Evaluation of the Effect of Air Pollution on Cognitive Functions, Cognitive Decline, and Dementia

Fettah Eren, Serefnur Ozturk

Department of Neurology, Faculty of Medicine, Selcuk University, School of Medicine, Konya, Turkey

Abstract

The incidence of dementia increases with aging. It is known that the disease brings with it many problems for patients and caregivers. Studies on the development of various treatment modalities for the disease continue. However, the main step in the management of this process is the identification of dementia risk factors. The prevalence of dementia is higher in those living in urban areas where exposure to air pollution and chemical effects is higher. This situation supports the relationship of air pollution, which has increased especially in the last decade, with the increase in cognitive decline and dementia frequency. Exposure to air pollution is one of the well-known causes of neurological diseases. This condition was associated with significant disability and early mortality. Although the close relationship between cerebrovascular diseases and air pollution is known, current studies also reveal the relationship between neuropsychiatric diseases and air pollution. It has been shown that microparticles inhaled through the respiratory system are responsible for this situation. Although individual sensitivity is prominent in the disease, the etiopathogenetic process remains relatively uncertain. Researchers have detected that the relationship between dementia and air pollution is because of the effects of increased proinflammatory mediators and reactive oxygen radicals. Evaluation of air pollution, which plays a role in the etiopathogenesis of dementia, in the light of current literature and revealing this relationship will provide important contributions in taking the necessary measures to prevent the disease.

Keywords: Air pollution, cognitive decline, cognitive functions, dementia, neurological diseases

INTRODUCTION

Studies on the effects of environmental pollutants on the central and peripheral nervous system have increased significantly, especially in the last decade. In line with a report recently published by the Lancet Commission, air pollution has been identified as an environmental risk factor associated with many systemic and neurological diseases. In addition, this situation is emphasized as one of the causes of early mortality.[1] Diseases caused by environmental pollution constitute 16% of global deaths, which is 15 times more than all war and violence events, and it causes mortality three times more than infective diseases, such as AIDS and tuberculosis. These results emphasize the seriousness of the effects of environmental pollutants on mortality. The World Health Organization (WHO) data showed that 12.6 million premature deaths occur annually because of unhealthy and unsuitable environmental conditions. The vast majority (~8.2 million) of these are caused by non-infective environmental pollution. The most common disease group caused by environmental pollutants is stroke and coronary artery disease. These diseases cause approximately five million of air pollution-related mortality.[2] Dementia, which is more common in adults and elderly individuals, has also been found to be associated with environmental pollution and is one of the important causes of mortality.[3]

Air pollution is the most common among all environmental risk factors. In the modern world, the rapid increase in the global industrial system, millions of vehicles in traffic, and the fuels used for heating are among the factors that cause air pollution. Outdoor air pollution, which is caused by exposure to agents with a particulate matter <2.5 µm (PM2.5), ranks fifth if all global health risk factors are taken into account, in line with 2015 data.[4] The current WHO data showed that approximately nine out of 10 people all over the world are exposed to air pollution for most of their lives. This situation can result in many neuro-vascular and neurocognitive diseases.[2,3]

According to the results of the Global Exposure-Mortality Model, more than 790,000 of the global premature deaths occur annually in Europe alone because of air pollution.[3]

Air pollution is one of the leading risk factors worldwide for non-infectious diseases, including cardiovascular, respiratory, metabolic diseases, and cancer. Studies conducted in recent years have shown that particulate matter causing air pollution has more harmful effects if the size is less than 2.5 µm (PM2.5).
These particulate substances have a greater potential to enter the systemic circulation and cause disease. The size of ultra-fine particulate matter is less than 0.1 µm (PM0.1). Because of their structural properties, these particulate substances can pass through the blood-brain barrier (BBB) more easily and invade the central nervous system (CNS) from the pulmonary system. This triggers a series of chemical reactions in the CNS. The underlying pathophysiological process has been found to be associated with the structural reactive surface or toxic components of particulate matter.[1,6] Increasing scientific evidence shows the relationship between increased neuroinflammation and reactive oxygen radicals (ROS) in the pathophysiology of neurodegenerative diseases, especially air pollution and dementia. Exposure to microparticle substances as a result of air pollution triggers pro-inflammatory mediators and ROS production through the microglial system.[7]

