Current Evidence for the Association between Air Pollution and Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder, and its global incidence is on the rise. There is increasing interest in understanding the role of air pollution in the development of human disease. Although the precise mechanisms are not understood, several epidemiological studies have reported a positive association between air pollution and the risk of PD. However, the various pollutants studied, endpoints measured, and differences in study design yield conflicting results. This review summarizes recent evidence regarding the relationship between particulate matter, ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide and PD. Limitations and challenges are also discussed, with suggestions for future work to understand the true effects of air pollution on PD.

Keywords: Air pollutant, air pollution, environmental factor, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder, and the precise pathomechanism is still unclear. Recent evidence has shown that genetic factors modulate the development of PD, but the majority of PD cases are sporadic, suggesting that environmental factors could be involved. Air pollution has been associated with multiple human health issues, especially of the respiratory system, which is the entry point of many pollutants into the body. In this article, we provide recent evidence of the association between air pollution and PD using a semi-systematic review approach.

METHODS AND RESULTS

Search strategy

Major air pollutants include coarse and fine particulate matter (PM) composed of organic and inorganic particles such as metals as well as gases such as ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and volatile organic compounds (VOCs). These air pollutants typically penetrate the lung and cardiovascular system via respiration, and their effects can lead to stroke, heart disease, lung cancer, and chronic obstructive pulmonary disease. Nine out of 10 individuals worldwide are estimated to breathe highly polluted air, and both ambient air pollution (outdoor) and household air pollution (indoor) cause approximately seven million deaths annually.[1] Although the association between exposure to air pollutants and PD is not well-understood, multiple studies have been conducted on the topic.

We performed an electronic search of PubMed for the literature published in the past 5 years, and the last search was conducted on December 12, 2021.[2] The following terms were used: "Parkinson disease," "Parkinson's disease," "particulate matter," "$PM_{2.5}$," "PM_{10}," "ozone," "O_3," "nitrogen dioxide,"

"NO_2," "sulfur dioxide," "sulphur dioxide," "SO_2," "carbon monoxide," "volatile organic compound," "VOC," and "air pollution." These terms were used in combination as a two-term search of a disease name and a pollutant name or the term "air pollution" (e.g., "Parkinson disease" and "particulate matter"). After removing duplicate articles and reviews and reviewing the abstracts for eligibility, we selected 17 records and five meta-analyses for the semi-systematic review. Figure 1 depicts the flowchart of study selection, and Tables 1 and 2 summarize the literature selected.

