PUBLIC HEALTH RESEARCH

Environmental Risk Factors of Parkinson's Disease: A Scoping Review

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ABSTRACT

Introduction	Risk factors for Parkinson's disease (PD) fall into three broad categories, namely environmental, genetic, and lifestyle factors. Identifying environmental factors that increase the risk of PD would allow these exposures to be reduced and the prevent disease while facilitating experimental investigation of mechanisms and intervention options. Thus, the aim of this review was to summarise the current evidence on the role of environmental factors in the development of PD.
Methods	All original articles published between 2018 and 2022 and written in English were searched from three databases, i.e., PubMed, Scopus Web of Science (WoS), using combination of primary keyword (PD and its MeSH and synonyms), and two secondary keywords; ("environment*") and risk (factor*).
Results	After a thorough screening process, 19 articles were included in this scoping review. The environmental risk factors examined in the included studies fell into five categories: a) pesticide exposure, b) heavy metals and organic solvent exposure, c) drug abuse and d) air pollution and e) source of water.
Conclusions	In summary, PD is a complex neurological disorder for which there are several environmental risk factors involved. Identifying and reducing exposure to these environmental factors could have a significant impact on the future occurrence of the disease.
Keywords	Parkinson's disease; environment; risk factors

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INTRODUCTION

Parkinson's disease (PD) is the second most prevalent age-related neurodegenerative disorder, following dementia. It primarily affects the dopamine-producing neurons in the substantia nigra of the brain and causes multiple motor and non-motor symptoms leading to progressive deterioration and is associated with comorbidities such as fall accidents.[1] PD is a degenerative and, progressive disease. When a significant number of neurons in the substantia nigra are killed or injured, symptoms of the disease start to occur.[2] In addition to a lifetime of drug dependence, patients with PD may require multiple hospitalisations. Furthermore, PD patients gradually lose their ability to work as their productivity decreases. They also rely heavily on their caregivers to complete everyday tasks.

The prevalence of PD has increased from 2.5 million patients in 1990 to 6.1 million patients in 2016.[3,4] It is predicted that 14.2 million people will have PD by 2040. Some scientists have considered to call the disease as non-infectious pandemic because of its rapid spread.[5] In general, the prevalence of the disease increases with age. The disease's prevalence varies from 41 per 100,000 persons in the fourth decade of life to more than 1,900 per 100,000 people in the eightieth decade of life.[6] Several studies found that estimation of the prevalence and incidence of PD were lower in Asian ppopulations than in non-Asian populations. In a door-to-door survey in Taiwan and Singapore, the prevalence of PD was estimated to be 113.1 and 61.9 per 100 000 people, respectively. This is lower than the results of surveys in Sicily (173.8) and Rotterdam (218.0).[7] In 2016, 1,856 PD patients were registered in Malaysia.[8] The number is expected to increase fivefold by 2040.[9]

The clinical diagnosis of PD is based on tremors at rest, bradykinesia and muscle rigidity, and the classic motor signs of PD.[2] Patients often report the bradykinesia of PD as "weakness" of the hand or leg, which is surprisingly undetected on strength tests. Postural instability which may lead to frequent falls which occurs only in the later stages of the disease.

The exact cause of PD is unknown, but it is believed to be an interaction of several factors. The risk factors for PD can be broadly characterised as sociodemographic, genetic, lifestyle and environmental. For example, age and gender are key demographic factors that increase the risk of PD. A family history of PD, as well as certain gene mutations, can increase the risk of developing PD. Meanwhile, smoking, and other lifestyle factors, such as coffee consumption and physical activity levels, have also been shown to impact the risk of PD.

Environmental exposures have been linked to PD risk for decades. Improved detection methods, larger study populations in case-control studies, better monitoring and reporting systems within patient populations have provided either new or updated evidence of an environmental 'link' with PD.[10] Hence, the objective of this review was to provide an overview of recent literature and current knowledge regarding the role of environmental factors in the development of PD. The identification of environmental risk factors for PD would facilitate exposure reduction and prevention efforts, as well as experimental research in disease mechanisms and intervention options.

METHODOLOGY

This review was conducted by adopting scoping review method as described by Arksey & O'Malley and further refined by Levac, Colquhoun, & O'Brien.[11,12] The method comprised of five stages, i.e. Stage 1: formulating the research questions; Stage 2: identifying relevant studies; Stage 3: selecting the literature; Stage 4: charting the data and Stage 5 collating, summarizing, and reporting the results. In making sure that we had a comprehensive review for reporting, we followed the PRISMA flow diagram (Figure 1) to filter for only relevant publications.[13]

Stage 1: Identifying the Research Questions

An initial literature search in search engines was done to get an idea regarding this research topic. After thoroughly examining this topic, two main research questions were developed, which were:

1. What are the environmental risk factors of PD?
2. How do we categorise the environmental risk factors of PD?

Stage 2: Identifying Relevant Studies

Keywords relevant to the study are identified. Then, a search strategy was formulated by the research team based on the keywords and their synonyms and Medical Subject Header (MeSH). Three electronic databases with a focus on health and healthcare were used which were PubMed, Scopus, and Web of Science (WoS).

