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IS AIR POLLUTION LINKED TO PARKINSON'S DISEASE? A 2018-2023 LITERATURE REVIEW

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Parkinson's disease (PD) is a progressive disorder that affects the nervous system. It is believed that a combination of genetic and environmental factors causes it. Multiple studies tried or are currently trying to find evidence that shows that breathing polluted air, second-hand smoking, or a specific alimentary habit/diet can put people at risk for developing PD. Polluted gasses and particulate matter have been known to enter through the lungs in the bloodstream and finally breach the blood-brain barrier, triggering inflammation and damaging nerve cells. We conducted a literature review regarding the link between PD and ambient exposure to environmental factors in different populations.

Keywords: air pollution, Parkinson's Disease.

INTRODUCTION

The association between air pollution and its effects on respiratory or cardiovascular diseases has been studied widely. According to the World Health Organization (WHO), 11,65% of deaths worldwide are due to air pollution. Furthermore, it has been reported that more than 80% of urban area residents are exposed to levels of air pollutants that exceed the limits set by the WHO[1].

Among the many contaminants that can be found in the ambient air, the most notable and commonly researched are: particulate matter (PM), which can further be divided into particles with aerodynamic diameter below 2,5 microm($PM_{2,5}$) and those above 10 microm (PM_{10}); ground-level ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2). It should be noted that an increase in the concentration of various pollutants of 10g/m^3 is deemed detrimental to health[2].

A meta-analysis from 2021 by Dominski *et al.*, which looked at 240 systematic reviews and meta-analyses on the topic of air pollutants and public health, the most common health outcomes affected by air pollution were respiratory diseases, stroke, as the most common cardiovascular disease, adverse birth outcomes, lung cancer, as the most common oncologic disorder and cognitive disfunction[2].

In recent years, there has been a rising interest in the relationship between exposure to air pollutants and central nervous system (CNS) disorders, such as neurodegenerative diseases. Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, surpassed only by Alzheimer's disease, affecting more than 6 million people across the world[3].

Due to their capacity for deep infiltration through the respiratory system, fine particles – $PM_{2,5}$ possibly cause the more severe health effects. The main mechanisms involved in the toxicity of this pollutant is oxidative stress through free radicals and activation of inflammatory cells. Moreover, its presence can lead to disruption of the antioxidative systems and to DNA damage. Particulate matter (PM_{10} and $PM_{2,5}$), as well as NO_2, which is highly irritative of the respiratory system, are linked to the development of respiratory diseases[2].

The hallmark of PD is the loss of dopamine-generating cells in the substantia nigra of the brain.

In addition, it has been proposed that alfa-synuclein accumulation begins in the olfactory bulb and gut, becoming more widespread in the brain as the disease progresses[4].

Air pollutants can disrupt the blood-brain barrier, entering the CNS, either by nasal inhalation and reaching the olfactory bulb, or by entering the lungs and translocating into systemic circulation. As a result, they cause oxidative stress, neuroinflammation and abnormal aggregation of proteins[5].

MATERIALS AND METHODS

We conducted a literature review regarding the link between PD and ambient exposure to environmental factors in different populations.

DATA SOURCES AND SEARCH STRATEGIES

A comprehensive search of the Pubmed database was conducted from April 2018 to April 2023, limited to the English language only, with no geographical limitations. The search strategy was designed and applied by the authors. We used the following keywords: „air pollution" and „Parkinson's Disease." We did not impose limitations regarding the placement of the keywords only to the title.

STUDY SELECTION

We applied the following inclusion criteria: 1. Populations with diagnosed clinical or preclinical PD; 2. Populations with measured exposure to air pollution; 3. Study type: cohort studies, case-control studies, descriptive studies; 4. Articles in the English language; 5. Human studies. We excluded systematic reviews, literature reviews and meta-analyses as well as animal or cell culture studies.

DATA EXTRACTION AND ANALYSIS

Two independent authors reviewed each title and abstract for eligibility criteria. Possible disagreements over the quality of the studies were solved via discussion with a third reviewer. Full-text papers were then assessed, and the following data were extracted: author, publication year, population, study type, number of subjects, type of exposure, outcome, and pollutants. Finally, the extracted data was summarized and included in a table.

RESULTS AND DISCUSSIONS

The results of our search are summarized in Figure 1.

