

# Air pollution and its current impact on Parkinson's disease: a systematic review

*Poluição atmosférica e seu impacto atual na doença de Parkinson: uma revisão sistemática*

*La contaminación del aire y su impacto actual en la enfermedad de Parkinson: una revisión sistemática*

Adriana Rocha Nunes<sup>1\*</sup>, Liebert Bernardes Carvalho<sup>2\*</sup>,  
Rodrigo Augusto da Silva<sup>3</sup>, Emanuel Silva Rovai<sup>4</sup>

\*Adriana Rocha Nunes and Liebert Bernardes Carvalho contributed equally to this work.

1.Program in Health Sciences, University of Taubaté. Taubaté-SP, Brazil. Orcid: <https://orcid.org/0009-0008-8749-6307>

2.Program in Health Sciences, University of Taubaté. Taubaté-SP, Brazil. Orcid: <https://orcid.org/0009-0008-5531-4978>

3.Program in Health Sciences, University of Taubaté. CEEpiRG - Center for Epigenetic Study and Genic Regulation, Program in Environmental and Experimental Pathology, Paulista University. São Paulo-SP, Brazil. Orcid: <https://orcid.org/0000-0002-7754-1855>

4.Program in Health Sciences, University of Taubaté. ICT-UNESP, Division of Periodontics, UNESP São Paulo State University. São José dos Campos-SP, Brazil. Orcid: <https://orcid.org/0000-0002-5044-0368>

## Resumo

**Introdução.** A doença de Parkinson (DP) é uma doença neurodegenerativa altamente prevalente que afeta milhões de pessoas em todo o mundo, caracterizada pela depleção de neurônios dopaminérgicos na substância negra. A fumaça transportada pelo ar é uma preocupação crescente e tem sido associada a processos inflamatórios agudos no corpo e a potenciais efeitos neurodegenerativos devido ao seu transporte para o cérebro através do bulbo olfatório. **Objetivo.** Esta revisão sistemática tem como objetivo avaliar o impacto da poluição atmosférica na DP. **Método.** A revisão seguiu as diretrizes *Reporting Preferred Items for Systematic Reviews and Meta-Analyses* (PRISMA) e foi registrada no *Prospective International Register of Systematic Reviews*. A busca eletrônica da literatura foi realizada nas seguintes bases de dados: PubMed, LILACS e BINACIS. **Resultados.** O processo de revisão identificou 2.703 artigos, dos quais 7 estudos atenderam aos critérios de inclusão e foram incluídos na revisão. Os estudos investigaram a relação entre DP e exposição a diversos poluentes atmosféricos, como PM<sub>2,5</sub>, NO<sub>2</sub>, CO. Estudos individuais forneceram resultados mistos, alguns não encontraram associações estatisticamente significativas, enquanto outros mostraram uma associação positiva entre a exposição à poluição atmosférica e a incidência de DP. Estudos que utilizam PM<sub>2,5</sub> como indicador de poluição atmosférica demonstraram consistentemente uma possível ligação com a incidência de DP. A exposição ao PM<sub>10</sub> e ao NO<sub>2</sub> também mostrou alguma evidência de associação com o risco de DP. **Conclusão.** Esta revisão sistemática sugere que pode haver uma associação entre a poluição do ar, especialmente a exposição ao PM<sub>2,5</sub>, e a incidência da DP.

**Unitermos.** Doença de Parkinson; poluição do ar; dióxido de nitrogênio; partículas; ozônio; monóxido de carbono

## Abstract

**Introduction.** Parkinson's disease (PD) is a highly prevalent neurodegenerative disease affecting millions worldwide, is characterized by the depletion of dopaminergic neurons in the substantia nigra. Airborne smoke is a growing concern and has been linked to acute inflammatory processes in the body and potential neurodegenerative effects due to its transport to the brain through the olfactory bulb. **Objective.** This systematic review aims to

assess the impact of air pollution on PD. **Method.** The review followed the Reporting Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in the Prospective International Register of Systematic Reviews. Electronic literature search was performed in the following databases: PubMed, LILACS and BINACIS. **Results.** The review process identified 2703 articles, of which 7 studies met the inclusion criteria and were included in the review. The studies investigated the relationship between PD and exposure to various air pollutants, such as PM<sub>2.5</sub>, NO<sub>2</sub> and CO. Individual studies provided mixed results, some found no statistically significant associations, while others showed a positive association between exposure to air pollution and the incidence of PD. Studies using PM<sub>2.5</sub> as an indicator of air pollution have consistently demonstrated a possible link with the incidence of PD. Exposure to PM<sub>10</sub> and NO<sub>2</sub> also showed some evidence of an association with PD risk. **Conclusion.** This systematic review suggests that there may be an association between air pollution, especially exposure to PM<sub>2.5</sub>, and the incidence of PD. **Keywords.** Parkinson's Disease; air pollution; nitrogen dioxide; particulate matters; ozone; carbon monoxide