Neurotoxicological studies, the number of which has been increasing in recent years, show that exposure to toxic particulate matter in the air causes oxidative stress and widespread neuroinflammation. In addition, experimental studies have shown that these neurotoxic substances trigger a chain of toxic reactions that affect more than one brain region.[8] Neuropathological studies, especially in children and young adults living in urban areas with high air pollution, have shown that there are signs of premature aging in the brain.[9] The results revealed the association of air pollution with a neurocognitive decline.

The purpose of this review is to make a general assessment of the impact of air pollution and particulate substances on the CNS, to reveal its effects on neurocognitive functions, and to present a current perspective.

**FACTORS CAUSING AIR POLLUTION**

Air pollution contains a heterogeneous toxicological structure created by many chemical substances and resulting from a chain of different chemical reactions. This heterogeneous structure contains particles suspended in the air, including organic carbon, elementary carbon, nitrate, sulfate, and metals (iron, vanadium, nickel, etc.); liquid droplets; gases (ozone (O3), carbon monoxide (CO), sulfur dioxide (SO₂), nitrogen oxides); gaseous organic compounds (e.g., non-methane volatile organic); polycyclic aromatic hydrocarbons; polychlorinated biphenyls; and bacterial endotoxins [Figure 1]. These components have increased their existence especially as a result of the industrial revolution and the dominance of urban life. The factors that cause air pollution in urban life mainly arise as a result of gas or vapor phase compounds arising from combustion. These compounds constitute approximately 90% of all air pollution and potentially cause serious systemic toxicity because of the high particulate matter count.[10]

Particulate matter in air pollution is classified into three main groups according to their size. These are ultrafine particulate matter (PM0.1) with an aerodynamic diameter less than 0.1 µm, the fine particulate matter between 0.1 and 2.5 µm, and coarse particulate matter (PM10) between 2.5 and 10 µm [Figure 2]. There is an inverse relationship between the size of the particulate matter diameter and its potential to cause adverse systemic and neurological effects. As the size of particulate matter decreases, its potential to cause adverse effects increases.[11,12] The reason for this is that as the size of particulate matter decreases, invasion into systemic and neuronal tissues becomes easier and as a result, the potential for negative effects increases.

**PATHOPHYSIOLOGY OF AIR POLLUTION-RELATED COGNITIVE DISORDERS**

Air pollution triggers many systemic diseases, especially vascular diseases, and causes a significant portion of global deaths. Accordingly, air pollution has been defined as a more serious risk factor for global deaths than smoking.[13]

Small-sized particulate matter resulting from air pollution impairs vascular endothelial function and triggers vascular inflammation and oxidative stress. This situation poses a serious risk particularly for neurovascular and cardiovascular diseases.[11] Air pollution creates more serious consequences when combined with hypertension, hyperlipidemia, and diabetes mellitus, which are classical risk factors for vascular endothelial structure.[14,15] Experimental and clinical studies show that air pollution disrupts the nitric oxide balance in vascular structures and induces the pathological process.[11]
For the vascular structures to maintain their antithrombotic, anti-inflammatory, and antioxidant effects, a solid endothelial structure is required. However, air pollution disrupts the vascular endothelial structure and creates a serious risk factor for vascular diseases.\(^{16}\) Considering that the frequency of dementia increases with the increase in vascular disease risk factors, the relationship between air pollution and dementia can be explained more easily.

