HHS Public Access

Author manuscript

J Clin Neurosci. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

J Clin Neurosci. 2017 September ; 43: 16–24. doi:10.1016/j.jocn.2017.04.028.

Clinical Effects of Air Pollution on the Central Nervous System; A Review

Robin M. Babadjouni[1,2,*], **Drew M. Hodis**[1,*], **Ryan Radwanski**[1,*], **Ramon Durazo**[1,2], **Arati Patel**[1,2], **Qinghai Liu**[1], and **William J. Mack**[1,2]

[1]Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

[2]Department of Neurosurgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

Abstract

The purpose of this review is to describe recent clinical and epidemiological studies examining the adverse effects of urban air pollution on the central nervous system (CNS). Air pollution and particulate matter (PM) are associated with neuroinflammation and reactive oxygen species (ROS). These processes affect multiple CNS pathways. The conceptual framework of this review focuses on adverse effects of air pollution with respect to neurocognition, white matter disease, stroke, and carotid artery disease. Both children and older individuals exposed to air pollution exhibit signs of cognitive dysfunction. However, evidence on middle-aged cohorts is lacking. White matter injury secondary to air pollution exposure is a putative mechanism for neurocognitive decline. Air pollution is associated with exacerbations of neurodegenerative conditions such as Alzheimer's and Parkinson's Diseases. Increases in stroke incidences and mortalities are seen in the setting of air pollution exposure and CNS pathology is robust. Large populations living in highly polluted environments are at risk. This review aims to outline current knowledge of air pollution exposure effects on neurological health.

Keywords

Air pollution; PM; Cognitive dysfunction; White matter disease; Stroke; Carotid artery disease

Introduction

The adverse effects of ambient air pollution on respiratory and cardiovascular health are firmly established. However, impact on the central nervous system (CNS) was first described only a decade ago.[1] A significant number of clinical and epidemiological studies indicate

Please address correspondence to: William J. Mack, MD 1520 San Pablo Street Suite 3800, Los Angeles, CA 90033, William.Mack@med.usc.edu phone: (323) 442-7512; fax: (323) 442 7543.

*These three authors contributed equally to the work.

adverse associations between air pollution and neurological disease, but mechanistic pathways remain elusive.

Ambient air pollution is a mixture of gases and particulate matter released into the surrounding air by stationary (industrial and household etc.) and mobile (vehicles, trains, ships etc.) sources.[2] The gaseous mixture is primarily composed of Carbon Monoxide (CO), Ozone (O_3), Nitrogen dioxide (NO_2) and Sulfur dioxide (SO_2).[2] These chemical constituents are all implicated in human pathophysiology. However, studies suggest particulate matter <250 nm ($PM_{2.5}$) as a principal antagonist due to small aerodynamic diameter and ability to traverse the alveolar region of the respiratory system.[3] Of relevance to the present review, $PM_{2.5}$ is also the component most consistently implicated in adverse neurological processes.[4]

Air pollution and particulate matter are persistent sources of neuroinflammation and reactive oxygen species (ROS); processes strongly related to the pathogenesis of CNS diseases.[4–6] Air pollution exposure is associated with exacerbated cognitive dysfunction and enhanced progression of neurodegenerative processes underlying Alzheimer's (AD) and Parkinson's diseases (PD). Further, studies demonstrate evidence of structural brain effects such as white matter injury. Exposure is also associated with adverse vascular effects. The relationship between stroke and air pollution has been established over the past decade. Growing evidence supports a role in facilitating the process of atherosclerosis, particularly carotid artery disease. Air pollution exposure strongly influences CNS development and disease. This review aims to examine clinical and epidemiological effects of air pollution and its association with CNS pathologies to better set the stage for further investigation.

Study identification

The database used in the preparation of this review was PubMed, accessing dates between 2004 and 2017. Search criteria were based off the four following primary sections: cognitive dysfunction, stroke, carotid artery disease and white matter damage (Table 1). A total of 482 articles were identified.

Inclusion criteria:

1. Clinical and epidemiological studies including human subjects.
2. Studies including all known constituents of air pollution.
3. Studies examining cognitive dysfunction, stroke, carotid artery disease, white matter damage.

Exclusion criteria:

1. All animal studies.

Publications were only included if they met inclusion criteria. Initial screening included screening title and abstract of articles with further screening of article text in certain cases. 243 articles were included in the initial screen. 95 relevant articles were included in the writing of this review (Figure 1).

Air pollution and Cognitive Dysfunction

An association between air pollution and CNS impairment was first reported in the year 2000 in a small cohort of men exposed to diesel exhaust.[1] Ever since, studies of the relationship between air pollution and cognitive function have been a point of focus. Residential proximity to a major roadway is a commonly accepted method for determining long-term air pollution exposure. Ranft et al. found that older individuals (ages 68–79), who lived near a major roadway for greater than 20 years, had an increased incidence of mild cognitive impairment. Authors also found a dose-response relationship between air pollution exposure and test performances.[7] A population based cohort study of 2.2 million individuals demonstrated an association between near-major-roadway residence and dementia incidence.[8] This finding was further supported by the U.S. Department of Veteran Affairs Normative Aging Study.[9] Major roadway proximity was associated with diminished verbal learning/memory, psychomotor speed, language, and executive functioning.[10] However, no associations are found for depressive symptoms.[11]

Particulate matter is an important element of near-roadway air pollution. Age and sex adjusted models suggest associations between particulate matter and cognitive dysfunction.[12, 13] A subset analysis of the Nurses' Health Study Cognitive Cohort demonstrated significant cognitive decline in elderly women exposed to $PM_{2.5}$.[14] A longitudinal study of a northern Sweden population conducted by Oudin et al. found an association between local traffic pollution and AD/vascular dementia.[15] Ailshire et al., still found an association between $PM_{2.5}$ and cognitive dysfunction after adjusting for social and economic factors (Table 2).[16]

Air pollution is linked to the pathogenesis of neurodegenerative diseases such as PD and AD, which are associated with pronounced cognitive dysfunction. This was first observed by Ritz et al., who demonstrated a 9% increase in risk of developing PD among individuals living in Copenhagen when compared to rural residents.[17] Exposure time period is an important factor. Long-term exposure (>12 years) to PM is associated with an increased risk for AD in the elderly (>60 years old).[18] Increases in annual $PM_{2.5}$ exposure are associated with time to first hospitalization for common neurodegenerative diseases (dementia, AD, and PD).[19] The associations between densely populated urban cities, poor socioeconomic environments, and high stress living conditions could potentially confound these relationships. Older adults with dementia demonstrate exacerbations with $PM_{2.5}$ exposure and high stress living conditions.[20] Calderon-Garciduenas et al., suggest that carriers of the APOE4 allele, an independent risk factor for AD, are at higher risk of developing AD by living in a polluted environment.[21] Air pollution causes neuroinflammation and accumulation of AB42 and alpha-synuclein in the brain, providing a potential mechanism for neurodegeneration.[21, 22] Sex steroid hormones modulate multiple inflammatory pathways (APOE4, obesity, air pollution) involved in the pathogenesis of AD.[23] For example, the Estrogen Receptor-2 (ESR2) allele is implicated in gene-environment interactions.[24]