PD

PD is the second most common neurodegenerative disorder after Alzheimer's disease. Clinical characterizations of PD include motor symptoms such as bradykinesia, resting tremor, rigidity, and postural instability and non-motor symptoms such as hyposmia, constipation, hypotension, rapid eye movement sleep behavior disorder, and cognitive impairment. The non-motor symptoms in particular have been identified as adversely affecting patients' quality of life.[3] The incidence and prevalence of PD have rapidly increased worldwide,[4]
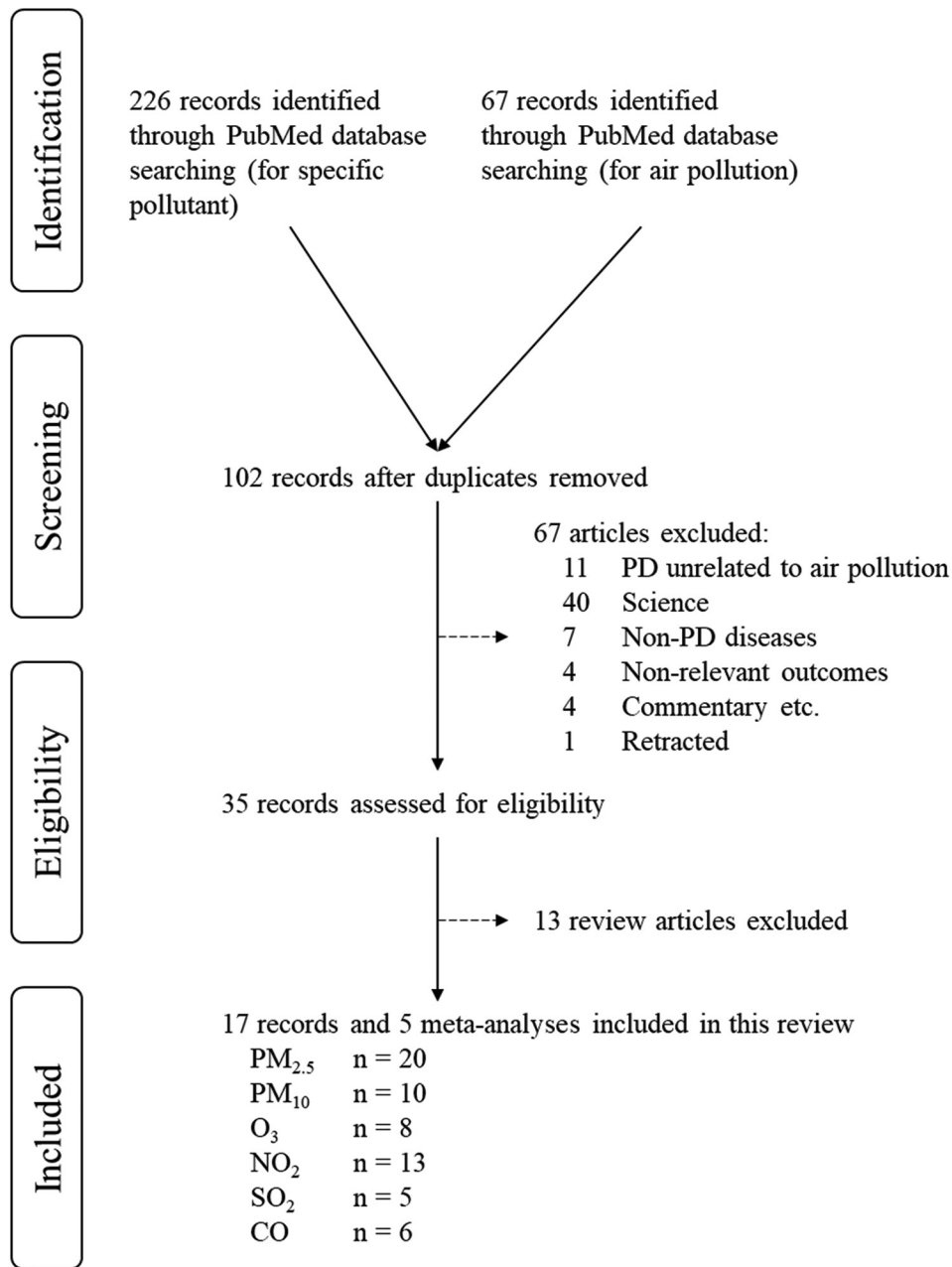
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Identification

226 records identified through PubMed database searching (for specific pollutant)

67 records identified through PubMed database searching (for air pollution)

Screening

102 records after duplicates removed

67 articles excluded:
- 11 PD unrelated to air pollution
- 40 Science
- 7 Non-PD diseases
- 4 Non-relevant outcomes
- 4 Commentary etc.
- 1 Retracted

Eligibility

35 records assessed for eligibility

13 review articles excluded

Included

17 records and 5 meta-analyses included in this review

$PM_{2.5}$	n = 20
PM_{10}	n = 10
O_3	n = 8
NO_2	n = 13
SO_2	n = 5
CO	n = 6

PD: Parkinson's disease

Figure 1: Flowchart for the systematic literature search on air pollution and PD

incurring both personal and societal socioeconomic burdens, as many neurological disorders cause disability.[5] The primary target of PD is the substantia nigra, and the disease manifests as a gradual loss of dopaminergic neurons, although other motor and non-motor circuits are also involved. The neuropathological hallmark of PD is the presence of intracellular Lewy bodies of α-synuclein proteins. The motor symptoms are attributable to the loss of dopaminergic neurons, so dopamine replacement therapy is the main therapeutic option in PD. Current dopaminergic pharmacotherapy consists of levodopa, dopamine receptor agonists, and monoamine oxidase type B inhibitors, and initial therapy is tailored by age, extent of parkinsonism, and tolerance of these drugs. In the advanced stage, device-aided therapies such as deep brain stimulation and levodopa-carbidopa intestinal gel infusion can be added. In addition, a multi-disciplinary care team of rehabilitation staff (physical, occupational, and speech and language therapists), nurses, pharmacologists, dietitians, psychiatrists, psychologists, and social workers can support the patients and their families throughout the time course of the disease.[6]