In the light of the data obtained as a result of experimental and clinical studies, oxidative stress resulting from various cellular, inflammatory, and molecular processes increases the risk of cerebrovascular and neuropsychiatric diseases by affecting the CNS. Despite all this information, there is still not enough information on the mechanisms between air pollution and neurocognitive disorders. Although it is known that this process occurs as a result of multifactorial interaction, a close relationship has been determined with many lifestyle changes. There are two possible ways that particulate matter from air pollution can reach the brain. The first of these is that particulate matter reaches the brain by the direct route. The direct contact of the nasal mucosa with the surrounding air creates an entry route to the CNS through the olfactory structure. Particularly small particles can reach other brain regions via olfactory neurons or trigeminal nerves. In addition, the second mechanism is reaching the brain via systemic inflammatory cells in the pulmonary structures, which has been shown to be the most frequently used route. The particulate matter here enters the systemic circulation through the alveolar region, especially through the phagocytic system, and then this structure passes through the BBB and invades the brain parenchyma [Figure 3].\(^{17,18}\)

Microparticle substances in the CNS cause neuronal damage through three main mechanisms.\(^{19}\) The first of these is that long-term air pollution causes systemic inflammation and triggers the proinflammatory process. This proinflammatory process changes the permeability of the BBB structure. As a result, ROS production increases in CNS as a result of neuroimmune interaction. This is the main mechanism contributing to the cognitive impairment and dementia phenotype, and the chronic oxidative process plays a fundamental role here.\(^{20,21}\) Apart from this, the second mechanism is the direct change of BBB permeability independent of the immune system of particulate matter. Third, particulate matter triggers sympathetic activation by affecting the autonomic nervous system.\(^{22,23}\)

Consequently, air pollution accelerates the accumulation of amyloid beta-42 (Ab-42), which is a known cause of neuronal dysfunction as a result of a complex interaction of all these mechanisms. Exposure to air pollution for a long time in the process causes Ab-42 peptide and neurofibrillary tangle formation in the brain.\(^{24}\)

**Studies on the Relationship Between Air Pollution and Neurocognitive Disease**

There are many clinical and experimental studies evaluating the effects of air pollution on the cardiovascular and respiratory systems. The effect of these relationships on morbidity and premature death is relatively well known. There are studies with less evidence about the effects of air pollution on CNS.\(^{25}\) Studies on this subject, especially in recent years, support the negative effects of microparticle substances that occur because of air pollution on brain health.

**Observational and epidemiological studies**

**The relationship between air pollution and dementia**

Two meta-analysis results on the relationship between microparticle substances resulting from air pollution and dementia have been published recently. Four large-scale cohort studies from the UK, Taiwan, Canada, and the USA involving more than 12 million people revealed that air pollution was associated with a more than three-fold increase in dementia risk (HR 3.26, 95% CI 1.20–5.31). Besides, as a result of subgroup analyzes, it was shown that it causes an approximately
five-fold increase in the risk of Alzheimer’s type dementia (HR 4.82, 95% CI 2.28–7.36). In the other meta-analysis in which the relationship between particulate matter and dementia was evaluated, 80 studies with wider participation covering 26 countries were evaluated. As a result, long-term exposure to air pollution-related particulate matter was associated with the risk of dementia (OR 1.16 95% CI 1.07–1.26) and especially Alzheimer’s type dementia (OR 3.26, 95% 0.84–12.74). Two recent studies clearly demonstrate the relationship between air pollution and dementia and cardiovascular diseases. A recent prospective study in Sweden demonstrated a causal and complex relationship between air pollution and heart failure, ischemic heart disease, stroke, and dementia. As a result, it was emphasized that the increased risk of dementia may be a product of the same pathophysiological process as cardiovascular diseases and stroke. Research has demonstrated that air pollution negatively affects cognitive functions along with an increased risk of cardiovascular disease. In support of these findings, a study reported from Italy showed that air pollution increases the risk of vascular dementia. However, the relationship between senile dementia and Alzheimer’s type dementia and air pollution has not been determined as clearly as vascular dementia. These findings are supported by several other studies. The findings show the relationship of air pollution with the development of many different dementias, especially vascular dementia.