Ozone (O_3) is strongly implicated in the pathophysiological influence of air pollution.[25] Substantial evidence supports respiratory health effects of O_3,[26–28] but more recent

studies show an association between O_3 exposure and dementia. Many factors can affect the severity of cognitive dysfunction due to O_3 exposure. Known influences include gender, body mass index (BMI), and presence of the APOE4 allele.[29] Epidemiological studies have examined the effects of O_3 on cognition. Long term O_3 exposure (14-years) is associated with increased risk for vascular dementia in the elderly.[18] Further, reduced exposure to O_3 is associated with decreased hospital admissions.[30] A study in Taiwan demonstrated that high O_3 concentration and particulate matter exposure were associated with a 211% and 138% increased risk of AD onset, respectively.[31] When considering populations susceptible to O_3, those with dementia due to neurodegenerative diseases are at risk for further exacerbation. Of note, other components of air pollution, such as NO_2 and CO are also associated with increased dementia risk.[32]

Discrete components of air pollution and their functional effects on cognition have been examined, albeit in a limited capacity. A single study demonstrated that PM is associated with lower verbal learning performance, NO_2 is inversely associated with logical memory abilities, and O_3 exposure is associated with lower executive functioning.[33]

Pediatric exposure to air pollution is of unique concern due to its adverse effect during critical years of central nervous system development. Young children in Mexico City exposed to PM and O_3 concentrations above the current USA standards exhibit vascular and perivascular damage in the prefrontal white matter region. The Neurovascular units (NVU), comprised of tight junctions in endothelial cells, basement membrane, and perivascular glial sheets, were compromised in these children. NVU stability is important for maintaining brain health, whereas disruption is linked to neurodegenerative diseases including AD.[34] Children with lifetime air pollution exposures demonstrate significant increases in serum high affinity antibodies to tight junctions and neural proteins. Importantly, exposed urban children have CSF antibodies for myelin basic protein.[35] Cyclooxygenase-2 (COX2) and interleukin-1B (IL-1B) are also unregulated in the olfactory bulb and frontal cortex.[36] Further, the children exhibit astrocytic build up of B-amyloid peptide (AB42) in the frontal cortex.[36] Air pollution leads to olfactory bulb pathology in young healthy individuals, with greater vulnerability in carriers of the APOE4 allele. Collectively, these findings suggest strong proinflammatory and immune-upregulating capacities of air pollution; which may contribute to the pathogenesis of neurodegenerative disease.

Substantial evidence suggests that inflammatory mechanisms contribute to cognitive impairment secondary to air pollution exposure.[5, 37] Deregulation of fasting blood glucose may represent an additional risk factor. PM exposure is associated with higher fasting blood glucose (FBG; an independent risk factor for dementia) levels in non-diabetic individuals. Studies suggest that air pollution exposure upregulates ICAM-1 expression due to reduced epigenetic methylation secondary to high FBG.[38] This, in turn, may increase the ability for inflammatory mediators to penetrate the blood-brain barrier, leading to increased CNS inflammation.

Metabolic and structural brain alterations are observed in individuals exposed to air pollution. Children with prenatal and lifetime exposures to particulate matter demonstrate decreased hippocampal metabolite ratios; biomarker changes associated with mild cognitive

impairment in mouse models of AD. This effect is exacerbated in APOE4 carriers.[39] Elevated levels of PM likely accelerate brain atrophy typically associated with aging.[40] Higher levels of PM exposure among community dwelling women >65 years of age are associated with significantly diminished white matter volumes on structural brain magnetic resonance imaging.[41]

Functional and structural CNS changes have been documented in both pediatric and elderly cohorts exposed to air pollution, however, little is known about mid-life exposures.

Air Pollution and White Matter Injury

Air pollution is associated with white matter injury, which can manifest as neurocognitive dysfunction. Voxel-based morphometry, a magnetic resonance imaging (MRI) technique that measures regional brain volumes and tissue concentration,[42] indicates that $PM_{2.5}$ exposure is associated with smaller white matter volumes in the subcortical areas of the external capsule, extreme capsule, and calcarine cortex of older women. Interestingly, no clear associations were found between $PM_{2.5}$ exposure and hippocampal volume, suggesting white matter damage as the primary insult.[43] Residence in a highly polluted environment is associated with white matter damage in children.[37, 44] A cohort of children living in Mexico City demonstrated subcortical and prefrontal white matter hyperintense lesions compared to aged matched controls.[37] These findings are further supported by experimental evidence in dogs.[37] Children carrying the APOE4 alleles demonstrated reductions in the right frontal white matter (Table 3).[45]

Air Pollution and Stroke

The impact of air pollution on ischemic/hemorrhagic stroke is under-recognized, yet substantial. The Global Burden of Disease Study 2013 found 29.2% of the global stroke burden was attributable to air pollution.[46] Satellite reconstruction of $PM_{2.5}$ concentrations across China reveals changes in spatial distribution over time. Strikingly, the 3.25% annual growth rate in stroke mortality is attributable to increased stroke incidences in areas of highest outdoor exposure to $PM_{2.5}$.[47] A recent study suggests that $PM_{2.5}$ increases stroke mortality rate, number of hospital admission days, and related healthcare costs.[48]

Meta Analyses of Air Pollution and Stroke

To date, several meta-analyses examining the association between air pollution and stroke incidence have been conducted. A recent meta-analysis of 20 epidemiological studies examined the association between stroke incidence/mortality and long-term exposure to PM. Exposure to PM_{10} (which included results from $PM_{2.5}$) resulted in pooled hazard ratios of 1.061 (95% CI, 1.018–1.105) and 1.080 (0.992–1.177) for stroke events and stroke mortality, respectively. A high degree of heterogeneity was found when results were stratified by continent. A positive correlation between long term PM_{10} exposure and stroke events was evident in Europe and North America, however results were more ambiguous in Asia.[49] A meta-analysis of 94 studies found stroke hospital admissions to be associated with high concentrations of CO, SO_2 and NO_2. Hospital admissions with subsequent mortality due to stroke were primarily associated with increases in $PM_{2.5}$ and PM_{10}, with

weaker, but still significant, effects with O_3.[50] Additional inconsistencies and non-significant associations are documented for analyses examining hospital admissions of certain stroke sub-types.[51] While greater caution should be exercised when interpreting these conclusions, they may prove informative for future studies. A 2014 meta-analysis including 34 studies examined the transient effects of air pollution. Findings suggest increased risk for hospitalization and subsequent stroke mortality following a transient increase in the following constituents: $PM_{2.5}$, PM_{10}, SO_2, CO and NO_2. Further, this study found a stronger association with ischemic versus hemorrhagic stroke.[52] The European Study of Cohorts for Air Pollution Effects (ESCAPE) project reported that small increases (5 um/m^3) in $PM_{2.5}$ were associated with 19% increased risk in stroke. Robust findings were manifest in those greater than 60 years of age and among never-smokers (Table 4).[53]

Air Pollution and Stroke Admissions

Levels of air pollution directly correlate with the number of ischemic stroke admissions to the emergency department.[54] Positive associations exist for both ischemic and hemorrhagic stroke. Studies examining the effect of air pollution on cerebrovascular hospital admissions likely underestimate the strength of associations due to study design.[55] As evidenced throughout this section, many of these relationships are more pronounced within specific demographic subgroups.