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## Resumen

**Introducción.** la enfermedad de Parkinson (EP) es una enfermedad neurodegenerativa altamente prevalente que afecta a millones de personas en todo el mundo, se caracteriza por el agotamiento de las neuronas dopaminérgicas en la sustancia negra. El humo en el aire es una preocupación creciente y se ha relacionado con procesos inflamatorios agudos en el cuerpo y posibles efectos neurodegenerativos debido a su transporte al cerebro a través del bulbo olfatorio. **Objetivo.** Esta revisión sistemática tiene como objetivo evaluar el impacto de la contaminación del aire en la EP. **Método.** La revisión siguió las pautas de presentación de informes de elementos preferidos para revisiones sistemáticas y metanálisis (PRISMA) y se registró en el Registro Internacional Prospectivo de Revisiones Sistemáticas. Se realizó una búsqueda de literatura electrónica en las siguientes bases de datos: PubMed, LILACS y BINACIS. **Resultados.** El proceso de revisión identificó 2703 artículos, de los cuales 7 estudios cumplieron con los criterios de inclusión y fueron incluidos en la revisión. Los estudios investigaron la relación entre la PD y la exposición a diversos contaminantes del aire, como PM<sub>2.5</sub>, NO<sub>2</sub> y CO. Los estudios individuales proporcionaron resultados mixtos, algunos no encontraron asociaciones estadísticamente significativas, mientras que otros mostraron una asociación positiva entre la exposición a la contaminación del aire y la incidencia de la EP. Los estudios que utilizan PM<sub>2.5</sub> como indicador de la contaminación del aire han demostrado consistentemente un posible vínculo con la incidencia de la EP. Además, la exposición a PM<sub>10</sub> y NO<sub>2</sub> también mostró cierta evidencia de una asociación con el riesgo de EP. Se evaluó el riesgo de sesgo de los estudios mediante la escala de Newcastle-Ottawa (NOS), y se consideró que todos tenían un riesgo de sesgo bajo. **Conclusión.** Esta revisión sistemática sugiere que puede haber una asociación entre la contaminación del aire, especialmente la exposición a PM<sub>2.5</sub>, y la incidencia de la EP.

**Palabras clave.** La enfermedad de Parkinson; la contaminación del aire; el dióxido de nitrógeno; las partículas; el ozono; el monóxido de carbono

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Research developed at University of Taubaté. Taubaté-SP, Brazil.

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**Corresponding author:** Rodrigo AF da Silva. Program in Environmental and Experimental Pathology, Paulista University (UNIP) and Program in Health Sciences, University of Taubate (UNITAU). Taubaté-SP, Brazil. Phones: +55 12 3880-0599, +55 11 5586-4171. E-mail: [dasilasilva.rodrico.a@gmail.com](mailto:dasilasilva.rodrico.a@gmail.com)

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## INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease in the world, characterized as a chronic and progressive disorder of the nervous system, affecting more than 6 million individuals globally<sup>1</sup>. It can be

described as a global pandemic due to the increase in life expectancy and population aging<sup>1</sup>. A Global Burden of Disease study reported that neurological disorders are currently the leading causes of disability worldwide, with high prevalence rates, disability, and age-standardized deaths, with PD showing the most pronounced growth of these disorders<sup>1</sup>. The most expressive risk factor in PD is age, with men being more prone than women, currently, more than 90 genetic risk loci have been identified, reinforcing a strong genetic component in the risk of the disease<sup>2</sup>.

PD is characterized by the depletion of dopaminergic neurons in the substantia nigra and progressive loss of normal motor function<sup>3</sup>. The main motor signs and symptoms PD are postural instability, tremor, rigidity, and progressive bradykinesia, whereas the non-motor symptoms are mood or behavioral changes, anxiety, depression, and apathy<sup>4</sup>. Although the etiopathogenesis of the disease is unknown, it is suggested that oxidative stress, inflammatory reactions, and mitochondrial dysfunction can play a major role<sup>5</sup>.

Air pollution has presented an avoidable health risk affecting the sick, the elderly, children, and the poor due to urban growth, industrialization, and global warming, which increases the urgency of pollution control in the modern world<sup>6</sup>. According to data from the World Health Organization (WHO), 90% of the world's population inhales air contaminated with high levels of pollutants, mainly in urban

areas, with approximately 7 million people dying each year from airborne particles polluted air<sup>3</sup>.