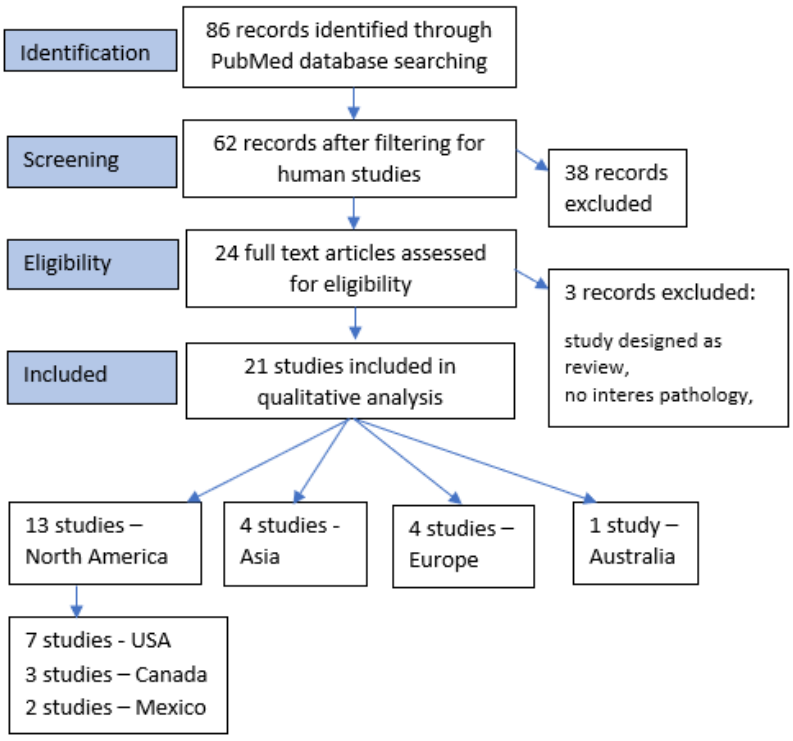

Figure 1. Data search results.

Data from the 21 studies included in the qualitative analysis have been selected and are presented in Table 1.

ASIA

In Asian countries, air pollutant levels are generally higher than those in other countries. Indeed, the mortality risk of stroke related to air pollution in Asia was 2-fold to 9-fold higher than those in North America and Europe.

In order to examine the potential link between exposure to particulate matter ($PM_{2,5}$ and PM_{10}), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and carbon monoxide (CO) and the risk of incident PD, a sizable retrospective cohort study from South Korea followed 78 830 participants from Seoul. The South Korean National Health Insurance Service provided population-based cohort data for the study. Retrospective data were gathered from January 2002 to December 2006, and prospective data were gathered from January 2007 to December 2015. The study tracked long-term exposure (5 years mean) by estimating annual air pollutants for all participants, considering mobility within Seoul, by tying annually updated individual addresses to the annual mean pollution levels from different monitoring locations.

According to their research, being exposed to nitric oxide (NO_2) was linked to a higher chance of developing Parkinson's disease (hazard ratio for highest quartile vs. lowest quartile, 1.41; 95% CI, 1.02-1.95; P for trend =.045). The authors hypothesize that the inflammation induced by NO_2 acts to amplify and propagate -synuclein based on a 2019 study that suggests that what separates those who develop PD from those who do not may be the presence of facilitators that amplify and spread the -synuclein aggregates along the vagus nerve and into the brainstem.

The incidence of PD was not, however, significantly correlated with exposure to $PM_{2,5}$, PM_{10}, O_3, SO_2, or CO. According to the authors, there is generally no correlation between PM and PD in studies with a wide range of exposure contrast (like their own). Therefore, they postulate that rather than the total amount of PM, the composition of PM, namely the presence of airborne metals like manganese, copper, and mercury, may be more significant. Moreover, the exposure levels to PM have shown a high degree of variability in the area, while exposure to NO_2 remained constant, which might have also influenced the results[6].

Another study used data from a prospective cohort of 47,516 participants recruited from July 2015 to January 2018 in Ningbo, China. This study used a prospective cohort study design to examine the relationship between air pollution, nearby green space, road proximity and the incidence of Parkinson's disease (PD). Using land-use regression models, the study calculated participants' long-term exposure to PM2.5, PM10, and NO_2, as well as their closeness to roadways and the quantity of greenery in their immediate surroundings using the Normalized Difference Vegetation Index.