Ambient temperature may influence air pollution and associated hospital admissions for stroke. $PM_{2.5}$ is associated with increased hemorrhagic stroke admissions on both warm (>23 C) and cold (< 23 C) days.[56] Further, $PM_{2.5}$ increases the relative risk of hospital admissions caused by ischemic stroke by 11% on warm days (>23 C) and by 4% on cold days (<23 C) in Taiwan.[57] Warm temperature (>13.5 C) was associated with increased hospital admissions for ischemic and hemorrhagic stroke during short-term exposure to $PM_{2.5}$, PM2.5–10 and PM_{10} individually.[58] Increased NO_2 exposure is positively associated with stroke admissions during the cold season in Wuhan, China, where air pollution concentrations are 50% greater in the winter.[59]

Specific constituents of $PM_{2.5}$ (nitrate, sulfate, organic carbon and elemental carbon) are individually associated with emergency room visits for hemorrhagic stroke.[60] Increases in same day 0_3 exposures are associated with a 1.9% higher total stroke hospitalization risk.[61] Men are more sensitive to the adverse effects of O_3,[61] and risk of hemorrhagic stroke hospitalization is higher among African American individuals than European Americans.[62] There is also a positive correlation between stroke admissions and NO_2 levels,[63] with long-term exposure increasing the risk of subsequent 30-day mortality.[64] Same day exposure to PM, SO_2, and O_3 are all associated with an increased risk of hospitalization due to stroke (Table 5).[65]

The effects of CO exposure on acute stroke remain unclear and potentially paradoxical. At low concentrations, CO may be neuroprotective, a phenomenon reinforced by experimental and clinical studies.[66] Consistent with these findings, Tian et al., recently reported a negative association between short-term CO exposure and emergency stroke hospitalizations.[67] By contrast, a recent meta-analysis demonstrated increased hospital admissions secondary to CO exposure.[50] Further study is warranted.

Air Pollution and Stroke Mortality

Exposures to PM_{10}, SO_2 and NO_2 increase the risk of stroke mortality.[68] In 2013, 1.37 million premature mortalities were associated with $PM_{2.5}$ in China, with 688 thousand of these mortalities attributed to stroke.[69] Air pollution is associated with stroke mortality, however specific subtypes of $PM_{2.5}$ that are attributable to this burden have yet to be ascertained.

Particle size and chemical constituents of PM may contribute to mortality associated with both ischemic and hemorrhagic strokes.[70] Among the chemical components of $PM_{2.5}$, Lin et. al demonstrated that exposures to organic carbon, elemental carbon, sulfate, nitrate, and ammonium are significantly associated with stroke mortality.[70] Long-term exposure to $PM_{2.5}$ was associated with an increased hazard of death up to 5 years after stroke, with trends favoring the ischemic subtype.[71] Residential proximity to a major roadway, a marker for air pollution, is associated with an increase in mortality rate among stroke survivors. The strongest association exists among individuals living within 100 meters from a major roadway.[72] A national multi-city time series study found that a 10 ug/m^3 increase in 2-day averaged $PM_{2.5}$ exposure is associated with a 1.76% increase in stroke incidence as well as an 1.18% increase in all cause mortality. A subset analysis found smoking and alcohol consumption were associated with greater $PM_{2.5}$ effects.[73] $PM_{<10}$, SO_2 and NO_2 exposures are significantly associated with total stroke, ischemic stroke, and hemorrhagic stroke mortalities. Further, individuals with co-morbid cardiac disease have an increased risk of ischemic stroke mortality when exposed to increased NO_2 levels (Table 6).[74]

Air pollution and cardiovascular risk factors for stroke

It is proposed that cardiovascular risk factors/mechanisms may play a critical role in the increases in stroke incidences evident on highly polluted days in urban cities. Elevations in daily maximum heart rate, heart block frequency, and atrial fibrillation are associated with O_3, NO_2 and PM.[75] Premature atrial contractions are also associated with long-term $PM_{2.5}$ exposure.[76] Short-term exposure (7 days) to PM_{10} and SO_2 is associated with cardioembolic stroke.[77] Qin et al. report that obese (BMI ≥ 30 kg/m^2) and overweight individuals (BMI 25–29 kg/m^2) may experience enhanced effects of air pollution and increased stroke risk.[78]

Public Policy and Health effects of Air Pollution on Stroke

The Environmental Protection Agency (EPA) sets policy and federal law to protect the American public from the health effects of air pollution. However, levels of air pollution generally found safe by the EPA are associated with increases in the risk of ischemic stroke within hours of exposure.[79] Epidemiological studies concerning the health effects of air pollution have principally focused on large population cities, with studies of rural populations lacking. Communities that meet the EPA's safe $PM_{2.5}$ standard still experience increases in overall mortality. Selection and information bias may contribute to gross underestimates of exposure levels.[80] In an effort to minimize the adverse health effects of air pollution, some states have passed smoke-free air laws. An 18.1% reduction in hospitalization due to stroke was seen in Florida due to such legislature.[81] Overall, smoke-free air laws are effective policy tools to reduce the incidence of stroke.

The Confounding effect of Asian Dust

Dust blown from the deserts of China and Mongolia comprise a natural phenomenon known as “Asian Dust.” PM_{10} is thought to be the primary constituent in Asian dust storms.[82] Storms are associated with increased risk of stroke hospital admissions that persists for two days following dust storms.[83] Asian studies must adjust their analysis for the confounding effect of Asian dust. Accounting for this adjustment, hemorrhagic and ischemic stroke mortality in Japan between the years of 2005 and 2010 were still increased due to same-day spikes in suspended particulate matter.[84]

Effects of Noise and Air Pollution on Stroke

Urban noise pollution potentially confounds the association between air pollution and stroke, however results are still ambiguous. A 2015 study by Hoffmann et al., demonstrated that long-term exposure to PM is associated with an increased risk of stroke, regardless of the subject’s exposure to noise.[85] However, another study that adjusted for these variables found road traffic noise is associated with ischemic stroke, while air pollution is not. Further investigations are needed.[86]

Air Pollution and Carotid Artery Disease

Carotid artery disease is a significant risk factor for stroke and cognitive impairment. In a 2010 report, Kunzli et al. demonstrated that residential proximity to a major roadway is associated with increased carotid intima-media thickness (CIMT).[87] Results from screening over 300,000 residents of New York, New Jersey and Connecticut demonstrated that $PM_{2.5}$ is an independent risk factor for carotid artery stiffness. When controlled for multiple cardiovascular risk factors, a 10 ug/mg^3 increase in $PM_{2.5}$ was associated with a two-fold increase in carotid artery stiffness.[88] African Americans living near a major roadway show a 6.67% increase in CIMT.[89] A meta-analysis, including 18,590 subjects in 8 studies, found considerable heterogeneity in the amount of CIMT thickness after $PM_{2.5}$ exposure. However, results suggested a positive correlation with mean values within the range associated with adverse cardiovascular events.[90] Short-term elevations in black carbon exposure, even up to 8 hours prior to clinical assessment, are associated with carotid artery stiffness.[91] The European Study of Cohorts for Air Pollution Effects (ESCAPE) study found positive, but non-significant, associations between $PM_{2.5}$ (as well as residence proximity to a major roadway) and increased CIMT.[92] A single 5-year prospective cohort study of 509 individuals did not find an association between long term exposure to air pollution and carotid artery atherosclerosis. However, the authors attribute these results to low ambient air pollution in the region of study and small study sample.[93] Air pollution is also linked to intracranial vascular disease. Among seniors, $PM_{2.5}$ increases resting cerebrovascular resistance and decreases cerebral blood flow velocity.[94]

Prenatal $PM_{2.5}$ and O_3 exposure are associated with carotid artery stiffness[95] and increased CIMT[96], respectively. Further, children living near major roadways exhibit increases in carotid artery stiffness.[97] The Multi-Ethnic Study of Atherosclerosis and Air Pollution reports long-term exposure to $PM_{2.5}$ is associated with increasing rates of CIMT progression. The authors also report that reductions in ambient air pollution lead to slowed

progression of carotid intima-media thickening.[98] Additional risk factors that may contribute to the effects of air pollution related to carotid-intima thickening include age, gender, and ethnicity. Elderly men[99] and those of Chinese ancestry[100] may exhibit greater CIMT when exposed to $PM_{2.5}$ (Table 7).