In older people, prolonged exposure to air pollution accentuated traffic-related cognitive impairments over 20 years<sup>7</sup>. Air pollution can contribute to the advancement of PD through the activation of chronic systemic inflammatory processes, and pollutants can directly affect the brain through their transport in the olfactory bulb, inducing systemic inflammation that leads to the production of alpha tumor necrotic factor (TNF- $\alpha$ ) or interleukin 1 beta (IL-1 $\beta$ ), by activating microglia, contributing to the neurodegenerative process<sup>8</sup>. Air pollution components can also accumulate in the gastrointestinal tract and modify the physiology of the intestinal mucosa, inducing  $\alpha$ -syn pathology. and/or altering the microbiome, both of which are implicated in the pathogenesis of PD<sup>9</sup>.

The Air Quality Standards (PQAr) establish limits for six primary atmospheric pollutants: Carbon Monoxide (CO<sub>2</sub>), Lead (Pb), Ozone (O<sub>3</sub>), Particulate Matter (PM), Sulfur Dioxide (SO<sub>2</sub>) and Nitrogen Dioxide (NO<sub>2</sub>), contributing to better management of air quality, with the main sources of these primary pollutants being motor vehicles, fuel burning, industrial boilers, dust particles and the like<sup>10</sup>. Particulate matter (PM), also called atmospheric aerosol, is characterized by physicochemical properties (e.g., shape, size, composition, interaction with sunlight) and mass/number concentration that can vary widely concerning

space and over time, making this mixture a highly heterogeneous set<sup>11</sup>.

Oxygen Monoxide, characterized by being a colorless, odorless, and tasteless gas, is produced by the incomplete combustion of hydrocarbons, representing an invisible danger<sup>12</sup>. Both carbon monoxide (CO) and nitric oxide (NO) pass quickly into the bloodstream, are highly soluble, and non-irritating, and their toxicity results mainly from successful competition with oxygen for binding to hemoglobin, which results in hypoxia tissue<sup>12</sup>. Ozone is a highly reactive oxidative gas formed by atmospheric chemical reactions involving emissions of nitrogen oxides (NO<sub>x</sub>) and precursor gases of volatile organic compounds<sup>13</sup>. The molecular conformation of O<sub>3</sub> is highly reactive and has oxidizing properties; when inhaled, the body's redox balance is altered<sup>14</sup>. O<sub>3</sub> gives rise to reactive oxygen species, such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hydroxyl radical (• OH), nitric oxide (• NO), which can induce changes in cell signaling, leading to loss of response regulation inflammation and maintain oxidative stress in the chronic state<sup>14</sup>.

In the elderly, prolonged exposure to air pollution accentuated traffic-related cognitive impairments over 20 years<sup>15</sup>. In a study in China, PM<sub>2.5</sub> was the most consistent and robust indicator of air pollution<sup>16</sup>, while in Denmark, results showed positive relationships with PD risk, with a 9% higher risk exposure to NO<sub>2</sub><sup>17</sup>. A population-based case-control study in Taiwan suggested that exposure to pollutants such as NO<sub>x</sub> and CO are related to traffic<sup>18</sup>.

However, in a study in Taiwan, the results indicated that only particulate matter, PM<sub>10</sub>, contributed significantly to the incidence of PD, with the remaining nine pollutants (SO<sub>2</sub>, O<sub>3</sub>, CO, NO<sub>x</sub>, NO, NO<sub>2</sub>, THC, CH<sub>4</sub> and NMHC) did not contribute<sup>19</sup>. Therefore, the objective of this systematic review will be to answer the question: "Does air pollution impact Parkinson's disease?"

## **METHOD**

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered in the International Prospective Register of Systematic Reviews – PROSPERO (ID: CRD42023421527)

### **Eligibility criteria**

The publications had the following inclusion criteria: (i) articles that assessed the impact of air pollution on PD; (ii) original studies published in English; (iii) observational cohort studies. Narrative reviews, case-control and cross-sectional studies, case series, case reports, in vitro and animal studies were excluded from the present systematic review.

### **Search strategy**

An extensive electronic literature search was performed in the following databases: PubMed, LILACS, and BINACIS until April 2023. The search strategies used were:

"Parkinson's Disease; air pollution; nitrogen dioxide; particulate matters; ozone; carbon monoxide; sulfur dioxide".

In the first phase, two reviewers independently analyzed the databases of identified titles and abstracts that met the inclusion criteria recorded in the report. Disagreements were resolved by discussion. In the second phase, the same reviewers analyzed the full texts of studies included in the first phase reasons for rejecting were recorded for each report.

### **Data extraction**

The following items were extracted from publications that met the inclusion criteria: author, year, country, study design, sample size, air pollution measurements (exposure to pollutants), covariates, statistical analysis, sensitivity analysis, clinical diagnosis of the PD, results, conclusions, conflict of interest and source of funding.