The study revealed that in single-exposure models, Parkinson's disease risk increased with PM2.5, PM10, NO2, and road proximity, with an HR of 1.51 (95%CI: 1.02, 2.24) per IQR (interquartile range) increase for PM2.5. However, surrounding green was associated with a decreased risk of PD, with an HR of 0.80 (95%CI: 0.65, 0.98) per IQR increase of NDVI.

(Normalized Difference Vegetation Index) in 300 m buffer. In two-exposure models, the associations of PM2.5 and surrounding green remained significant, whereas the associations of NO_2 and road proximity weakened towards unity.

The authors noted that the high PM2.5 exposure level in this specific cohort contributed to a significantly bigger impact size compared to other studies. The median exposure level to air pollution was 38.23 g/m^3 [7].

Given the hypothesis that environmental factors may influence gene expression through epigenetic regulation, Karakis *et al.* looked into the relationship between the onset of Parkinson's disease (PD) and cumulative exposure to potentially modifiable ambient exposures. 3343 incident PD cases and 31,324 non-PD controls from Southern Israel were included in the study. Based on monitoring sites, annual average exposures were calculated. The results were reported as an effect of exposure to the 75th percentile relative to the 50th percentile of each pollutant, accumulated over the five years prior to the PD diagnosis.

The odds ratios (OR) for a negative impact of PM_{10} and sun radiation (SR) were 1.06 (95% CI: 1.02; 1.10) and 1.23 (95% CI: 1.08; 1.39), respectively, in the study. Notably, the project's coverage area had been progressively more exposed to dust storms, the main component of which is PM_{10} particles, and is therefore regarded as a significantly exposed area.

Table 1

Data selected after search strategy completion for qualitative analysis

AUTHOR	PUBLICATION YEAR	POPULATION	STUDY DESIGN	NO. OF SUBJECTS	TYPE OF EXPOSURE	OUTCOME	AIR POLLUTION
S. JO ET.AL	2021	South Korea	retrospective cohort	78 830	long-term	PD development	PM 2.5, PM10, NO2, O3, SO2, CO
Z. YU ET AL	2021	China	prospective cohort	47 516	long-term	PD development	PM 2.5, PM10, NO2, roadways proximity, greenery
Y. KARAKIS	2023	Southern Israel	case control	34 667	long-term	PD development	PM 2.5, PM10, sun radiation, O3, NO2, ambient temperature
H. LEE	2022	South Korea	prospective cohort	313 355	long-term	PD development	PM 2.5
F. SALIMI	2020	Australia	cross-sectional cohort	240 000	long-term	PD development	PM 2.5
S. SHIN	2018	Canada	retrospective cohort	2 194 519	long-term	PD development	PM 2.5, NO2, ozone
W. YUCHI	2020	Canada	retrospective cohort	678 000	long-term	PD development	road proximity, air pollution (PM 2.5, black carbon, NO2, NO), noise, greenery
N. ZHAO	2021	Canada	retrospective cohort	3 209 100	long-term	PD mortality	PM 2.5, NO2, ozone
L. CALDERON GARCIDUENAS	2018	Mexico	pathological pathway description	179	long-term	PD markers in the olfactory bulb	PM 2.5
L. CALDERON GARCIDUENAS	2020	Mexico	pathological pathway description	186	long-term	PD markers in the brainstem	PM 2.5
T. COLE-HUNTER	2023	6 European Countries (Sweden, Denmark, France, Netherlands, Germany, Austria)	prospective 7 cohort	271 720	long-term	PD mortality	PM 2.5 and eight of its components, NO2, BC, O3
L. RODRIGUEZ LOUREIRO	2022	Belgium	prospective cohort	1 134 502	long-term	PD mortality	PM 2.5, NO2
R. TORO ET AL	2019	Netherlands	matched case control	436 cases 854 controls	long-term	PD development	NO2, NOx, PM2.5, PM10, PM 2.5-10
V. FLEURY	2021	Switzerland	case control	1 115 cases 12 614 controls	long-term	PD development	NO2, PM10
L. SHI	2020	USA	retrospective cohort	63 038 019 956 653 PD	long-term	PD development	PM 2.5
M. YITSHAK-SADE	2021	USA	retrospective cohort case-crossover	30 079 287 8.8% CDBD	short-term 24 hrs	all cause emergency admissions of PD patients	PM 2.5
Y. WEI	2019	USA	case-crossover	95 277 169	short-term 24 hrs	short-term 24hrs	PM 2.5
E. VAN WIJNGAARDEN	2021	USA New York	retrospective cohort case-control	63 287 11 215 PD	long-term for individual PM	PD aggravation	PM 2.5 (secondary sulfate, secondary nitrate, biomass burning, diesel, spark-ignition emissions, pyrolyzed organic rich, road dust)
Y. NUNEZ	2021	USA New York	retrospective cohort	121 982 PD	long-term	PD aggravation	PM 2.5
Y. NUNEZ	2021	USA New York	retrospective cohort	197 545	long-term	PD aggravation	PM 2.5 (black carbon, organic matter,, nitrate, sulfate, sea salt, soil particle)
S.H. RHEW	2021	USA North Carolina	case control	empirically estimation / 100.000	long-term	PD mortality	PM 2.5