Conclusion

Air pollution from urban environments affects the central nervous system in a multitude of ways. Exposures impact cognitive function, stroke risk, and carotid artery disease. Pediatric and elderly populations are highly vulnerable due to CNS development and aging processes. Compiling and contextualizing current evidence should provoke thought and future investigations focused on improving health outcomes.

Acknowledgments

Funding

This research was supported by National Institute of Health grant ES024936 to W.J.M.

References

1. Kilburn KH. Effects of diesel exhaust on neurobehavioral and pulmonary functions. Archives of environmental health. 2000; 55:11–7. [PubMed: 10735514]
2. Krzyzanowski M, Cohen A. Update of WHO air quality guidelines. Air Quality, Atmosphere & Health. 2008; 1:7–13.
3. Harrison RM, Yin J. Particulate matter in the atmosphere: which particle properties are important for its effects on health? The Science of the total environment. 2000; 249:85–101. [PubMed: 10813449]
4. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, et al. The outdoor air pollution and brain health workshop. Neurotoxicology. 2012; 33:972–84. [PubMed: 22981845]
5. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 2009; 32:506–16. [PubMed: 19716187]
6. Campbell A, Oldham M, Becaria A, Bondy SC, Meacher D, Sioutas C, et al. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. Neurotoxicology. 2005; 26:133–40. [PubMed: 15527881]
7. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. Environmental research. 2009; 109:1004–11. [PubMed: 19733348]
8. Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. The Lancet.
9. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. Environmental health perspectives. 2011; 119:682–7. [PubMed: 21172758]
10. Wellenius GA, Boyle LD, Coull BA, Milberg WP, Gryparis A, Schwartz J, et al. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: results from the MOBILIZE Boston Study. J Am Geriatr Soc. 2012; 60:2075–80. [PubMed: 23126566]
11. Wang Y, Eliot MN, Koutrakis P, Gryparis A, Schwartz JD, Coull BA, et al. Ambient air pollution and depressive symptoms in older adults: results from the MOBILIZE Boston study. 2014
12. Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. Neurotoxicology. 2009; 30:231–9. [PubMed: 19150462]

13. Ailshire JA, Clarke P. Fine particulate matter air pollution and cognitive function among US older adults. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2015; 70:322–8.
14. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. Archives of internal medicine. 2012; 172:219–27. [PubMed: 22332151]
15. Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study. Environmental health perspectives. 2016; 124:306–12. [PubMed: 26305859]
16. Ailshire JA, Crimmins EM. Fine particulate matter air pollution and cognitive function among older US adults. American journal of epidemiology. 2014:kwu155.
17. Ritz B, Lee PC, Hansen J, Lassen CF, Ketzel M, Sorensen M, et al. Traffic-Related Air Pollution and Parkinson's Disease in Denmark: A Case-Control Study. Environmental health perspectives. 2016; 124:351–6. [PubMed: 26151951]
18. Wu YC, Lin YC, Yu HL, Chen JH, Chen TF, Sun Y, et al. Association between air pollutants and dementia risk in the elderly. Alzheimers Dement (Amst). 2015; 1:220–8. [PubMed: 27239507]
19. Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, et al. Long-term PM2.5 Exposure and Neurological Hospital Admissions in the Northeastern United States. Environmental health perspectives. 2016; 124:23–9. [PubMed: 25978701]
20. Ailshire J, Karraker A, Clarke P. Neighborhood social stressors, fine particulate matter air pollution, and cognitive function among older U.S. adults. Social science & medicine (1982). 2017; 172:56–63. [PubMed: 27886528]
21. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008; 36:289–310. [PubMed: 18349428]
22. Calderon-Garciduenas L, Reed W, Maronpot RR, Henriquez-Roldan C, Delgado-Chavez R, Calderon-Garciduenas A, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004; 32:650–8. [PubMed: 15513908]
23. Uchoa MF, Moser VA, Pike CJ. Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors. Front Neuroendocrinol. 2016; 43:60–82. [PubMed: 27651175]
24. Fehsel K, Schikowski T, Janner M, Huls A, Voussoughi M, Schulte T, et al. Estrogen receptor beta polymorphisms and cognitive performance in women: associations and modifications by genetic and environmental influences. J Neural Transm (Vienna). 2016; 123:1369–79. [PubMed: 27629499]
25. Huang YC. Outdoor air pollution: a global perspective. Journal of occupational and environmental medicine. 2014; 56(Suppl 10):S3–7. [PubMed: 25285972]
26. Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. Ozone and short-term mortality in 95 US urban communities, 1987–2000. Jama. 2004; 292:2372–8. [PubMed: 15547165]
27. Levy JI, Chemerynski SM, Sarnat JA. Ozone exposure and mortality: an empiric bayes metaregression analysis. Epidemiology (Cambridge, Mass). 2005; 16:458–68.
28. Chan CC, Wu TH. Effects of ambient ozone exposure on mail carriers' peak expiratory flow rates. Environmental health perspectives. 2005; 113:735–8. [PubMed: 15929897]
29. Calderon-Garciduenas L, Jewells V, Galaz-Montoya C, van Zundert B, Perez-Calatayud A, Ascencio-Ferrel E, et al. Interactive and additive influences of Gender, BMI and Apolipoprotein 4 on cognition in children chronically exposed to high concentrations of PM2.5 and ozone. APOE 4 females are at highest risk in Mexico City. Environmental research. 2016; 150:411–22. [PubMed: 27376929]
30. Linares C, Culqui D, Carmona R, Ortiz C, Diaz J. Short-term association between environmental factors and hospital admissions due to dementia in Madrid. Environmental research. 2017; 152:214–20. [PubMed: 27810678]

31. Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. Journal of Alzheimer's disease : JAD. 2015; 44:573–84. [PubMed: 25310992]
32. Chang KH, Chang MY, Muo CH, Wu TN, Chen CY, Kao CH. Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: a population-based retrospective cohort study. PloS one. 2014; 9:e103078. [PubMed: 25115939]
33. Gatto NM, Henderson VW, Hodis HN, St John JA, Lurmann F, Chen JC, et al. Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology. 2014; 40:1–7. [PubMed: 24148924]
34. Calderon-Garciduenas L, Reynoso-Robles R, Vargas-Martinez J, Gomez-Maqueo-Chew A, Perez-Guille B, Mukherjee PS, et al. Prefrontal white matter pathology in air pollution exposed Mexico City young urbanites and their potential impact on neurovascular unit dysfunction and the development of Alzheimer's disease. Environmental research. 2016; 146:404–17. [PubMed: 26829765]
35. Calderon-Garciduenas L, Vojdani A, Blaurock-Busch E, Busch Y, Friedle A, Franco-Lira M, et al. Air pollution and children: neural and tight junction antibodies and combustion metals, the role of barrier breakdown and brain immunity in neurodegeneration. Journal of Alzheimer's disease : JAD. 2015; 43:1039–58. [PubMed: 25147109]
36. Calderon-Garciduenas L, Franco-Lira M, Torres-Jardon R, Henriquez-Roldan C, Barragan-Mejia G, Valencia-Salazar G, et al. Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. Toxicol Pathol. 2007; 35:154–62. [PubMed: 17325984]
37. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain and cognition. 2008; 68:117–27. [PubMed: 18550243]
38. Peng C, Bind MC, Colicino E, Kloog I, Byun HM, Cantone L, et al. Particulate Air Pollution and Fasting Blood Glucose in Nondiabetic Individuals: Associations and Epigenetic Mediation in the Normative Aging Study, 2000–2011. Environmental health perspectives. 2016; 124:1715–21. [PubMed: 27219535]
39. Calderon-Garciduenas L, Mora-Tiscareno A, Melo-Sanchez G, Rodriguez-Diaz J, Torres-Jardon R, Styner M, et al. A Critical Proton MR Spectroscopy Marker of Alzheimer's Disease Early Neurodegenerative Change: Low Hippocampal NAA/Cr Ratio Impacts APOE varepsilon4 Mexico City Children and Their Parents. Journal of Alzheimer's disease : JAD. 2015; 48:1065–75. [PubMed: 26402110]
40. Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke. 2015; 46:1161–6. [PubMed: 25908455]
41. Chen JC, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, et al. Ambient air pollution and neurotoxicity on brain structure: Evidence from women's health initiative memory study. Annals of neurology. 2015; 78:466–76. [PubMed: 26075655]
42. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage. 2001; 14:21–36. [PubMed: 11525331]
43. Casanova R, Wang X, Reyes J, Akita Y, Serre ML, Vizuete W, et al. A Voxel-Based Morphometry Study Reveals Local Brain Structural Alterations Associated with Ambient Fine Particles in Older Women. Frontiers in human neuroscience. 2016; 10:495. [PubMed: 27790103]
44. Calderon-Garciduenas L, Engle R, Mora-Tiscareno A, Styner M, Gomez-Garza G, Zhu H, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. Brain and cognition. 2011; 77:345–55. [PubMed: 22032805]
45. Calderon-Garciduenas L, Mora-Tiscareno A, Franco-Lira M, Zhu H, Lu Z, Solorio E, et al. Decreases in Short Term Memory, IQ, and Altered Brain Metabolic Ratios in Urban Apolipoprotein epsilon4 Children Exposed to Air Pollution. Journal of Alzheimer's disease : JAD. 2015; 45:757–70. [PubMed: 25633678]

46. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet Neurology. 2016; 15:913–24. [PubMed: 27291521]
47. Liu M, Huang Y, Ma Z, Jin Z, Liu X, Wang H, et al. Spatial and temporal trends in the mortality burden of air pollution in China: 2004–2012. Environment international. 2017; 98:75–81. [PubMed: 27745948]
48. Ginsberg GM, Kaliner E, Grotto I. Mortality, hospital days and expenditures attributable to ambient air pollution from particulate matter in Israel. Israel journal of health policy research. 2016; 5:51. [PubMed: 27879970]
49. Scheers H, Jacobs L, Casas L, Nemery B, Nawrot TS. Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke: Meta-Analytical Evidence. Stroke. 2015; 46:3058–66. [PubMed: 26463695]
50. Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ (Clinical research ed). 2015; 350:h1295.
51. Wang Y, Eliot MN, Wellenius GA. Short-term changes in ambient particulate matter and risk of stroke: a systematic review and meta-analysis. Journal of the American Heart Association. 2014; 3
52. Yang WS, Wang X, Deng Q, Fan WY, Wang WY. An evidence-based appraisal of global association between air pollution and risk of stroke. International journal of cardiology. 2014; 175:307–13. [PubMed: 24866079]
53. Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. Environmental health perspectives. 2014; 122:919–25. [PubMed: 24835336]
54. Alimohammadi H, Fakhri S, Derakhshanfar H, Hosseini-Zijoud SM, Safari S, Hatamabadi HR. The Effects of Air Pollution on Ischemic Stroke Admission Rate. Chonnam medical journal. 2016; 52:53–8. [PubMed: 26866000]
55. Lokken RP, Wellenius GA, Coull BA, Burger MR, Schlaug G, Suh HH, et al. Air pollution and risk of stroke: underestimation of effect due to misclassification of time of event onset. Epidemiology (Cambridge, Mass). 2009; 20:137.
56. Chiu HF, Chang CC, Yang CY. Relationship between hemorrhagic stroke hospitalization and exposure to fine particulate air pollution in Taipei, Taiwan. Journal of toxicology and environmental health Part A. 2014; 77:1154–63. [PubMed: 25119737]
57. Chiu HF, Yang CY. Short-term effects of fine particulate air pollution on ischemic stroke occurrence: a case-crossover study. Journal of toxicology and environmental health Part A. 2013; 76:1188–97. [PubMed: 24283370]
58. Huang F, Luo Y, Guo Y, Tao L, Xu Q, Wang C, et al. Particulate Matter and Hospital Admissions for Stroke in Beijing, China: Modification Effects by Ambient Temperature. Journal of the American Heart Association. 2016; 5
59. Xiang H, Mertz KJ, Arena VC, Brink LL, Xu X, Bi Y, et al. Estimation of short-term effects of air pollution on stroke hospital admissions in Wuhan, China. PloS one. 2013; 8:e61168. [PubMed: 23593421]
60. Chen SY, Lin YL, Chang WT, Lee CT, Chan CC. Increasing emergency room visits for stroke by elevated levels of fine particulate constituents. The Science of the total environment. 2014; 473–474:446–50.
61. Xu X, Sun Y, Ha S, Talbott EO, Lissaker CT. Association between ozone exposure and onset of stroke in Allegheny County, Pennsylvania, USA, 1994–2000. Neuroepidemiology. 2013; 41:2–6. [PubMed: 23548644]
62. Montresor-Lopez JA, Yanosky JD, Mittleman MA, Sapkota A, He X, Hibbert JD, et al. Short-term exposure to ambient ozone and stroke hospital admission: A case-crossover analysis. Journal of exposure science & environmental epidemiology. 2016; 26:162–6. [PubMed: 26329139]
63. Santurtun A, Ruiz PB, Lopez-Delgado L, Sanchez-Lorenzo A, Riancho J, Zarrabeitia MT. Stroke: Temporal Trends and Association with Atmospheric Variables and Air Pollutants in Northern Spain. Cardiovascular toxicology. 2016