### **Study risk of bias assessment**

The risk of bias was assessed using the Newcastle-Ottawa scale (NOS). The NOS comprised eight questions about study group selection (ie, Parkinson's diagnosis correlated with exposure to air pollution). Scores ranged from 0 to 9 points. Studies with 7-9 stars were classified as low risk of bias, 4-6 stars moderate risk of bias, and 0-3 stars high risk of bias. Analyzes of the quality of the studies were

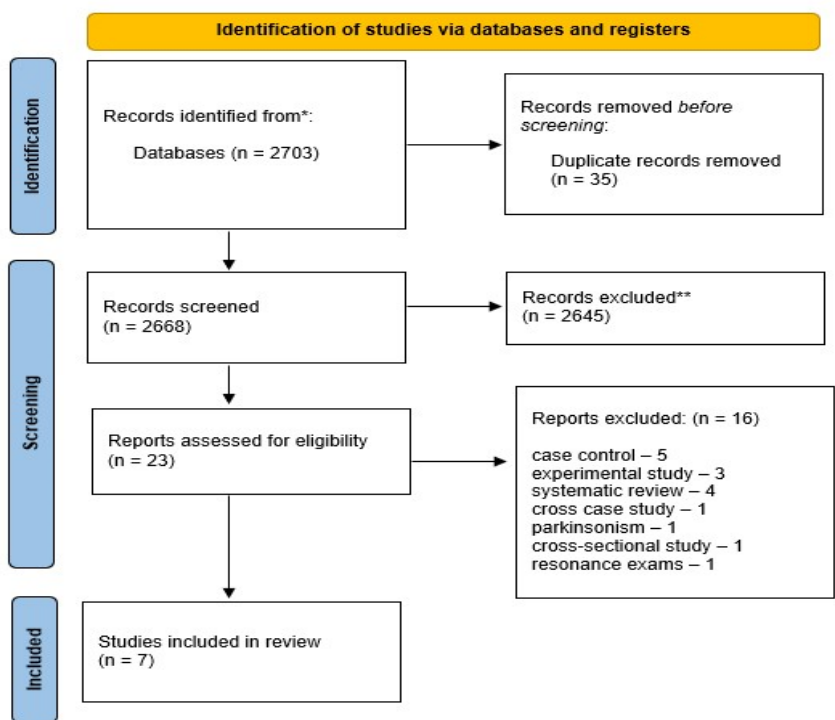
performed using three criteria (selection criteria, comparability criteria, and outcome assessment).

## RESULTS

### Study selection

The search selection process resulted in a total of 2703 articles identified from electronic databases, 2645 were excluded after reviewing the titles or abstracts. In the second phase, full text of 23 articles were assessed. Then, 16 articles were excluded. In the end, seven publications were included in this review<sup>20–26</sup>. Details of the search strategy are provided in the Flow Diagram (Figure 1).

Figure 1. Study Flow Diagram. Graphic representation of the selection and validation process of articles during the writing of the systematic review.





## Results of individual studies

The characteristics and results of the included studies are depicted in Table 1 and 2. One study reported results in Canada<sup>20</sup>, three in the United States<sup>21,22,24</sup>, two in South Korea<sup>23,26</sup>, and one in China<sup>25</sup>. In Ontario, prolonged exposure, specifically to PM<sub>2.5</sub>, has increased the incidence of PD<sup>20</sup>. However, in a US nested case-control study of PM<sub>2.5</sub> and PM<sub>10</sub> exposures in PD patients, no strong evidence was observed linking the patient-exposure relationship in the entire study population, except women and non-smokers who had a high probability of PD<sup>27</sup>.

About fine particulate exposure and clinical worsening in neurodegenerative diseases in New York State, of all first hospitalizations for PD, 9.5% were primary diagnoses, and a nonlinear positive for PM<sub>2.5</sub> was estimated to correlate with PD<sup>21</sup>. In US male patients, in models adjusted for age, period, smoking, region, and population density, no statistically significant associations were observed between air exposure and the risk of PD, with small sensitivity analyses for PM<sub>10</sub> and PM<sub>2.5</sub>, tended more towards a "protective" effect<sup>22</sup>. Moderate evidence of an increased risk associated with PM<sub>2.5</sub> exposure among smokers and significant positive associations between PM<sub>10</sub> among women<sup>27</sup>.