The relationship between air pollution and cognitive functions

It is known that exposure to chronic air pollution causes long-term neuronal degeneration and cognitive dysfunction because of cumulative neurotoxic effects. The data of a study conducted in the USA showed that long-term exposure to particulate matter and nitrogen dioxide (NO2) causes a significant regression in cognitive functions in the elderly population. As a result of a study conducted on the elderly population in Italy showed that air pollution increases the risk of vascular dementia. However, the relationship between senile dementia and Alzheimer’s type dementia and air pollution has not been determined as clearly as vascular dementia. These findings are supported by several other studies. The findings show the relationship of air pollution with the development of many different dementias, especially vascular dementia.

Experimental animal studies

Considering the experimental animal studies evaluating the effects of air pollution on cognitive functions, the importance and pathogenesis of this issue can be better understood. Exposure of animals to particulate matter and/or NO2 triggers a chain of structural and chemical events in the brain. Exposure to particulate matter triggers many neurodegenerative disease processes, especially dementia. As a result, it was shown that cognitive deficits and memory impairment occur as a result of exposure to air pollution. Air pollution disrupts the balance of neurotransmitters in the CNS, increases the activity of neuronal inflammatory cells, and triggers a series of reactions with impaired BBB structure. Exposure to air pollution in the intrauterine and/or postpartum period leads to deterioration of neuronal functions and neurodevelopmental diseases. A number of differences are observed in the structural features of the brain of animals exposed to the chemical effects of air pollution. Cerebral cortical atrophy and ventriculomegaly are among the most common structural changes. Besides it was shown that there are a number of functional changes as well as structural changes. In particular, activation of microglia plays a key role in this process. The increase in microglia activity reveals the release of a number of neurotoxic cytokines, especially tumor necrosis factor-α and interleukin 1 (IL-1), and ROS activity.

The relationship between air pollution and dementia in experimental studies

In a study using an experimental Alzheimer’s disease mouse model, it was shown that the formation of Ab-42 increased and the neuropathological process progressed with exposure to air pollution caused by exhaust gas. However, clinically, any effect on spatial working memory was not demonstrated when mice were evaluated with the Y-maze and X-maze tests. In addition, no effects were shown on inflammatory markers IL-1, chemokine (CC motif) ligand 5, and monocyte chemoattractant protein-1. In a similar experimental study on rats, it was shown that air pollution triggered the glial inflammatory response via Toll-like receptor-4. In line with these results, it was revealed that air pollution is associated with neuroinflammation, cognitive slowing, and a dementia-like picture. Yan et al. in an experimental study conducted with NO2 inhalation, the modulation change of prostaglandin E2 via cyclooxygenase-2 affects astrocyte and microglia function and creates a process similar to Alzheimer’s disease. In addition, the results showed that spatial learning and memory were impaired, and there was significant Ab-42 accumulation, similar to Alzheimer’s disease. It was shown that because of exposure of rats to nanoparticle substances, dementia-like clinical symptoms occur with increased neuroinflammatory mediators (Ab-42, ROS, hydrogen peroxide, and NO2). In a recent study, it was shown that neuronal amyloidogenesis is increased through oxidative damage in mice exposed to traffic-derived nanoparticle substances, and this process is closely related to dementia.

The relationship between air pollution and cognitive functions in experimental studies

In a study conducted on aged mice with experimental Alzheimer’s disease, it was shown that selective behavioral and
cognitive changes occur as a result of giving ultra-microparticle substances to the environment.\[^{46}\] In a study conducted on mice evaluated with repetitive learning, memory, and compulsive behavior program, a significant decline in cognitive functions was detected with the administration of ultra-microparticle substances to the environment and inhalation of these substances.\[^{47}\] Similar to the dementia process, the slowdown in cognitive functions was found to be associated with microglia activation. As a result of the effect of particulate matter on microglia cells, learning and memory functions are negatively affected.\[^{48}\] Long-term exposure to solvents, volatile organic, and/or inorganic compounds retards cognitive functions. It was shown that learning function is impaired in mice exposed to volatile organic compounds and CO. Impairment of cognitive functions in these subjects has been associated with disruption of neurotransmitter balance in the brain and induction of oxidative stress.\[^{49}\]

