO_4	1.8	0.0
Total Hydrocarbons	1.8	0.0
Total Suspended Particles (TSP)	0.9	0.0
Traffic-Related Air Pollution (TRAP)	1.8	6.5
Volatile Organic Compounds (VOCs)	0.0	3.3

Table 4.

Internalizing Outcomes Assessed (Literature Search 1)

Internalizing Outcomes	N (%)
Animal Studies	
Elevated Plus Maze	10 (37)
Open Field	10 (37)
Forced Swim	9 (33)
Running Wheel - Voluntary Activity	4 (15)
Tail Suspension Test	4 (15)
Light Dark Box	3 (11)
Marble Burying Test	2 (7)
Elevated Zero Maze	1 (4)
Hole Board Test	1 (4)
Novelty Suppression Feed Test	1 (4)
Sucrose Preference Test	1 (4)
Cricket predation test	1 (4)
Grooming behaviors	1 (4)
Human Studies	
Center for Epidemiologic Studies Depression Scale (CES-D)	18 (21)
Emergency Department Visits	8 (10)
Hospital admissions for depression	8 (10)
Patient Health Questionnaire-9 (PHQ9)	6 (7)
Geriatric Depression Scale (GDS)	5 (6)
SCL-90	5 (6)
CBCL Anxious/Depressed	4 (5)
Hospital Anxiety and Depression Scale (HADS)	4 (5)
Behavior Assessment System for Children - 2 (BASC2)	3 (4)
Doctor Diagnosis of Major Depressive Disorder	3 (4)
Use of anti-depressant medication	3 (4)
28-item Inventory of Depression Symptomatology (IDS)	2 (2)
Children’s Depression Inventory (CDI)	2 (2)
Diagnostic Interview Schedule	2 (2)
Edinburg Postnatal Depression Scale (EPDS)	2 (2)
Hospital admissions for anxiety	2 (2)
Insurance claims for depression using ICD-9, ICD-10 codes	2 (2)
Kessler Psychological Distress Scale (K6)	2 (2)
Presence or absence of depressiveness (such as a feeling of sadness or hopelessness lasting more than 2 consecutive weeks)	2 (2)
Self-reported history of depression disorders	2 (2)
Semi-structured Composite International Diagnostic Interview (SCID)	2 (2)
Spence Children’s Anxiety Scale (SCAS)	2 (2)

Internalizing Outcomes	**N (%)**
Suicide attempts	2 (2)
Medical Symptoms Questionnaire (MSQ)	1 (1)
Crown Crisp Phobic Anxiety Scale	1 (1)
Deficient Emotional Self-Regulation (DESR)	1 (1)
Mini International Neuropsychiatric Interview (MINI)	1 (1)
“Have you ever felt sadness or despair in the last two consecutive weeks in the recent year”?	1 (1)
Use of anxiety medication	1 (1)
Self-reported history of anxiety disorders	1 (1)
Hedonic Unhappiness	1 (1)
ICPC codes for Depression or Anxiety	1 (1)
Depression Screener for Teenagers (DesTeen)	1 (1)
Beck Anxiety Inventory (BAI)	1 (1)
Multidimensional Anxiety Scale Children (MASC)	1 (1)
40-item four dimensional symptom questionnaire (4DSQ)	1 (1)
Beck Depression Inventory (BDI)	1 (1)
Strength and Difficulties Questionnaire (SDQ)	1 (1)
Insurance claims for anxiety using ICD-9, ICD-10 codes	1 (1)
Cause of death was suicide (ICD-10 codes)	1 (1)
Frequency of depressed emotions in recent months	1 (1)
K10-distress	1 (1)
University of Wales Institute of Science and Technology (UWIST) Mood Adjective Check List (MACL)	1 (1)
Generalized Anxiety Disorder (GAD-7) scale	1 (1)
General Health Questionnaire (GHQ-12)	1 (1)
Composite International Diagnostic Interview (CIDI)	1 (1)
Structured clinical interview (DSM-IV)	1 (1)
“Has a doctor diagnosed or treated you for depression during the last year (12 months)?”	1 (1)
State-Trait Anxiety Inventory (STAI)	1 (1)
Outpatient anxiety visits	1 (1)
Outpatient depression visit	1 (1)
SF-36	1 (1)
Search words related to anxiety	1 (1)

Table 5.