Table 1. Study of populations, diagnosis of Parkinson's and conclusion.

| Author<br>(Country)   | Study Design  | Study population<br>Data base  | Ascertainment of<br>Parkinson's disease  | Conclusion   |
|---|---|--|--|--|
| Shin <i>et al.</i><br>2018 <sup>20</sup><br><br>(Canada)            | Retrospective<br>population-<br>based cohort<br>study | <b>N:</b> 2 194 519 individuals<br><b>Incidents PD:</b> 38.475 individuals<br><b>Average age:</b> age range of 55 to 85 years.<br>Ontario Population Health and Environment Cohort (ONPHEC) – Institute for Clinical Evaluative Sciences (ICES). | One physician claim followed by a drug claim.  | Exposure to air pollution, especially PM <sub>2.5</sub> , was found to be related to incident PD.  |
| Nunez <i>et al.</i><br>2021 <sup>21</sup><br><br>(United States)    | Retrospective<br>cohort study                         | <b>N:</b> 391 694 individuals.<br><b>Incidents PD:</b> 212,8 (354,0) individuals<br><b>Average age:</b> PD: 76<br>New York Department of Health Statewide Planning and Research Cooperative System (SPARCS)                                      | Use of Ninth Revision of the International Classification of Diseases (ICD-9-CM). Primary and secondary discharge codes were used to identify patients.  | Were found to indicate that 1-y exposure to PM <sub>2.5</sub> in levels permissible by the current national standards potentially contributes to clinical disease aggravation in PD.   |
| Palacios <i>et al.</i><br>2017 <sup>22</sup><br><br>(United States) | Prospective<br>Cohort study                           | <b>N:</b> 50 352 individuals<br><b>Incidents PD:</b> 550 individuals<br><b>Average age:</b> age range of 40 to 75 years<br><br>Health Professionals Follow-up Study (HPFS)   | Cases are reported in biennial questionnaires. The patient reporting PD is asked for consent to contact the neurologist. The responsible neurologist completes a questionnaire to confirm the diagnosis of PD. | No association was observed between exposure to air pollution measured as cumulative exposure to PM <sub>10</sub> , PM <sub>2.5</sub> , and PM <sub>2.5-10</sub> at a participant's mailing address and PD risk in a US-based study of men.  |
| Lee <i>et al.</i><br>2017 <sup>23</sup><br><br>(South Korea)        | Cohort,<br>Stratified case-<br>crossover study        | <b>N:</b> 314 individuals.<br><b>Incidents PD:</b> 391 individuals<br><b>Average age:</b> age range of 65 to 74 years.<br>National Health Insurance Service-National Sample Cohort (NHIS-NSC)  | Information about patient demographics and medical treatment.  | The study suggests that short-term exposure to air pollution may increase the risk of worsening PD.  |
| Shi <i>et al.</i><br>2020 <sup>24</sup><br><br>(United States)      | Longitudinal<br>cohort study                          | <b>N:</b> 63 038 019 individuals<br><b>Incidents PD:</b> 77,016 individuals<br><b>Average age:</b> 69,9 years<br><br>Medicare Provider Analysis and Review   | Use of the International Classification of Diseases (ICD) for primary and secondary diagnoses.   | The study provided evidence that exposure to mean annual PM <sub>2.5</sub> is significantly associated with an increased risk of first hospitalization with PD, AD and selected dementias.   |
| Zhebin <i>et al.</i><br>2021 <sup>25</sup><br><br>(China)           | Prospective<br>cohort study                           | <b>N:</b> 46.839 individuals<br><b>Incident PD:</b> 206 individuals<br><b>Average age:</b> 62,27 years<br><br>Health Information System (HIS) - Wonders Big Data Management Platform   | Subjects were invited to the local hospital to undergo a face-to-face interview and health examination.  | The study concluded that PM <sub>2.5</sub> and PM <sub>10</sub> were associated with increased incident PD, while green surroundings were associated with decreased risk of PD.  |
| Jo <i>et al.</i><br>2021 <sup>26</sup><br><br>(South Korea)         | Nationally<br>representative<br>cohort                | <b>N:</b> 176.875 individuals<br><b>Incident PD:</b> 338 individuals<br><b>Average ages:</b> age range of 54,4 to 66,5 years<br><br>Korea National Health Insurance Service (NHIS) – Seoul Public Health and Environment Research Institute      | Diagnosis based on NHI criteria by a neurologist.  | A statistically significant association was identified between the risk of PD and exposure to NO <sub>2</sub> over the last 5 years, especially at high levels of exposure. No evidence was found of an association between PD risk and exposure to PM <sub>2.5</sub> , PM <sub>10</sub> , O <sub>3</sub> , SO <sub>2</sub> or CO. |

n: number, PD: Parkinson disease, PM<sub>2.5</sub>: suspended particles with a diameter of less than 2.5 micrometers, PM<sub>10</sub>: particles 10 micrometers or less in diameter, O<sub>3</sub>: ozone, SO<sub>2</sub>: sulfur dioxide or CO: carbon monoxide, NO<sub>2</sub>: nitrogen dioxide.