In many experimental studies, it has been shown that exposure to chemical compounds and particulate matter impairs neuronal behavior. It has been clarified that exposure to PM2.5, SO\(_2\), and NO\(_x\) triggers this process by causing mitochondrial dysfunction.\[^{6,50}\] It has been shown that exposure of mice to particulate matter from air pollution affects maternal behavior and impairs the ability to recognize new generations. It has been revealed that exposure to dusty particulate matter in the environment in addition to chemicals triggers the cerebral inflammatory response, reveals oxidative stress, and impairs hippocampal functions.\[^{22,49}\] In all these studies, it has been indicated experimentally that air pollution adversely affects cognitive functions through many different mechanisms. It has been revealed that this process does not occur with a single mechanism, but is the product of a complex process.

**Conclusion**

In this review, literature on the effect of air pollution on cognitive functions and its relationship with dementia has been summarized. Cognitive dysfunction, which occurs as a result of a complex interaction of many pathophysiological mechanisms, occurs in particular as a result of local and/or systemic inflammation and oxidative stress. Considering that people living in many parts of the world are exposed to air pollution for the majority of their lives, it is obvious that there is a serious health problem that can be attributed cumulatively. Because the studies on this subject are mostly experimental, the data obtained prevent reaching a definite conclusion. In addition, the fact that neurodegenerative diseases such as dementia occur as a result of a relatively complex etiopathogenetic process makes it difficult to establish a primary relationship. The duration, dose, and variety of exposure to particulate matter because of air pollution can also cause different results. However, when the results of all studies are examined, it is clearly seen that there is a relationship between air pollution, cognitive dysfunction, and dementia. Air pollution reveals the picture of dementia by increasing age-related oxidative changes in the brain.

In addition to all these, air pollution is not an individual risk factor, such as smoking, immobility, alcohol use, and an unhealthy diet. This problem is a serious public health problem that concerns the whole society and has the potential to cause disease in large masses. Besides, the effects of air pollution on human health are of high interest to the scientific and public communities. Considering today’s conditions in which industrialization has increased, the problem of air pollution is increasing gradually. If the risk of neurocognitive disease can be reduced as a result of controlling air pollution, there will be enormous potential for cost savings in health care as well as individual benefits. The main step in solving this problem will be emphasizing the relationship of air pollution with neurocognitive diseases such as dementia. Further work is needed to establish large cohorts and standardized data that will allow us to obtain stronger results.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Landrigan PJ, Fuller R, Acosta N Jr, Adeyi O, Arnold R, Basu NN, et al. The Lancet Commission on pollution and health. Lancet 2018;391:462-512.
2. World Health Organization. Preventing disease through healthy environments: A global assessment of the burden of disease from environmental risks. Available from: https://apps.who.int/iris/handle/10665/204585. [Last accessed on 2016 May 11].
3. Hahad O, Lelieveld J, Birklein F, Lieb K, Daiber A, Münzel T. Ambient air pollution increases the risk of cerebrovascular and neuropsychiatric disorders through induction of inflammation and oxidative stress. Int J Mol Sci 2020;21:4306.
4. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estepe K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. Lancet 2017;389:1907-18.
5. Lelieveld J, Klingmüller K, Pozzer A, Pöschl U, Faini M, Daiber A, et al. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Eur Heart J 2019;40:1590-6.
6. Costa LG, Cole TB, Coburn J, Chang YC, Doo K, Roqué PJ. Neurotoxicity of traffic-related air pollution. Neurotoxicology 2017;59:133-9.
7. Wang Y, Xiong L, Tang M. Toxicity of inhaled particulate matter on the central nervous system: Neuroinflammation, neuropsychological effects and neurodegenerative disease. J Appl Toxicol 2017;37:644-67.
8. Block ML, Calderón-Garcidueñas L. Air pollution: Mechanisms of neuroinflammation and CNS disease. Trends Neurosci 2009;32:506–16.
9. Calderón-Garcidueñas L, Torres-Jardón R, Kulesza RJ, Mansour Y, González-González LO, González-Maciel A, et al. Alzheimer disease starts in childhood in polluted Metropolitian Mexico City: A major health crisis in progress. Environ Res 2020;183:109137.
10. Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 2010;121:2331-78.
11. Münzel T, Gori T, Al-Kindi S, Deanfield J, Lelieveld J, Daiber A, et al. Effects of gaseous and solid constituents of air pollution on endothelial function. Eur Heart J 2018;39:3543-50.
12. Yang Z, Mahendran R, Yu P, Xu R, Yu W, Goddellawattage S, et al. Health effects of long-term exposure to ambient PM\(_{2.5}\) in Asia-Pacific: A systematic review of cohort studies. Curr Environ Health Rep
Long-term exposure to air pollution and hospitalization for Alzheimer's disease. J Environ Public Health 2012;2012:472751.