Ozone (O_3) was similarly negatively associated with PD. However, the relationship was only marginally significant, with an OR of 1.12 (95% CI: 0.99; 1.25).

However, NO_2 showed a protective effect, suggesting that PD cases had lesser exposure to this pollutant (OR: 0.94 (95%CI: 0.90; 0.98)). Furthermore, PD sufferers were more likely to have been exposed to lower ambient temperatures 5 years before disease onset (OR: 0.90 (95% CI: 0.81; 1.00)). One interesting finding from this study was that immigrants entering in Israel after 1989 appeared to be more prone to O_3 and SR exposure. The absence of the dose-response impact of SR in Israeli-born people (OR = 0.67, 95% CI: 0.40; 1.13), the moderate effect of SR in immigrants who arrived before 1989 (OR = 1.17, 95% CI: 0.98; 1.40), and the comparatively high effect of SR in recent immigrants (OR = 1.25, 95% CI: 1.25; 2.38), all point to a degree of SR adaptation[8].

Hyewon *et al.* tracked 313,355 members of the National Health Insurance Service-National Sample Cohort in South Korea from 2007 to 2015 to advance our understanding of the relationship between chronic exposure to $PM_{2.5}$ and the risk of Parkinson's disease (PD). Incidence PD was defined as the initial diagnosis accompanied by the prescription of an anti-PD drug during the study period, and long-term PM exposure was measured as the five time-varying average concentrations estimated for the prior 1 to 5 years for each year.

The results indicated a statistically significant link between long-term $PM_{2.5}$ exposure and the onset of PD – hazard ratio (HR) of incident PD per interquartile range increase for the previous year was 1.08. The connection was stronger in older participants, males, those from urban areas, and who had comorbid conditions (HR: 1.10–1.20)[9].

AUSTRALIA

A study conducted in Australia found limited evidence of associations between long-term exposure to NO_2 or $PM_{2,5}$ and PD. Using information from almost 240,000 cohort members of the 45 and Up Study, NSW, the authors of this study conducted a cross-sectional examination of long-term exposure to $PM_{2.5}$ and NO_2 concentrations and the prevalence of PD. The participants' residential address's annual average NO_2 and $PM_{2.5}$ concentrations were calculated using satellite-based land use regression models. After correcting for various individual- and area-level factors, logistic regression was performed to estimate the relationships between these pollutants and any instances of diagnosed PD.

PD was diagnosed in 1,428 (0.6%) of the 236,390 patients with complete data. The cohort's annual mean values of $PM_{2.5}$ and NO_2 were 5.8 and 11.9 $\mu g.m^{-3}$, respectively, and were favorably but not statistically significantly correlated with PD. Notably, the aforementioned exposure levels are lower in this study than those that yielded statistically significant results. A 1 $\mu g\ m^{-3}$increase in $PM_{2.5}$ had an odds ratio of 1.01 (95% confidence interval (CI): 0.98–1.04). A 5 $\mu g.m^{-3}$ rise in NO_2 had an adjusted hazard ratio of 1.03 (95% CI: 0.98 – 1.08). Greater relationships for NO_2 were seen in subgroup analysis among former smokers OR 1.11 (95% CI: 1.02 – 1.20) per 5 $\mu g.m^{-3}$ increase, while there was no such association in current smokers. The study also revealed a negligible protective effect of smoking. These results might point to the possibility that smoking modifies the effect of exposure to air pollution and PD in a non-specific way.

