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Review article

Clinical effects of air pollution on the central nervous system; a review

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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.

1. 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 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.

2. 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.

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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"

2.1. 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.

2.2. 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 (Fig. 1).

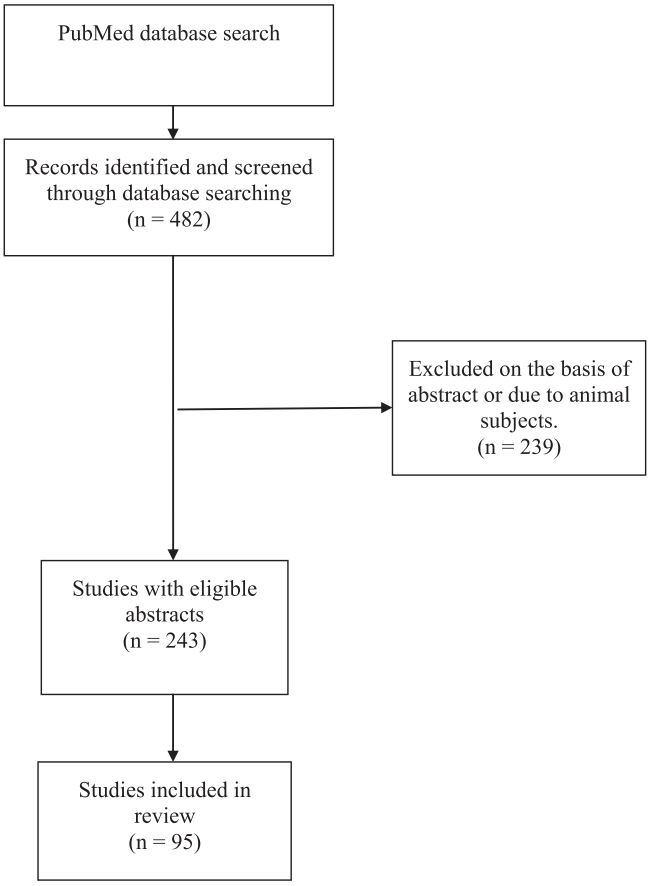

Fig. 1. Search strategy.

3. 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