PM

PM is a complex mixture of solid particles and liquid droplets suspended in the atmosphere that contains metals, dust,

Table 1: Studies included in this review; air pollutants and Parkinson's disease (publication year and alphabetical order)

Authors	Years of publication	Exposure	Study period	Sample size	Location of study	PD-associating outcome
Fleury et al.[9]	2021	PM_{10}, NO_2	2003-2012 for PD and 2010 for pollutant	1,115 PD and 12,614 controls	Switzerland	PD prevalence
Jo et al.[20]	2021	$PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, CO	2007-2015	78,830 participants	Korea	Incident PD
Nunez et al.[11]	2021	$PM_{2.5}$	2000-2014	197,545 PD first hospitalization	USA	PD first hospitalization (as PD aggravation)
Rhew et al.[13]	2021	$PM_{2.5}$	2007-2014	Study group and control group with 1,665,073 and 357,574 person-years	USA	Disease-specific mortality and hospital admissions
van Wijngaarden et al.[12]	2021	$PM_{2.5}$	2005-2016	63,287 hospital admissions	USA	Admission
Yitshak-Sade et al.[10]	2021	$PM_{2.5}$	2000-2014	30,079,287 admissions	USA	Admission
Yu et al.[8]	2021	$PM_{2.5}$, PM_{10}, NO_2	2015-2018	47,516 participants	China	Incidence of PD
Zhao et al.[24]	2021	O_3 ($PM_{2.5}$, NO_2 for adjusted model)	2001-2016	3.5 million adults	Canada	Death from PD
Salimi et al.[21]	2020	$PM_{2.5}$, NO_2	2006-2009	236,390 participants	Australia	Prevalence of PD
Shi et al.[15]	2020	$PM_{2.5}$	2000-2016	63,038,019 individuals	USA	First hospital admission
Yuchi et al.[14]	2020	$PM_{2.5}$, NO_2, NO, black carbon	Exposure 1994-98, follow-up 1999-2003	~ 678,000 residents	Canada	Incidence of PD
Toro et al.[22]	2019	$PM_{2.5}$, PM_{10}, $PM_{2.5\ -\ 10}$, NO_2, NOx	2010-2012	1,290 subjects	Netherlands	Development of PD
Wei et al.[16]	2019	$PM_{2.5}$	2000-2012	95,277,169 admissions	USA	Admission
Shin et al.[17]	2018	$PM_{2.5}$, O_3, NO_2	2001-2013	2,194,519 individuals	Canada	Incident PD
Chen et al.[19]	2017	PM_{10}, O_3, NO_2, NO, NOx, SO_2, CO, etc	2000-2013	1,060 PD and 4,240 controls	Taiwan	Incidence of PD
Lee et al.[18]	2017	$PM_{2.5}$, O_3, NO_2, SO_2, CO	2002-2013	14,774 admissions	Korea	Emergency hospital admission (as PD aggravation)
Palacios et al.[23]	2017	$PM_{2.5}$, PM_{10}, $PM_{2.5\ -\ 10}$	1988-2010	50,352 men with 550 PD	USA	Incident PD

PD: Parkinson's disease.

Table 2: Meta-analyses included in this review; air pollutants and Parkinson's disease (publication year and alphabetical order)

Authors	Years of publication	Exposure	Disease	Number of included articles
Han *et al.*[25]	2020	$PM_{2.5}$, PM_{10}, O_3, NO_2, NOx, CO	PD	20
Wang *et al.*[28]	2020	$PM_{2.5}$, PM_{10}	PD	6
Fu *et al.*[27]	2019	$PM_{2.5}$	PD, stroke, dementia, AD, ASD	80
Kasdagli *et al.*[26]	2019	$PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, O_3, NO_2, NOx, SO_2, CO	PD	15
Hu *et al.*[29]	2019	$PM_{2.5}$, PM_{10}, O_3, NO_2, NOx, SO_2, CO	PD	10

AD: Alzheimer's disease, ASD: autism spectrum disorder, PD: Parkinson's disease.

and chemical compounds. Particle size has been related to physiological effects, and smaller particles can penetrate the respiratory tract deeply.[7] Coarse particles have a diameter of 2.5–10 μm and are termed PM_{10}, fine particles have a diameter ≤2.5 μm and are termed $PM_{2.5}$, and ultra-fine particles are smaller than 100 nm and are termed $PM_{0.1}$. Multiple studies have investigated the relationship between $PM_{2.5}$ or PM_{10} and PD, and therefore, these types are discussed in this review.