The authors hypothesize that changing demographic characteristics, study methodologies, and various PM chemical compositions at various locales may be responsible for the disparate findings across the literature[10].

CANADA

There have been 3 large epidemiological cohort studies, regarding the link between air pollution and PD conducted on Canadian populations published in the last 5 years.

Shin S. *et al.*, in a population-based retrospective study published in 2018, aimed to assess the influence of specific air-polluting particles on the risk of developing PD[11]. The group used the ONPHEC (Ontario Population Health and Environment Cohort) – a cohort including a wide population,[12] restricted to the subjects that on baseline (2001) were not diagnosed with PD and were between 55–85 years old. After these restrictions, the number of included subjects was 2 194 519. Based on previous studies regarding the etiopathology of PD[13], that starts long before the diagnosis based on motor symptoms, the authors decided to investigate the link between air pollution levels during a 5 year period, from several years before the motor debut of the disease (using mathematical models), thus showing the implication of these particles in the development of PD.

For this study, 3 types of air pollution components were measured: $PM_{2.5}$(particulate matter with under 2.5 micrometers diameter), NO_2, and ozone. Analyzing the data, Shin *et al.* observed that 1.8% of the studied population had been diagnosed with PD until study completion (2013), the risk of developing the disease increasing with raised levels of air pollution, with the most significant link to $PM_{2.5}$ exposure (each 3.8 microgram/m^3 increase, leads to 4% higher risk for PD).

Another retrospective populational study, published in 2020 by Yuchi *et al.*, regarding a Vancouver cohort[14]. The approximately 678000 subjects cohort has been constructed using the Medical Service Plan information[15], by selecting subjects aged at baseline (1999) between 45–84 years, who were not diagnosed with the neurodegenerative diseases evaluated (PD, dementia, and multiple sclerosis). The authors evaluated exposure during a long-term period (1994–1998) prior to cohort selection through a series of factors: road proximity, air pollution ($PM_{2.5}$, black carbon, NO_2, NO), noise, and greenery. The follow-up period was from 1999–2003, and 4201 of the included subjects developed PD in this time frame. The analysis of exposure demonstrated that road proximity is significantly linked to an increased risk of PD, this association might be mediated by air pollution, especially $PM_{2.5}$ exposure.

A third Canadian study regarding the nationwide population, investigated the link between pollution and mortality, as opposed to the previous ones that were focused on the link between exposure and the risk of disease appearance. The study was published in 2021 by N. Zhao *et al.* and used data from the Canadian Census Health and Environment Cohort[16] following 3 209 100 subjects from the years 2001 to 2013. The main outcome regards ozone exposure, but $PM_{2.5}$ and NO_2 levels have also been studied. As suggested by physio-pathological pathways, disease aggravation through pollution exposure is a long-term process, so the time lag between exposure and death occurrence has been selected at 1 year, for an exposure time set at 10 years. In the studied time period, 8500 PD deaths occurred in the cohort, with a slight but statistically significant (Hazard Ratio=1.09) increased risk of PD death in case of high ozone exposure.

These retrospective cohort studies are high-quality studies, including a large number of participants, considering the time lag between exposure and negative outcome and identifying covariants (like socioeconomic status) and confounders. They have some limitations, mainly their retrospective data selection, little clinical data about the patient-associated diseases, PD evolution, mobility, work environment, etc. They do not evaluate the primary cause of death and associated diseases[17], not including cofounder factors like smoking etc. Also, only the study of Shin *et al.* [11] evaluated quantitative exposure–outcome associations, while the others provided only comparative qualitative statistical data. The data provided by the Canadian researchers in the last 5 years strongly suggest the necessity of air pollution reduction strategies for better management of PD.

MEXICO

Two studies regarding the pathogeny of air pollution involvement in PD development have been published by the group headed by L. Calderon Garciduenas in 2018 and 2020, respectively. In addition, the group had published pathology studies before and thus created a 203 *post-mortem* subjects sample with sudden death from prior studies [18].