Table 2. Exposure to pollutants, Statistical Analysis, Covariates e funding.

| Author (Country)  | Pollutants<br>annual pollutants  | Statistical Analyses   | Covariates   | Study funding   |
|---|--|--|--|---|
| Shin <i>et al.</i><br>2018 <sup>20</sup><br><br>(Canada)            | <b>Pollutants:</b> PM <sub>2,5</sub> -<br>NO <sub>2</sub> - O <sub>3</sub><br><b>Annual pollutants</b><br>PM <sub>2,5</sub> - 9,8 µg/m <sup>3</sup><br>NO <sub>2</sub> - 14,7 ppb<br>O <sub>3</sub> - 49,8 ppb   | Multi-level, radon-effects<br>and Cox proportional hazards<br>models.  | Age, Sex,<br>Socioeconomic status,<br>region and pre-existing<br>comorbidities.  | Health Canada<br>Public Health Ontario<br>(PHO) - Institute for<br>Clinical - Evaluative<br>Sciences (ICES)   |
| Nunez <i>et al.</i><br>2021 <sup>21</sup><br><br>(United States)    | <b>Pollutants:</b> PM <sub>2,5</sub><br><b>Annual pollutants</b><br>PM <sub>2,5</sub> - 8,1 µg/m <sup>3</sup>  | Log-linear model generalized<br>additive mixed models<br>(quasi-Poisson regression).   | Socioeconomic status,<br>Smoking, percentage of<br>obesity, county<br>urbanization level,<br>2013 six-level urban-<br>rural classification<br>scheme for county.   | None.   |
| Palacios <i>et al.</i><br>2017 <sup>22</sup><br><br>(United States) | <b>Pollutants:</b> PM,<br>PM <sub>2,5</sub> , PM <sub>2,5-10</sub><br><b>Annual pollutants</b><br>PM - 0,85 µg/m <sup>3</sup><br>PM <sub>2,5</sub> - 0,97 µg/m <sup>3</sup><br>PM <sub>2,5-10</sub> - 0,88 µg/m <sup>3</sup>   | Separate time-varying Cox<br>proportional hazards models.  | Age, time period,<br>smoking, region and<br>population density.  | National Institutes of<br>Health (NIH)  |
| Lee <i>et al.</i><br>2017 <sup>23</sup><br><br>(South Korea)        | <b>Pollutants:</b> PM <sub>2,5</sub> -<br>NO <sub>2</sub> - SO <sub>2</sub> - CO - O <sub>3</sub><br><b>Annual pollutants</b><br>PM <sub>2,5</sub> - 1,61 µg/m <sup>3</sup><br>NO <sub>2</sub> - 2,35 ppb<br>SO <sub>2</sub> - 1,54 ppb<br>CO - 1,46 ppm<br>O <sub>3</sub> - 1,17 ppb  | Conditional logistic<br>regression   | Sex, Age and season-<br>specific associations<br>between air pollution an<br>PD aggravation.   | Global Research<br>Laboratory - National<br>Research Foundation of<br>Korea - Ministry of<br>Environment of Korea -<br>Correspondence<br>Program for Changes. |
| Shi <i>et al.</i><br>2020 <sup>24</sup><br><br>(United States)      | Pollutants: PM <sub>2,5</sub><br>Annual pollutants<br>PM <sub>2,5</sub> - 9,7 µg/m <sup>3</sup>  | Cox-equivalent re-<br>parameterized Poisson<br>stratified quasi-Poisson<br>model and time-varying<br>annual mean PM <sub>2,5</sub><br>concentrations.  | Neighborhood-level<br>socioeconomic status<br>factors, effects at low<br>PM <sub>2.5</sub> concentrations,<br>change in potential<br>effect by sex, race, age,<br>Medicaid eligibility.  | Health Effects Institute<br>National - Institute of<br>Environmental Health<br>Sciences - National<br>Institute on Aging<br>HERCULES Center                   |
| Zhebin <i>et al.</i><br>2021 <sup>25</sup><br><br>(China)           | Pollutants: PM <sub>2,5</sub> -<br>PM <sub>10</sub> - NO <sub>2</sub><br>Annual pollutants<br>PM <sub>2,5</sub> - 38,23 µg/m <sup>3</sup><br>PM <sub>10</sub> - 60,87 µg/m <sup>3</sup><br>NO <sub>2</sub> - 34,64 µg/m <sup>3</sup>   | Usage model and regression,<br>Normalized Difference<br>Vegetation Index (NDVI) and<br>Cox proportional hazard<br>Models.  | Demographic factors,<br>lifestyle, body mass<br>index (BMI), smoker,<br>current alcohol<br>consumption, physical<br>activity and tea<br>consumption.   | Research Center for Air<br>Pollution - Health of<br>Zhejiang University<br>- Research Funds for<br>Central Universities                                       |
| Jo <i>et al.</i><br>2021 <sup>26</sup><br><br>(South Korea)         | <b>Pollutants:</b> PM <sub>2,5</sub> -<br>PM <sub>10</sub> - NO <sub>2</sub> - O <sub>3</sub> - SO <sub>2</sub><br>- CO<br><b>Annual Pollutants</b><br>PM <sub>2,5</sub> - 26,5 µg/m <sup>3</sup><br>PM <sub>10</sub> - 55,5 µg/m <sup>3</sup><br>NO <sub>2</sub> - 0,033 ppm<br>SO <sub>2</sub> - 0,0053 ppm<br>CO - 0,59 ppm<br>O <sub>3</sub> - 0,019 ppm | Time-dependent Cox<br>proportional hazards<br>regression model<br>constrained cubic regression<br>splines and fully conditional<br>specification method. All<br>data analyses were<br>performed using SAS<br>Enterprise Guide software<br>version 7.1 (SAS Institute).<br>Constrained cubic splines in<br>Cox regression models were<br>presented using the rms and<br>spline packages in R software<br>version 3.3.3 (The R<br>Foundation). | Age, sex, type of health<br>plan and preexisting<br>comorbidities.<br>Diagnosis of medical<br>comorbidities, including<br>hypertension, Diabetes,<br>dyslipidemia, chronic<br>kidney disease,<br>congestive heart<br>failure, ischemic heart<br>disease, and traumatic<br>brain injur. Body mass<br>index, physical activity,<br>smoking habits and<br>alcohol habits. | none.   |