Neurobiological outcomes assessed (Literature Search 2)

Neurobiological Outcomes Assessed	N (%) of Articles
Inflammatory Reactions (COX-2, NF-KB, Cytokines, T-lymphocytes, HO-1, Nrf-2, TLR4, PGE2, MMP9)	36 (39.1)
Dendritic Spine Length or Neurite Changes	19 (20.7)
Neurotransmitters or neuromodulator metabolites and receptors (Dopamine, serotonin, noradrenaline, glutamate, NMDA, ARC mRNA, GAD67)	18 (19.6)
Oxidative stress markers (protein carbonyl, Mn-SOD, GPx, SDH, ROS, FoxO 3a, CAT, SOD, GSH, T-AOC, MDA, NQO1, UBIQ-RD)	16 (17.4)
Microglia (Iba1)	13 (14.1)
Necrotic Processes (apoptosis, JNK1, Caspase 3, TUNEL, LC3ii/I, Caspase-8,9, Bax, Bcl-2, MMP14)	12 (13.0)
Amyloid (APP, Abeta42, ADAM10, BACE1)	11 (12.0)
Altered Astrocytes (GFAP, S100beta)	11 (12.0)
Immune Reactions (iNOS, MyD88, NFKB1, ADAMTS1, p65, NLRP3)	10 (10.9)
Altered cell proliferation (p53, karyopycnosis, karyolysis, cyclin D, FoxO 1a, Lin28, Kbtbd8, mir-574–5p, ACE1)	9 (9.8)
Brain volumes	9 (9.8)
Neurotrophins (NGF, BDNF, CREB, p-CREB)	8 (8.7)
Synaptic changes (EPSCs, PSD-95, fEPSP, PNNs, PV-positive interneurons, VAMP2, GAP43, SYP, VGLUT1, VGLUT2, VGAT)	8 (8.7)
Altered neurogenesis (doublecortin, Neu-N, EdU, Sox2, Trb2)	7 (7.6)
Lipid Peroxidation (MDA, TBA-RS)	6 (6.5)
Mitochondrial Changes (SOD-2, MitoSox fluorescence, cytochrome c, Presenilin 1 and 2, JC-, Ndufa1, Ndufa2, Atp5h, total aconitase activity)	6 (6.5)
Altered DNA (global methylation, Dnmt1, H3K9me2/me3, γ-H2A.X)	5 (5.4)
Heavy metal deposits (Cr, Co, Ti, Li, Be, Al, Ni, Se, Cd, Ba, Pb) or Nanoparticle Deposits	4 (4.3)
Endoplasmic Retiuclum changes (Syx5, Ildr2. Caspase-12)	3 (3.3)
Genes associated with neuronal development (AUTS2, neurocan, IGf1)	3 (3.3)
Activated Neurons (c-Fos)	2 (2.2)
Alterations in neuronal migration (Dcx)	2 (2.2)
Arachidonic Acid Metabolites (methyl arachidonic acid, linoleicacid, 8-isoprostane)	2 (2.2)
Blood Brain Barrier Integrity (plasma-derived IgG, ZO-1)	2 (2.2)
Cerebrovascular changes (Ang II-AT1)	2 (2.2)
Decreased number of neurons	2 (2.2)
Memory related kinases, genes (PKA, PKC, CaMKIIalpha, ADAM11)	2 (2.2)
Myelin Alterations (MBP)	2 (2.2)
Spectroscopy (MRS)	2 (2.2)
Swollen and damaged cells (vaculoes, neuropil)	2 (2.2)
White Matter Lesions	2 (2.2)
Aspartic Acid Metabolites (aspartic acid, asparagine, homoserine)	1 (1.1)
Autism (ASD) Genes expression - Shank3	1 (1.1)
Ca2+ signaling pathway-related genes	1 (1.1)

Neurobiological Outcomes Assessed	**N (%) of Articles**
Cerebral Microbleeds (Iron deposits, hemosiderin)	1 (1.1)
Cholesterol metabolites (desmosterol, lanosterol, campesterol)	1 (1.1)
Diffusion Tensor Imaging (DTI)	1 (1.1)
Energy metabolites (citric acid, succinic acid, malic acid, maltose, and creatinine)	1 (1.1)
Genes involved in bronchial smooth muscle cells (ADRB2)	1 (1.1)
Glucocorticoid receptors	1 (1.1)
Inositol phosphate metabolites (myto-inositol-1-phosphate, methyl-phosphate, myo-inositol)	1 (1.1)
Misfolded proteins (BiP)	1 (1.1)
Neuronal Plasticity measures (tenascin c)	1 (1.1)
Tau-related pathology (AT8, Tau5, tau protein phosphorylation)	1 (1.1)
Thyroid hormone signaling pathway genes (Prkca, Med12l, Ep300, Slc16a10)	1 (1.1)