In 2018 they published a post-mortem descriptive analysis of [19] of 179 young subjects' brains and olfactory bulbs that died of sudden death from 2004 to 2008. All subjects have been residents of the Metropolitan area of Mexico City (MMC), a highly air-polluted residency. The group analyzed the cumulative $PM_{2.5}$ levels correlated to each subject's residency and time of exposure in relation to the presence of pathogenetic markers in the olfactory bulb linked to neurodegenerative diseases, including PD. The results have shown a tendency of increased neurodegenerative disease markers in the brain, but without reaching statistical significance. Nonetheless, this study provides a clearer view of the assumed pathways of PD pathogenesis and proof of early alfa synuclein accumulation.

In 2020 the group published another paper focusing on more specific disease development, such as Alzheimer's and PD[20]. Using the same original sample exposed to high air pollution from MMC, they selected 186 post-mortem subjects for brainstem and substantia nigra analysis. The study generates a large number of conclusions, among which of interest for our review are strong evidence of abnormal proteins in the brain of pollution-exposed young adults, the involvement of the gastrointestinal tract as a direct gateway to the brainstem for abnormal protein formation, and air

polluters access, metal-rich nanoparticles are involved in neurodegenerative disease development.

Though mainly descriptive, these pathology studies based on a population without a clinical PD diagnosis offer a valuable perspective on the mechanisms involved in the early preclinical stages of PD and the implication of various risk factors in these initial phases of disease progression. In addition, they allow sufficient evidence for strategies of air pollution interventions and early diagnosis protocols in exposed individuals.

EUROPE

In the last five years, we retrieved four European-based studies matching our search criteria that assessed the link between exposure to gaseous pollutants or fine particles and PD.

Most studies focus on the link between long-term exposure to air pollutants and PD incidence, while evidence of PD premature mortality from ambient air pollution remains scarce.

The "Effects of Low-Level Air Pollution: A Study in Europe" (ELAPSE) project pooled data from seven cohorts recruited in the 1990s or early 2000s in six European countries, aiming to find an association between long-term exposure to PM2.5 and eight of its components, NO_2, BC, O3, and mortality from PD. The exposure data were based on the year 2010. The final analyses included 271,720 participants, of which 381 died from PD at a mean age of 66.9 years, during a mean follow-up time of 19.7 years. The authors observed significant positive associations between PM2.5 long-term exposure and PD mortality and suggestive positive associations evident for NO2 and BC. Potassium was the PM2.5 component described to have the strongest association with premature PD mortality, usually detected in soil dust, traffic, and biomass burning. Contrary to other studies, there was an inverse relationship between O3 and PD mortality, which was no longer statistically significant in two-pollutant models with PM2.5. The authors observed these associations in lower-BMI individuals, with progressed PD and disease-related weight loss. These findings persisted at levels of air pollutant concentrations well below current EU air quality standards, in agreement with previous results. A strength of this study is the large sample size achieved by pooling seven cohorts. Its limitations include the low number of deaths due to PD, as the diagnosis is not well documented in death certificates, and many die from competing diseases[21].

Rodriguez-Loureiro *et al.* published a follow-up cohort study from 2001–2014 on a population of 1,134,502 individuals aged over 60 years old that resided in the five largest urban areas in Belgium. The authors set to evaluate the correlation between long-term exposure to green spaces, measured using the Normalized Difference Vegetation Index, and general or specific neurodegenerative disease mortality, considering its role in reducing air pollutant concentrations (PM2.5 and NO_2). They observed a reduced risk for general neurodegenerative disease mortality when considering air pollution but no benefic association between greenness and PD mortality[22].

As previously stated, current literature mostly encompasses articles related to the association between air pollution and PD development, having inconsistent results. Neuroinflammation, oxidative stress, and dopamine system–related neurotoxicity have been mentioned when discussing exposure to ambient air pollutants. We discuss two case reports that have analyzed their effect on the occurrence of PD.

Using a multi-center PD case-control study, Rosario Toro *et al.* recruited 436 patients with PD (initially diagnosed between January 2006 to December 2011) and 854 matched controls (patients diagnosed with non-neurodegenerative and peripheral neurological diseases) from five hospitals located in four cities in The Netherlands. A 16-year-long exposure to air pollutants such as NO_2, NOx, PM2.5, PM10, PM 2.5-10 at the residential address of participants was predicted through a regression model, with the average participant starting age being 53. Overall, no statistically significant, positive relationship between air pollution and PD incidence was observed. It is possible that, for PM2.5 and PM10, there was insufficient contrast in air pollution exposure. A sub-group analysis found evidence suggesting that non-smoking women might be at elevated risk[23].