n: number, PD: Parkinson disease, PM<sub>2,5</sub>: suspended particles with a diameter of less than 2.5 micrometers, PM<sub>10</sub>: particles 10 micrometers or less in diameter, O<sub>3</sub>: ozone, SO<sub>2</sub>: sulfur dioxide or CO: carbon monoxide, NO<sub>2</sub>: nitrogen dioxide.

In the study on short-term air pollution exposure to PD, of the five air pollutants ( $\text{PM}_{2.5}$ ,  $\text{NO}_2$ ,  $\text{SO}_2$ ,  $\text{O}_3$ , and  $\text{CO}$ ), all were highly correlated with each other, except for  $\text{O}_3$ , which were not or were poorly correlated with climate variables<sup>23</sup>. In the study conducted in Medicare (USA), concentrations of  $\text{PM}_{2.5}$  were generally higher in the eastern US compared to the western US (except California)<sup>24</sup>. Long-term exposure to  $\text{PM}_{2.5}$  was significantly positively associated with both PD and AD<sup>24</sup>. Among the modifying effects, more significant  $\text{PM}_{2.5}$  effect estimates were found among individuals in more urban versus less urban areas<sup>25</sup>. During the average follow-up of 3.5 years on air pollution, surrounding greenery, road proximity and Parkinson's disease, 206 cases incident to PD were identified<sup>25</sup>. Positive associations of  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  with incident PD were found, and a positive trend was also observed for the relationship between  $\text{NO}_2$  and PD<sup>25</sup>.

An inverse relationship of proximity to the road with the incidence of PD was also observed, and a higher level of surrounding green was correlated with a lower risk of PD<sup>25</sup>. In Ontario, Canada, a large population-based cohort of 31,557 cases found that living near heavy traffic was not associated with PD risk (HR=0.99, 95% CI: 0.97; 1.01 for transformed distance in log-up roads)<sup>28</sup>. However, another population-based cohort in Vancouver, Canada, with 4,201 cases reported that road proximity was positively associated with PD (HR=1.12, 95% CI: 0.91; 1.38 to live 50 m from highways)<sup>29</sup>. In the association of  $\text{NO}_2$  and other exposures to air pollution using data from the Korean National Health

Insurance Service, those who most developed PD were older<sup>23</sup>. Shi *et al.* 2020 performed an age-specific analysis and their result found a greater effect in individuals aged 65 to 74 years than in individuals  $\geq 75$  years, however, the difference was not significant in terms of the short-term association between PM 2.5 and PD hospitalizations<sup>24</sup>. NO<sub>2</sub> exposure was associated with an increased risk of PD, even after adjusting for age, gender, type of insurance, and lifestyle<sup>23</sup>. However, no statistically significant associations were found between the other air pollutants (PM<sub>2.5</sub>, PM<sub>10</sub>, O<sub>3</sub>, SO<sub>2</sub> and CO) and the risk of PD incidence in the adjusted and unadjusted analyses<sup>23</sup>.