Rao X, Zhong J, Brook RD, Rajagopalan S. Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. Antioxid Redox Signal 2018;28:797-818.

Calderón-Garcidueñas L, Solt-AC, Henriquez-Roldán C, Torres-Jardón R, Nuse B, Herrit 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.

Wilson SJ, Miller MR, Newby DE. Effects of diesel exhaust on cardiovascular function and oxidative stress. Antioxid Redox Signal 2018;28:819-36.

Moulton PV, Yang W. Air pollution, oxidative stress, and Alzheimer’s disease. J Environ Public Health 2012;2012:472751.

Calderón-Garcidueñas L, Solt-AC, Henriquez-Roldán C, Torres-Jardón R, Nuse B, Herrit 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.

Hajipour S, Farhood Y, Gharib-Naseri MK, Goudarzi G, Rashno M, Maleki H, et al. Exposure to ambient dusty particulate matter impairs spatial memory and hippocampal LTP by increasing brain inflammation and oxidative stress in rats. Life Sci 2020;242:117210.

Hajat A, Diez Roux AV, Castro-Diehl C, Cosselman K, Golden SH, Hazelehurst MF, et al. The association between long-term air pollution and urinary catecholamines: Evidence from the multi-ethnic study of atherosclerosis. Environ Health Perspect 2019;127:57007.

Calderón-Garcidueñas L, Kavanagh M, Block M, D’Angiulli A, Delgado-Chávez R, Torres-Jardón R, et al. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. J Alzheimers Dis 2012;28:93-107.

Brook RD, Rajagopalan S. Air pollution and cardiovascular events. N Engl J Med 2007;356:2104-5.

Tsai TL, Lin YT, Hwang BF, Nakayama SF, Tsai CH, Sun XL, et al. Fine particulate matter is a potential determinant of Alzheimer’s disease: A systematic review and meta-analysis. Environ Res 2019;177:108638.

Fu P, Guo X, Cheung FMY, Yung KKL. The association between PM10 exposure and neurological disorders: A systematic review and meta-analysis. Sci Total Environ. 2019;655:1240-8.

Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D, et al. Association between cardiovascular disease and long-term exposure to air pollution with the risk of dementia. JAMA Neurol 2020;77:801-9.

Ilango SD, Chen H, Hystad P, van Donkelaar A, Kwong JC, Tu K, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: A population-based cohort study. Int J Epidemiol 2020;49:36-44.

Czaja F, Renzi M, Garza B, Cavaliere C, Cavaliere M, Michelozzi P, Forastiere F, et al. Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study. Environ Health 2019;18:72.

Thiankhwak K, Chattipakorn N, Chattipakorn SC. PM2.5 exposure in association with AD-related neuropathology and cognitive outcomes. Environ Pollut 2022;292:118320.