A new perspective was used in a case-control study from Geneva, exploring the spatial dependence of PD prevalence. The authors identified clusters of PD and compared them to the distribution of relevant environmental risk factors. They included 1115 patients diagnosed with PD over a 10-year study period (2003–2012), as well as 12,614 controls over the age of 40. The individual-level PD clusters identified through georeferenced data superimposed on the spatial distributions of

NO2 and PM10 concentrations, detecting a significant positive association[24].

Although we are looking at contrasting results when reviewing studies conducted on the European population, acknowledging the possible role of air pollution in PD could prompt the formulation of official public health recommendations.

UNITED STATES OF AMERICA

We comprised seven studies conducted in the United States of America over the last five years that have examined the relationship between air pollution and Parkinson's disease.

The current National Ambient Air Quality Standard for annual PM 2.5 levels is 12 μg/m^3.

Three studies investigate the effect on PM 2.5 exposure on Medicare Enrollees over long-term[25] and short-term, defined as 24 hours high PM 2.5[26,27].

Medicare is a federally funded health insurance program in the United States that primarily provides health insurance coverage for people who are 65 years of age or older. The study designs like retrospective cohorts[25,26] and case-crossover[27], allowed the inclusion of numerous subjects, making them of the robust epidemiologic evidence.

Shi L. *et al.*, in a population-based study (full cohort of 63 038 019, out of which 956653 with PD), published in 2020 investigated the association between long-term exposure to ambient fine particulate matter (PM2.5) and the risk of developing neurological disorders such as Parkinson's disease. The study used a longitudinal cohort design and analyzed data on Medicare beneficiaries from 2000 to 2016 in the United States. The authors aimed to determine whether there is an association between long-term exposure to PM2.5 and the risk of developing neurological disorders while also accounting for other factors that may influence the risk of these disorders.

They used daily PM 2.5 predictions at 1 km^2 spatial resolution across the contiguous United States from a model calibrated with daily PM 2.5 concentrations measured at 2156 monitors and ICD codes (for Parkinson's or Alzheimer's) to identify admissions as principal or secondary diagnosis. The data was provided from the US Environmental Protection Agency's Air Quality System database and IMPROVE monitoring network.

They concluded that long-term exposure to PM2.5 was positively associated with an increased risk of developing Parkinson's disease, Alzheimer's disease, and other dementias. However, both diseases have long, insidious onsets, and the exact timing of the onset is unknown, with diagnosis occurring at a neurologist's office. The study highlights the importance of reducing air pollution levels to protect public health, particularly for vulnerable populations, including the elderly and those with underlying health conditions, even for those already exposed to low PM 2.5 concentrations[25].

Wei *et al.* investigate the association between short-term exposure to fine particulate matter (PM2.5) and hospital admission risks and costs. The study, done on Medicare inpatient hospital claims totaling 95277169, employed a time-stratified, case-crossover design to analyze data on admissions and air pollution levels from 2000 to 2012 in 43 US urban areas. The authors aimed to comprehensively assess the health effects over the short-term (24h) of PM 2.5 exposure by examining the relationship between PM 2.5 concentrations and hospital admission for several specific health conditions.

Wei concluded that for each 1 μg/m^3 increase in lag 0–1 PM 2.5, the absolute increase in the risk of hospital admissions for the disease groups ranged from 0.02 to 0.68 /10 m people at risk/day.

They also estimated the associated healthcare costs of PM2.5-related hospital admissions in the Medicare population. For diseases with a previously known association, such as Parkinson's disease, each 1 μg/m^3 increase in short-term exposure to PM 2.5 was associated with an annual increase of 3642 in hospital admissions and 69$m in care costs.

The findings emphasize the importance of reducing PM2.5 levels to protect public health and reduce healthcare costs and suggest the revision of WHO air quality guidelines[27].

The third study[26] on Medicare patients with chronic debilitating brain disorders, including dementia, Parkinson's disease, and multiple sclerosis, investigates the association between short-term exposure to ambient fine particulate matter (PM2.5) and hospital admissions. M. Yitshak-Sade *et al.* assess the risk of being hospitalized in high vs. low PM 2.5 exposure, using the 24-h standard NAAQS of 35 μg/m^3. The study used a case-crossover design and analyzed hospital admission data and air pollution levels from 2000 to 2010 in the United States. The inference approach was that each zip code, on a given day, could have been exposed to an either low (< 17 μg/m^3) or high (>17 μg/m^3) PM 2.5 level on a matched sample of 30079287 admissions, 8.8% with CDBD.