64. Andersen ZJ, Kristiansen LC, Andersen KK, Olsen TS, Hvidberg M, Jensen SS, et al. Stroke and long-term exposure to outdoor air pollution from nitrogen dioxide: a cohort study. Stroke. 2012; 43:320–5. [PubMed: 22052517]
65. Nascimento LF, Francisco JB, Patto MB, Antunes AM. Environmental pollutants and stroke-related hospital admissions. Cadernos de saude publica. 2012; 28:1319–24. [PubMed: 22729262]
66. Motterlini R, Otterbein LE. The therapeutic potential of carbon monoxide. Nature reviews Drug discovery. 2010; 9:728–43. [PubMed: 20811383]
67. Tian L, Qiu H, Pun VC, Ho KF, Chan CS, Yu IT. Carbon monoxide and stroke: A time series study of ambient air pollution and emergency hospitalizations. International journal of cardiology. 2015; 201:4–9. [PubMed: 26282452]
68. Chen R, Zhang Y, Yang C, Zhao Z, Xu X, Kan H. Acute effect of ambient air pollution on stroke mortality in the China air pollution and health effects study. Stroke. 2013; 44:954–60. [PubMed: 23391765]
69. Liu J, Han Y, Tang X, Zhu J, Zhu T. Estimating adult mortality attributable to PM2.5 exposure in China with assimilated PM2.5 concentrations based on a ground monitoring network. The Science of the total environment. 2016; 568:1253–62. [PubMed: 27266521]
70. Lin H, Tao J, Du Y, Liu T, Qian Z, Tian L, et al. Differentiating the effects of characteristics of PM pollution on mortality from ischemic and hemorrhagic strokes. International journal of hygiene and environmental health. 2016; 219:204–11. [PubMed: 26652230]
71. Desikan A, Crichton S, Hoang U, Barratt B, Beevers SD, Kelly FJ, et al. Effect of Exhaust-and Nonexhaust-Related Components of Particulate Matter on Long-Term Survival After Stroke. Stroke. 2016; 47:2916–22. [PubMed: 27811334]
72. Wilker EH, Mostofsky E, Lue SH, Gold D, Schwartz J, Wellenius GA, et al. Residential proximity to high-traffic roadways and poststroke mortality. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2013; 22:e366–72. [PubMed: 23721619]
73. Dai L, Zanobetti A, Koutrakis P, Schwartz JD. Associations of fine particulate matter species with mortality in the United States: a multicity time-series analysis. Environmental health perspectives. 2014; 122:837–42. [PubMed: 24800826]
74. Qian Y, Zhu M, Cai B, Yang Q, Kan H, Song G, et al. Epidemiological evidence on association between ambient air pollution and stroke mortality. Journal of epidemiology and community health. 2013; 67:635–40. [PubMed: 23661720]
75. Cakmak S, Kauri L, Shutt R, Liu L, Green MS, Mulholland M, et al. The association between ambient air quality and cardiac rate and rhythm in ambulatory subjects. Environment international. 2014; 73:365–71. [PubMed: 25226341]
76. O'Neal WT, Soliman EZ, Efird JT, Judd SE, Howard VJ, Howard G, et al. Fine particulate air pollution and premature atrial contractions: The REasons for Geographic And Racial Differences in Stroke study. Journal of exposure science & environmental epidemiology. 2016
77. Chung JW, Bang OY, Ahn K, Park SS, Park TH, Kim JG, et al. Air Pollution Is Associated With Ischemic Stroke via Cardiogenic Embolism. Stroke. 2017; 48:17–23. [PubMed: 27899751]
78. Qin XD, Qian Z, Vaughn MG, Trevathan E, Emo B, Paul G, et al. Gender-specific differences of interaction between obesity and air pollution on stroke and cardiovascular diseases in Chinese adults from a high pollution range area: A large population based cross sectional study. The Science of the total environment. 2015; 529:243–8. [PubMed: 26022408]
79. Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, et al. Ambient air pollution and the risk of acute ischemic stroke. Archives of internal medicine. 2012; 172:229–34. [PubMed: 22332153]
80. Lee M, Koutrakis P, Coull B, Kloog I, Schwartz J. Acute effect of fine particulate matter on mortality in three Southeastern states from 2007–2011. Journal of exposure science & environmental epidemiology. 2016; 26:173–9. [PubMed: 26306925]
81. Loomis BR, Juster HR. Association of indoor smoke-free air laws with hospital admissions for acute myocardial infarction and stroke in three states. Journal of environmental and public health. 2012; 2012:589018. [PubMed: 22778759]

82. Cheng MT, Lin YC, Chio CP, Wang CF, Kuo CY. Characteristics of aerosols collected in central Taiwan during an Asian dust event in spring 2000. Chemosphere. 2005; 61:1439–50. [PubMed: 16005941]
83. Kang JH, Liu TC, Keller J, Lin HC. Asian dust storm events are associated with an acute increase in stroke hospitalisation. Journal of epidemiology and community health. 2013; 67:125–31. [PubMed: 22826296]
84. Yorifuji T, Kashima S. Associations of particulate matter with stroke mortality: a multicity study in Japan. Journal of occupational and environmental medicine. 2013; 55:768–71. [PubMed: 23787566]
85. Hoffmann B, Weinmayr G, Hennig F, Fuks K, Moebus S, Weimar C, et al. Air quality, stroke, and coronary events: results of the Heinz Nixdorf Recall Study from the Ruhr Region. Deutsches Arzteblatt international. 2015; 112:195–201. [PubMed: 25838021]
86. Sorensen M, Luhdorf P, Ketzel M, Andersen ZJ, Tjonneland A, Overvad K, et al. Combined effects of road traffic noise and ambient air pollution in relation to risk for stroke? Environmental research. 2014; 133:49–55. [PubMed: 24906068]
87. Kunzli N, Jerrett M, Garcia-Esteban R, Basagana X, Beckermann B, Gilliland F, et al. Ambient air pollution and the progression of atherosclerosis in adults. PloS one. 2010; 5:e9096. [PubMed: 20161713]
88. Newman JD, Thurston GD, Cromar K, Guo Y, Rockman CB, Fisher EA, et al. Particulate air pollution and carotid artery stenosis. Journal of the American College of Cardiology. 2015; 65:1150–1. [PubMed: 25748098]
89. Wang Y, Wellenius GA, Hickson DA, Gjelsvik A, Eaton CB, Wyatt SB. Residential Proximity to Traffic-Related Pollution and Atherosclerosis in 4 Vascular Beds Among African-American Adults: Results From the Jackson Heart Study. American journal of epidemiology. 2016; 184:732–43.
90. Akintoye E, Shi L, Obaitan I, Olusunmade M, Wang Y, Newman JD, et al. Association between fine particulate matter exposure and subclinical atherosclerosis: A meta-analysis. European journal of preventive cardiology. 2016; 23:602–12. [PubMed: 26025448]
91. Provost EB, Louwies T, Cox B, Op't Roodt J, Solmi F, Dons E, et al. Short-term fluctuations in personal black carbon exposure are associated with rapid changes in carotid arterial stiffening. Environment international. 2016; 88:228–34. [PubMed: 26773393]
92. Perez L, Wolf K, Hennig F, Penell J, Basagana X, Foraster M, et al. Air pollution and atherosclerosis: a cross-sectional analysis of four European cohort studies in the ESCAPE study. Environmental health perspectives. 2015; 123:597–605. [PubMed: 25625785]
93. Gan WQ, Allen RW, Brauer M, Davies HW, Mancini GB, Lear SA. Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: a prospective cohort study. BMJ open. 2014; 4:e004743.
94. Wellenius GA, Boyle LD, Wilker EH, Sorond FA, Coull BA, Koutrakis P, et al. Ambient fine particulate matter alters cerebral hemodynamics in the elderly. Stroke. 2013; 44:1532–6. [PubMed: 23709640]
95. Breton CV, Mack WJ, Yao J, Berhane K, Amadeus M, Lurmann F, et al. Prenatal Air Pollution Exposure and Early Cardiovascular Phenotypes in Young Adults. PloS one. 2016; 11:e0150825. [PubMed: 26950592]
96. Breton CV, Wang X, Mack WJ, Berhane K, Lopez M, Islam TS, et al. Childhood air pollutant exposure and carotid artery intima-media thickness in young adults. Circulation. 2012; 126:1614–20. [PubMed: 22896588]
97. Iannuzzi A, Verga MC, Renis M, Schiavo A, Salvatore V, Santoriello C, et al. Air pollution and carotid arterial stiffness in children. Cardiology in the young. 2010; 20:186–90. [PubMed: 20219153]
98. Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, Diez Roux AV, et al. Fine particulate air pollution and the progression of carotid intima-medial thickness: a prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution. PLoS medicine. 2013; 10:e1001430. [PubMed: 23637576]

99. Wilker EH, Mittleman MA, Coull BA, Gryparis A, Bots ML, Schwartz J, et al. Long-term exposure to black carbon and carotid intima-media thickness: the normative aging study. Environmental health perspectives. 2013; 121:1061–7. [PubMed: 23820848]

100. Jones MR, Diez-Roux AV, O'Neill MS, Guallar E, Sharrett AR, Post W, et al. Ambient air pollution and racial/ethnic differences in carotid intima-media thickness in the Multi-Ethnic Study of Atherosclerosis (MESA). Journal of epidemiology and community health. 2015; 69:1191–8. [PubMed: 26142402]

Highlights

- Clinical and epidemiological studies have established adverse effects of air pollution on the central nervous system.
- Air pollution is associated with cognitive dysfunction, Alzheimer's Disease and Parkinson's disease.
- Air pollution is associated with structural brain effects and white matter injury.
- Adverse outcomes in stroke and carotid artery disease are associated with air pollution.
- This review examines the clinical effects of air pollution on neurological health.