Studies on the relationship between PM and PD have reported inconsistent findings. PM has been reported recently to increase both the incidence of PD and hospital admissions for symptom exacerbation.[8-19] One geospatial analysis showed that PD prevalence was higher in urban centers where mean annual PM_{10} and NO_2 levels were high.[9] Conversely, several studies did not find an association between PM and the risk or aggravation of PD,[20-23] and the concentrations of $PM_{2.5}$ were reported to exert little impact on the observed associations between long-term exposure to O_3 and mortality in PD patients.[24] Among meta-analyses published in the past 3 years, three concluded an association between $PM_{2.5}$ and the risk of PD,[25-27] but two did not.[28,29]

O_3

O_3 gas is a powerful oxidant in industrial, medical, and consumer use. Ground-level O_3 is inhalable and can lead to adverse health effects. Vulnerable populations include children, older adults, and individuals with certain lung conditions such as asthma and chronic obstructive pulmonary disease. In addition, working or exercising outdoors can increase exposure.[30] Ground-level O_3 is formed in the atmosphere by photochemical reactions between sunlight and pollutant precursors such as nitrogen oxides and VOCs emitted by vehicles, power plants, industrial boilers, refineries, chemical plants, and other sources.[31,32] Because this is a photochemical reaction, O_3 levels are likely to increase to harmful levels under warm conditions and peak in summer. Similar to other pollutants, O_3 can be transported by air currents over long distances.[32]

Recent evidence regarding the association between O_3 and PD is inconsistent, with some studies linking the pollutant to mortality and the incidence of PD[17,24] and other studies reporting no association.[18-20] Zhao and colleagues assessed long-term exposure to O_3 and PD-related deaths in Canada using Cox proportional hazard models and reported that the fully adjusted hazard ratio was 1.09 (95% confidence interval: 1.04–1.14).[24] In contrast, a study in Korea reported that exposure to O_3 was not associated with the risk of PD (hazard ratio: 0.83; 95% confidence interval: 0.51–1.35).[20] Three recent meta-analyses concluded that O_3 increases the risk of PD,[25,26,29] although one of these calculated only a marginally or borderline significant higher risk of PD (relative risk: 1.01; 95% confidence interval: 1.00–1.02).[25]

NO_2

NO_2 is a reddish-brown gas emitted from human activities that involve combustion of fossil fuels at high temperatures.[33] NO_2 is toxic to the respiratory system, promoting the development of asthma and potentially increasing susceptibility to respiratory infections, and vulnerable populations include patients with asthma, children, and older adults.[34] Because nitrogen oxides react with other chemicals in the atmosphere to form both PM and O_3,[34] the adverse effects of NO_2 should be considered in tandem with those of other pollutants.

The evidence regarding an association between NO_2 and PD is inconsistent. Three studies published in 2021 reported a link between NO_2 and the risk of PD,[8,9,20] and one calculated a hazard ratio for the highest versus lowest quartile of 1.41 (95% confidence interval: 1.02–1.95).[20] Other recent studies concurred,[14,17,18] and one reported that short-term exposure to NO_2 aggravated PD.[18] In contrast, three studies reported no association between long-term exposure to NO_2 and the risk of PD.[19,21,22]

Meta-analyses on the topic have also reported inconsistent conclusions. Han *et al.*[25] and Hu *et al.*[29] reported an association between NO_2 exposure and a higher risk of PD, whereas Kasdagli *et al.*[26] found an indication of an association between long-term exposure and the relative risk of PD, but the association did not reach the nominal level of significance. As with $PM_{2.5}$, the additional effect of NO_2 concentration as a variable on the association between long-term exposure to O_3 and PD-related mortality was negligible.[24]

SO_2

SO_2 is a colorless gas emitted from both the burning of fossil fuels by power plants and other industrial facilities[35] and natural sources such as volcanos.[36] SO_2 exhibits some

anti-oxidant and anti-microbial properties and is therefore used as a food additive. However, acute exposure to SO_2 can irritate the eye, mucous membrane, skin, and respiratory tract and result in the development of bronchospasm, pulmonary edema, pneumonitis, and acute airway obstruction.[37] Furthermore, long-term exposure to SO_2 may aggravate chronic pulmonary conditions such as asthma.[37]