It has been observed that in addition to inducing the disease, high air pollution exposure increases the risk of being hospitalized due to other causes.

The study found that short-term exposure to PM2.5 was associated with an increased risk of hospital admissions among Medicare enrollees with chronic debilitating brain disorders, particularly for those with Parkinson's disease (2.53% increase).

Wei *et al.*[27] found significant increases in the risk for Pneumonia and UTI for the cohort studied.

Three articles published in 2021 studied the correlation between clinical aggravation and hospital admission in neurodegenerative diseases and exposure to long-term fine particle air pollution for New York State (NYS)[28–30].

E. Van Wijngaarden *et al.* analyzed data from 63287 Medicare beneficiaries (11215 with PD) in the NYS and looked at the hospital admissions for neurodegenerative diseases between 2005 and 2016. The researchers also used data from the Environmental Protection Agency to estimate the levels of fine particulate matter in everyone's zip code of residence[28].

The authors used ambient PM 2.5 measurements at six monitoring sites across NYC and SPARCS to evaluate associations between increases in PM 2.5 and hospitalizations over extended periods of up to a year. They concluded that increases in ambient PM 2.5 concentrations are not associated with increases in hospital admission rates.

Another study, by Y. Nunez, aimed to investigate the association between long-term exposure to PM 2.5 and aggravation in Alzheimer's and Parkinson's and ALS, using first hospitalization as surrogate for aggravation.

The study population was obtained through SPARCS data on first hospitalizations, and the focus was 1-y exposure window from 2000 to 2014. Data were included from all 62 NYS counties.

The findings of the study suggest a non-linear association between PD and PM 2.5 that plateaued above 11 μg/m^3 (1.14 for a PM 2.5 increase from 8.1 to 10.4 μg/m^3). The study also found that specific patient subpopulations (< 70 years) are likely to present higher vulnerability to exposure[29].

Another article published by Y Nunez *et al.* characterized the association between specific PM 2.5 components such as black carbon BC, organic matter OM, nitrate, sulfate, sea salt SS, soil particle, and PD first hospitalization. They used a multi-pollutant mixed quasi-Poisson model with county-specific random intercepts to estimate RR over 1-year exposure.

A total of 197545 patients with PD were observed using SPARCS data from 2000 to 2014 over 62 NYS counties. The RR for PD aggravation was 1.06 per one standard deviation increase in nitrate concentrations and 1.06 for the corresponding increase in OM concentrations. For BC, they unexpectedly found a nonlinear negative association above the 96th concentration percentile (1.3 μg/m^3).

The study's main limitation was that first hospitalization data is likely to miss a number of the total cases of PD aggravation and potentially misclassify some non-PD related hospitalizations as aggravation episodes[30].

Rhew S. *et al.* investigated the relationship between long-term exposure to low-dose PM2.5 and the risk of developing Alzheimer's disease, non-Alzheimer's dementia, and Parkinson's disease. The study, designed as case-control, used SCHS data on disease-specific mortality and data on exposure to PM 2.5 from NASA, from 2007 to 2014 to assess the risk of neurodegenerative diseases associated with exposure to PM2.5.

They used satellite-based data with the GWR approach to extend the data on PM 2.5 measures to NC regions with sparse locations of PM 2.5 ground monitors. In addition, NC populations aged 65+, living in zip codes with ambient PM 2.5 level exceeding 10 μg/m^3 were included.

The study found that long-term exposure to low-dose PM 2.5 was associated with an increased risk of Alzheimer's disease and non-Alzheimer's dementia, but not Parkinson's disease[31].

CONCLUSIONS

There is conclusive evidence that links air pollution to the development of PD, depending on the length of exposure, type of particle, and levels of pollutants.

Most studies found statistically significant proof that air pollution is associated with higher PD mortality rates, depending on the length of exposure, type of particle, and levels of pollutants.

We found heterogeneous study designs (case-control studies, prospective and retrospective cohort studies, descriptive studies) carried out on vastly different populations with various results. Still, most found links between at least one type of pollutant and PD.

Most studies offer sufficient evidence to support the implementation of efficacious national strategies for reducing air pollution and for risk factor reduction in neurodegenerative diseases.

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