### **Risk of bias assessment**

Risk of bias assessment of the studies was evaluated according to the NOS domains (Table 3). All the seven studies included<sup>20-26</sup>, were considered to have low risk of bias.

### **DISCUSSION**

The association between exposure to atmospheric particulate matter and the risk of developing Parkinson's disease (PD) has been the subject of several epidemiological studies. However, the heterogeneity of these studies and the diversity in their approaches make the evidence still incipient.

Table 3. Newcastle-Ottawa Scale (NOS).

| Author<br>(Country)  | Study Design  | Selection criteria<br>(maximum 4) | Comparability<br>criteria<br>(maximum 2) | Outcome<br>criteria<br>(maximum 3) | Total<br>(maximum 10) |
|--|---|-----------------------------------|--|------------------------------------|-----------------------|
| Shin <i>et al.</i><br>2018 <sup>20</sup><br>(Canada)                       | retrospective<br>population-<br>based cohort<br>study | 4                                 | 2  | 3                                  | 9                     |
| Nunez <i>et al.</i><br>2021 <sup>21</sup><br>(United States)               | retrospective<br>cohort study                         | 4                                 | 2  | 3                                  | 9                     |
| Palacios <i>et al.</i><br>2017 <sup>22</sup><br>(United States)            | prospective<br>cohort study                           | 3                                 | 2  | 3                                  | 8                     |
| Lee <i>et al.</i><br>2017 <sup>23</sup><br>(South Korea)                   | cohort,<br>Stratified case-<br>crossover study        | 4                                 | 2  | 3                                  | 9                     |
| Lihua Shi et<br>Shi <i>et al.</i><br>2020 <sup>24</sup><br>(United States) | cohort study  | 4                                 | 2  | 3                                  | 9                     |

A study examined long-term data from more than 3 million people and found a significant association between exposure to fine particles (PM<sub>2.5</sub>) and an increased risk of developing PD<sup>30</sup>. This association was reinforced by other similar studie<sup>31</sup>, which also reported associations between exposure to air pollutants and disease development. Furthermore, studies in animal models have suggested that exposure to air pollutants, including particulate matter, may trigger neuroinflammatory changes, oxidative stress and mitochondrial dysfunction, processes that are involved in the pathogenesis of PD<sup>32</sup>. Despite this evidence, most PD cases in the studies were obtained through administrative health databases, which makes it difficult to identify possible undiagnosed cases, considering that traces of dementia can be preceded by several years before clinical diagnosis<sup>21,25,26</sup>.

This may introduce bias in the results, as some cases may be underestimated.

The heterogeneity of the studies is also manifested in relation to the types of exposure evaluated. In some single-exposure studies, prolonged exposure to air pollution and proximity to roads were associated with an increased risk of PD, while the presence of green areas showed an inverse association<sup>25</sup>. Furthermore, differences in concentrations of pollutants between the areas studied may also contribute to the variation in results. For example, compared to a study in Denmark, in Copenhagen, NO<sub>2</sub> concentrations were higher, and the interaction with the surrounding green showed lower levels of pollutants, which influenced the results<sup>25</sup>. Other factors that may introduce bias into studies are the impossibility of accurately measuring personal exposure or exposure to indoor pollutants<sup>22,25</sup>. Furthermore, the time at which patients are admitted can influence the results since many PD cases are diagnosed in advanced stages of the disease<sup>20-26</sup>.

Despite the sensitivity analyses performed to reduce the potential confounding effect, such as adjustments for other pollutants and the use of Cox random effects models Shin<sup>20,26</sup>, the studies still have limitations. In some cases, the diagnosis of PD is based on imaging tests, such as PET-CT, which may influence the identification of patients with the disease<sup>26</sup>. Thus, although the available evidence suggests that exposure to air pollution may be associated with the incidence of PD, it is important to highlight that the

heterogeneity of the studies, the diversity of approaches and methodological limitations make the current evidence still incipient. More research is needed to better understand the extent of this association and to identify appropriate prevention and intervention strategies. The risk of bias and study heterogeneity should be considered when interpreting the results and making inferences about the relationship between exposure to atmospheric particulate matter and Parkinson's disease. However, the association between exposure to fine particulate matter and an increased risk of developing the disease, as well as the underlying biological mechanisms involved, supports the hypothesis that air pollution plays a role in the pathogenesis of Parkinson's disease, human autopsy studies and experiments on rodents support the hypothesis that air pollution is correlated with increased inflammation and oxidative stress in the CNS<sup>33,34</sup>. Therefore, CNS inflammation and oxidative stress are important findings in PD brains linked to air pollution that need further study.

## **CONCLUSION**

This systematic review suggests that there may be an association between air pollution, especially exposure to PM<sub>2.5</sub>, and the incidence of Parkinson's disease. More studies are needed to confirm these findings.



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