A recent study reported that exposure to SO_2 was not associated with an increase in the risk of PD,[20] whereas other studies reported inconsistent results and varied in design. Lee *et al*.[18] reported that short-term exposure to SO_2 aggravated PD, and Chen *et al*.[19] reported that long-term exposure to SO_2 did not affect the incidence of PD. Two meta-analyses published in 2019 concluded that SO_2 exposure does not affect the risk of PD.[26,29]

CO

CO is a colorless, tasteless, and odorless gas[38] emitted by vehicles and industrial processes that involve combustion of fossil fuels.[39] CO binds hemoglobin with a much greater affinity than oxygen and forms carboxyhemoglobin, which has reduced oxygen-carrying capacity, causing acute hypoxia that could be followed by delayed (2–40 days) neuropsychological sequelae such as levodopa-resistant parkinsonism with brain white-matter T2-weighted hyperintensities.[40,41]

Lee *et al*.[18] reported that short-term exposure to 0.1 ppm CO increased emergency hospital admissions in patients with existing PD, indicating exacerbations, and a later study concluded that CO was not associated with the risk of PD.[20] One recent meta-analysis reported that exposure to CO was associated with the risk of PD,[29] but two other meta-analyses did not find an association,[25,26] and one of these calculated a relative risk of 1.32 (95% confidence interval: 0.82–2.11), which was positive but not significant.[25]

VOCs

We did not find articles published over the past 5 years that assessed the association between VOCs and PD.

DISCUSSION

An extensive body of evidence exists on the association between air pollution and human disease, especially in the respiratory system. The effects of air pollution on neurological disorders such as PD are in debate and vary by setting, cohort, endpoint, and design, suggesting difficulties in arriving at a conclusion. Several challenges should be considered. First, how do we define exposure? The concentrations of air pollutants vary by location, human activity, and airflow (such as the differences between indoor and outdoor air). In addition, many neurodegenerative disorders are related to age, and quantifying long-term exposure is difficult. PD is hypothesised to develop pathologically before the appearance of motor symptoms.[42] Among early non-motor symptoms, rapid eye movement sleep behavior disorder is considered a strong indicator of the future development of PD.[42] Interestingly, Zhang

et al.[43] reported that suspected rapid eye movement sleep behavior disorder may be a consequence of CO poisoning. This suggests that exposure to air pollutants in the prodromal phase of PD should be considered in association studies. In addition, careful interpretation of association is required when evaluating the endpoints of prevalence and incidence. For example, it is possible that subjects already diagnosed with PD move to large cities close to advanced medical facilities, resulting in an apparently but artificially high prevalence or incidence in large cities that is not related to local exposure levels. Second, multiple studies and meta-analyses did not find an association between air pollution and PD, implying that stronger risk factors may overwhelm the true effect of air pollution. For example, mutations in the genes *SNCA*, *LRRK2*, *PRKN*, *PINK1*, and *GBA* have been associated with the risk of PD,[6] as have environmental or lifestyle factors such as cigarette smoking, coffee consumption, and intake of vitamin E.[44] Environmental toxicants such as pesticides, solvents, and heavy metals may modulate the risk of developing PD,[45] masking the true effect of air pollution. Ethnicity-specific genetic factors may also modify the association. Third, reflecting the difficulties in assessing the length and extent of exposure to air pollutants in population studies, variations in study design in the literature may have biased the results of the meta-analyses. Therefore, the high heterogeneity in most of these meta-analyses may affect the conclusions drawn. Finally, air pollutants occur in mixtures and react with each other, negating the utility of single-pollutant models in evaluating PD risk and requiring multi-pollutant effect models. Considering these critical limitations, the current literature is insufficient to identify the precise effects of air pollution on the risk of PD. To address these limitations and the underlying challenges, prospective studies that control these factors are warranted. In the most extreme case, we should also consider the possibility that there is no association between air pollution and PD.

In conclusion, this review summarized recent evidence regarding the effect of air pollution on PD as limited and controversial. Policies, however, to reduce air pollution may reduce the risk of PD worldwide nonetheless. Because air pollutants can transport across countries and regions, international joint research on this topic could clarify the public health impact of air pollution on the development of PD.

Conflicts of interest
There are no conflicts of interest.

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