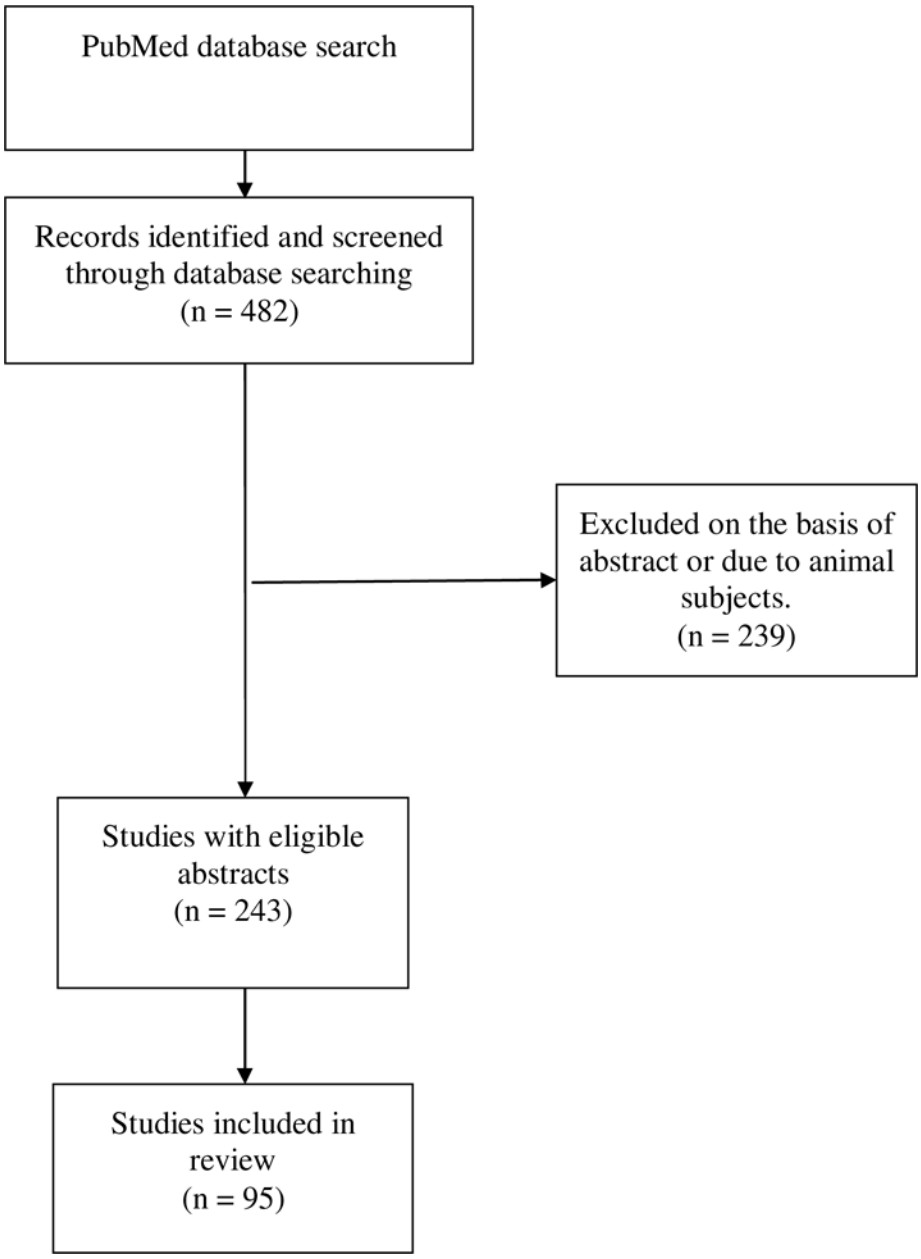

Figure 1.
Search strategy.

Table 1

Search Criteria

Section	Search Terms
Cognitive dysfunction	• “nPM” or “air pollution” and “dementia” • “nPM” or “air pollution” and “Alzheimer’s”
Stroke	• “nPM” or “air pollution” and “stroke” • “nPM” or “air pollution” and “hypoperfusion”
Carotid Artery Disease	• “nPM” or “air pollution” and “carotid artery”
White Matter Damage	• “nPM” or “air pollution” and “white matter injury”

Table 2

Air Pollution and Cognitive Dysfunction

Author	Study	N	Age (years)	Air Pollutants	Summary
Kilburn et al., 2000 [1]	Effects of diesel exhaust on neurobehavioral and pulmonary functions	16	42–60	Diesel Exhaust	Significant association of diesel exhaust with decreased performance on neuropsychological tests
Ranft et al., 2009 [7]	Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly.	399	68–79	PM_{10}	Significant association of PM_{10} with mild cognitive impairment
Chen et al., 2017 [8]	Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study	~2.2 million	55–85	$PM_{2.5}$, NO_2, roadway proximity	Significant association of air pollution and roadway proximity with increased dementia incidence
Power et al., 2011 [9]	VA Normative Aging Study	680	50–99	Black Carbon	Significant association of black carbon with poor cognitive performance in older men
Wellenius et al., 2012 [10]	Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors	765	≥65	Roadway proximity	Roadway proximity associated with decreased verbal learning/memory, psychomotor speed, language, and executive functioning
Wang et al., 2014 [11]	Ambient air pollution and depressive symptoms in older adults: results from the MOBILIZE Boston study	732	≥65	Roadway pollution	No association between ambient air pollution and depressive symptoms
Chen & Schwartz, 2009 [12]	Neurobehavioral effects of ambient air pollution on cognitive performance in US adults.	1764	20–59	$PM_{2.5}$, O_3	Significant association of $PM_{2.5}$ and O_3 with poor results on neurobehavioral tests
Ailshire & Clarke, 2015 [13]	2001/2002 Americans' Changing Lives Study	780	≥55	PM2.5	Significant association of PM2.5 and cognitive dysfunction
Weuve et al., 2012 [14]	Nurses' Health Study Cognitive Cohort	19,409	70–81	PM_{10}, $PM_{2.5}$	Significant association of PM_{10} and $PM_{2.5}$ with cognitive decline in older women
Oudin et al., 2016 [15]	Betula Study	1,806	55–85	NOx	Significant association of NOx and AD/vascular dementia
Ailshire & Crimmins, 2014 [16]	Health and Retirement Study	13,996	50–102	$PM_{2.5}$	Significant association of $PM_{2.5}$ with episodic memory impairment

J Clin Neurosci. Author manuscript; available in PMC 2018 September 01.