Oudin A, Andersson J, Sundström A, Nordin Adolfsson A, Oudin Åström D, Adolfsson R, et al. Traffic-related air pollution as a risk factor for dementia: No clear modifying effects of APOEε4 in the Betula cohort. J Alzheimers Dis 2019;71:733-40.

Kulick ER, Wellenius GA, Boehme AK, Joyce NR, Schupf N, Kaufman JD, et al. Long-term exposure to air pollution and trajectories of cognitive decline among older adults. Neurology 2020;94:1782-92.

Lo YC, Lu YC, Chang YH, Kao S, Huang HB. Air pollution exposure and cognitive function in Taiwanese older adults: A repeated measurement study. Int J Environ Res Public Health 2019;16:2976.

Zhang X, Chen X, Zhang X. The impact of exposure to air pollution on cognitive performance. Proc Natl Acad Sci U S A 2018;115:9193-7.

Kim H, Noh J, Noh Y, Oh SS, Koh SB, Kim C. Gender difference in the effects of outdoor air pollution on cognitive function among elderly in Korea. Front Public Health 2019;7:375.

Tonne C, Elbaz A, Beevers S, Singh-Manoux A. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology 2014;25:674-81.

Allen JL, Klocke C, Morris-Schaffer K, Conrad K, Sobolewski M, Cory-Slechta DA. Cognitive effects of air pollution exposures and potential mechanistic underpinnings. Curr Environ Health Rep 2017;4:180-91.

Pelch KE, Bolden AL, Kwiatkowski CF. Environmental chemicals and autism: A scoping review of the human and animal research. Environ Health Perspect 2019;127:46001.

Allen JL, Oberdorster G, Morris-Schaffer K, Wong C, Klocke C, Sobolewski M, et al. Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: Parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. Neurotoxicology 2017;59:140-54.

Jayaraj RL, Rodriguez EA, Wang Y, Block ML. Outdoor ambient air pollution and neurodegenerative diseases: The neuroinflammation hypothesis. Curr Environ Health Rep 2017;4:166-79.

D’Angiulli A, Severe Urban Outdoor Air Pollution and Children’s Structural and Functional Brain Development, From Evidence to Precautionary Strategic Action. Front Public Health 2018;6:95.

Hullmann M, Albrecht C, van Berlo D, Gerlofs-Nijland ME, Wahle T, Boots AW, et al. Diesel engine exhaust accelerates plaque formation in a mouse model of Alzheimer’s disease. Part Fibre Toxicol 2017;14:35.

Woodward NC, Levine MC, Haghani A, Shimohammad F, Safarri A, Sioutas C, et al. Toll-like receptor 4 in glial inflammatory responses to air pollution in vitro and in vivo. J Neuroinflammation 2017;14:84.

Yan W, Yun Y, Ku T, Li G, Sang N. NO2 inhalation promotes Alzheimer’s disease-like progression: Cyclooxygenase-2-derived prostaglandin E2 modulation and monocacylglycerol lipase inhibition-targeted medication. Sci Rep 2016;6:22429.

Durga M, Devasena T, Rajasekar A. Determination of LC50 and sub-chronic neurotoxicity of diesel exhaust nanoparticles. Environ Toxicol Pharmacol 2015;40:615-25.

Cacciottolo M, Morgan TE, Safarri AA, Shimohammad F, Forman HJ, Sioutas C, et al. Traffic-related air pollutants (TRAP-PM) promote neuronal amyloidogenesis through oxidative damage to lipid rafts. Free Radic Biol Med 2020;147:242-51.

Jew K, Herr D, Wong C, Kennell A, Morris-Schaffer K, Oberdorster G, et al. Selective memory and behavioral alterations after ambient ultrafine particulate matter exposure in aged 3xTgAD Alzheimer’s disease mice. Part Fibre Toxicol 2019;16:45.

Cory-Slechta DA, Allen JL, Conrad K, Marvin E, Sobolewski M. Developmental exposure to low level ambient ultrafine particle air pollution and cognitive dysfunction. Neurotoxicology 2018;69:217-31.