Table 3

Air Pollution and White Matter Injury

Author	Study	N	Air Pollutants	Summary
Casanova et al., 2016 [43]	A Voxel-Based Morphometry Study Reveals Local Brain Structural Alterations Associated with Ambient Fine Particles in Older Women	1365	$PM_{2.5}$	Significant association of $PM_{2.5}$ exposure with smaller white matter volumes in the subcortical areas of the external capsule, extreme capsule, and calcarine cortex of older women
Calderon-Garciduenas et al., 2008 [37]	Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs	73	O_3, PM_{10}, SO_2, NO_2, CO, Pb	Significant association of highly polluted environment with white matter damage in children, namely the presence of subcortical and prefrontal white matter hyperintense lesions compared to aged matched controls
Calderon-Garciduenas et al., 2015 [45]	Decreases in Short Term Memory, IQ, and Altered Brain Metabolic Ratios in Urban Apolipoprotein 4 Children Exposed to Air Pollution	50	$PM_{2.5}$, O_3	Children carrying the APOE e4 alleles demonstrated reductions in the right frontal white matter

Table 4

Meta Analyses of Air Pollution and Stroke

Author	Study	Number of studies	Air Pollutants	Summary
Scheers et al., 2015 [49]	Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke: Meta-Analytical Evidence	20 studies	$PM_{2.5}$, PM_{10}	Increase in stroke events and stroke mortality. Continental geographic variability shown
Shah et al., 2015 [50]	Short term exposure to air pollution and stroke: systematic review and meta-analysis	94 studies	$PM_{2.5}$, PM_{10}, SO_2, CO and NO_2	Increases in hospital admissions and mortality due to stroke
Wang et al., 2014 [51]	Short-term changes in ambient particulate matter and risk of stroke: a systematic review and meta-analysis	45 studies	$PM_{2.5}$, PM_{10}	Increases in total cerebrovascular disease mortality
Yang et al., 2014 [52]	An evidence-based appraisal of global association between air pollution and risk of stroke	34 studies	$PM_{2.5}$, PM_{10}, SO_2, CO and NO_2	Transient increases in air pollution increase risk of stroke hospitalization and mortality

Table 5

Air Pollution and Stroke Admissions

Author	Study	N	Air Pollutants	Summary
Alimohammadi et al., 2016 [54]	The Effects of Air Pollution on Ischemic Stroke Admission Rate	379	PM_{10}, $PM_{2.5}$, NO_2, O_3 and SO_2	Air pollution levels correlate with ischemic stroke admission
Chiu et al., 2014 [56]	Relationship between hemorrhagic stroke hospitalization and exposure to fine particulate air pollution in Taipei, Taiwan	2.64 million	$PM_{2.5}$	Air temperature influences air pollution and hospital admissions for stroke
Xiang et al., 2013 [59]	Estimation of short-term effects of air pollution on stroke hospital admissions in Wuhan, China	10,663 hospital admissions	NO_2	NO_2 levels during the cold season is associated with increase stroke admissions
Chen et al., 2014 [60]	Increasing emergency room visits for stroke by elevated levels of fine particulate constituents	3,362	nitrate, sulfate, organic carbon and elemental carbon	Each individual constituent associated with hemorrhagic stroke
Xu et al., 2013 [61]	Association between ozone exposure and onset of stroke in Allegheny County, Pennsylvania, USA, 1994–2000	26,210	O_3	Same day O_3 exposure associated with increase total stroke hospitalization risk
Montresor-Lopez et al., 2016 [62]	Short-term exposure to ambient ozone and stroke hospital admission: A case-crossover analysis	35,413	O_3	O_3 associated with increased stroke hospitalization for African Americans compared to European Americans

Table 6

Air Pollution and Stroke Mortality

Author	Study	N	Air Pollutants	Summary
Chen et al., 2013 [68]	Acute effect of ambient air pollution on stroke mortality in the China air pollution and health effects study	~45 million	PM_{10}, SO_2 and NO_2	PM_{10}, SO_2 and NO_2 increase the risk of stroke mortality
Liu et al., 2016 [69]	Estimating adult mortality attributable to PM2.5 exposure in China with assimilated PM2.5 concentrations based on a ground monitoring network	*	$PM_{2.5}$	Increases in premature mortalities and stroke
Lin et al., 2016 [70]	Differentiating the effects of characteristics of PM pollution on mortality from ischemic and hemorrhagic strokes	5.5 million	organic carbon, elemental carbon, sulfate, nitrate, and ammonium	Increase in stroke mortality
Desikan et al., 2016 [71]	Effect of Exhaust- and Nonexhaust-Related Components of Particulate Matter on Long-Term Survival After Stroke	357,308	$PM_{2.5}$	increase mortality risk up to 5 years post stroke
Wilker et al., 2013 [72]	Residential proximity to high-traffic roadways and post stroke mortality	1,683	Roadway proximity	Highway proximity increases mortality rate among stroke survivors
Dai et al., 2014 [73]	Associations of fine particulate matter species with mortality in the United States: a multicity time-series analysis	4,473,519	$PM_{2.5}$	Increased risk of stroke and all-cause mortality
Qian et al., 2013	Epidemiological evidence on association between ambient air pollution and stroke mortality	13.8 million	PM_{10}, SO_2 and NO_2	Transient increases in air pollution associated with total, ischemic and hemorrhagic strokes

Table 7

Air Pollution and Carotid Artery Disease

Author	Study	N	Air Pollutants	Summary
Kunzli et al., 2010 [87]	Ambient air pollution and the progression of atherosclerosis in adults	1483	Road proximity and $PM_{2.5}$	Increase in CIMT
Newman et al., 2015 [88]	Particulate air pollution and carotid artery stenosis	307,444	$PM_{2.5}$	An independent risk factor for carotid artery stiffness
Wang et al., 2016 [89]	Residential Proximity to Traffic-Related Pollution and Atherosclerosis in 4 Vascular Beds Among African-American Adults: Results From the Jackson Heart Study	4,800	Road proximity	African Americans show increase in CIMT
Akintoye et al., 2016 [90]	Association between fine particulate matter exposure and subclinical atherosclerosis: A meta-analysis	11,947	$PM_{2.5}$	CIMT values within range of adverse cardiovascular events
Provost et al., 2016 [91]	Short-term fluctuations in personal black carbon exposure are associated with rapid changes in carotid arterial stiffening	54	Black carbon	Short term elevations associated with carotid artery stiffness
Perez et al., 2015 [92]	Air pollution and atherosclerosis: a cross-sectional analysis of four European cohort studies in the ESCAPE study	9,183	Road proximity and $PM_{2.5}$	Positive, but non-significant associations with increased CIMT
Gan et al., 2014 [93]	Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: a prospective cohort study	509	black carbon, fine particles, nitrogen dioxide and nitric oxide	No association with carotid artery atherosclerosis
Breton et al., 2016 [95]	Prenatal Air Pollution Exposure and Early Cardiovascular Phenotypes in Young Adults	768	$PM_{2.5}$ and O_3	Prenatal exposure, increases in carotid artery stiffness
Breton et al., 2012 [96]	Childhood air pollutant exposure and carotid artery intima-media thickness in young adults	861	$PM_{2.5}$ and O_3	Prenatal exposure, increases in CIMT
Iannuzzi et al., 2010 [97]	Air pollution and carotid arterial stiffness in children	52	Road proximity	Increases in carotid artery stiffness
Adar et al., 2013 [98]	Fine particulate air pollution and the progression of carotid intima-medial thickness: a prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution	5,660	$PM_{2.5}$	Reductions slowed CIMT progression
Wilker et al., 2013 [99]	Long-term exposure to black carbon and carotid intima-media thickness: the normative aging study	380	Black carbon	Increase in CIMT in elderly men