This review involved three layers of searches that consisted of the primary keyword (PD and its MeSH and synonyms), and two secondary keywords; ("environment*") and risk (factor*). The keywords were combined using relevant Boolean operators "AND" and searched via the identified databases.

The search strings used for the databases were summarised in Table . The literature search was completed in January 2023.

Table 1 Search strings for the databases

Database	Search String
PubMed	((((((((((("Parkinson disease") OR ("Idiopathic Parkinson Disease")) OR ("Idiopathic Parkinson's Disease")) OR ("Lewy Body Parkinson Disease")) OR ("Lewy Body Parkinson's Disease")) OR ("Paralysis Agitans")) OR ("Parkinson Disease, Idiopathic")) OR ("Parkinson's Disease")) OR ("Parkinson's Disease, Idiopathic")) OR ("Parkinson's Disease, Lewy Body")) OR ("Primary Parkinsonism")) AND (environment*)) AND ("risk factor*")
WoS	(((((((((ALL=(Parkinson Disease)) OR ALL=(Idiopathic Parkinson Disease)) OR ALL=(Idiopathic Parkinson's Disease)) OR ALL=(Lewy Body Parkinson Disease)) OR ALL=(Lewy Body Parkinson's Disease)) OR ALL=(Paralysis Agitans)) OR ALL=(Parkinson Disease, Idiopathic)) OR ALL=(Parkinson's Disease)) OR ALL=(Parkinson's Disease, Idiopathic)) OR ALL=(Parkinson's Disease, Lewy Body)) OR ALL=(Primary Parkinsonism) AND ALL=("risk factor*") AND ALL=(environment*)
Scopus	(TITLE-ABS-KEY ("parkinson disease") OR TITLE-ABS-KEY ("idiopathic parkinson disease") OR TITLE-ABS-KEY ("idiopathic parkinson's disease") OR TITLE-ABS-KEY ("lewy body parkinson disease") OR TITLE-ABS-KEY ("lewy body parkinson's disease") OR TITLE-ABS-KEY ("paralysis agitans") OR TITLE-ABS-KEY ("parkinson disease, idiopathic") OR TITLE-ABS-KEY ("parkinson's disease") OR TITLE-ABS-KEY ("parkinson's disease,idiopathic") OR TITLE-ABS-KEY ("parkinson's disease, lewy body") OR TITLE-ABS-KEY ("primary parkinsonism") AND TITLE-ABS-KEY (environment*) AND TITLE-ABS-KEY ("risk factor"))

The inclusion criteria for this review were all types of original articles with human studies written in Malay or English from 2018 -2022. Scoping and systematic reviews were excluded from the study. Studies, which were not available in full text were also excluded, Results yielded from the databases were exported out and combined into a spreadsheet, and a citation manager.

Stage 3: Study Selection
The combined list of the articles was then screened for duplicates. After that, the title, abstract and full text of the remaining articles were checked against the inclusion and criteria to check for the suitability of the articles for this study. Two authors (FSAJ and ANA) screened the titles and abstracts independently based on the research questions. Disagreements were resolved through discussion with a third researcher (NA) to reach consensus.

Stage 4: Charting the data
Relevant data from the final selected articles that were able to answer research questions and objectives of this review were extracted and sorted in a finding table, in a form of a spreadsheet. The information, which was included in the finding tables were the title, country of the study and their findings.

Stage 5: Collating, summarizing, and reporting the results
The data was summarized in a descriptive manner and presented in a table.

RESULTS

The Figure 1 illustrated the systematic process of study selection in this research endeavour. Initially, a comprehensive search was conducted on three databases: Pubmed, Scopus, and WoS, yielding a total of 4209 records. Following this, a meticulous curation process began, involving the removal of duplicate entries and the identification of studies deemed ineligible through the use of automation tools. This step whittled down the initial pool to a more manageable 420 records, which were then subjected to a rigorous screening process. Within this phase, 386 records were excluded for not meeting the predefined inclusion criteria, leaving 54 records for potential inclusion in the study. However, it was discovered that 9 of these records could not be retrieved, leaving a final set of 45 studies to be assessed for eligibility. After a meticulous evaluation, 19 of these studies were ultimately included in the review.

The studies were summarised in Figure 1. Five articles were published in 2022, while there are seven and three articles published in 2021 and 2020, respectively. The remaining four articles were published in 2019 and 2018. Studies in the United States of America (USA) contribute four of the studies, followed by two each from South Korea and Italy. There is one study each from Morocco, Mexico, Phillipines, China, England, Switzerland, Turkey, Hungary, Brasil, Egypt and Canada. Based on the study design, seven studies were case control, six were cross-sectional, four were cohort and two were case report. Our studies found five environmental factors associated with PD. Nine studies addressed exposure to pesticides [14–22] while six studies addressed exposure to heavy metals and organic solvents.[5,14,23–26] Other three factors linked with PD were drug abuse [31] source of water [14,22,26] and air pollution.[27–30]

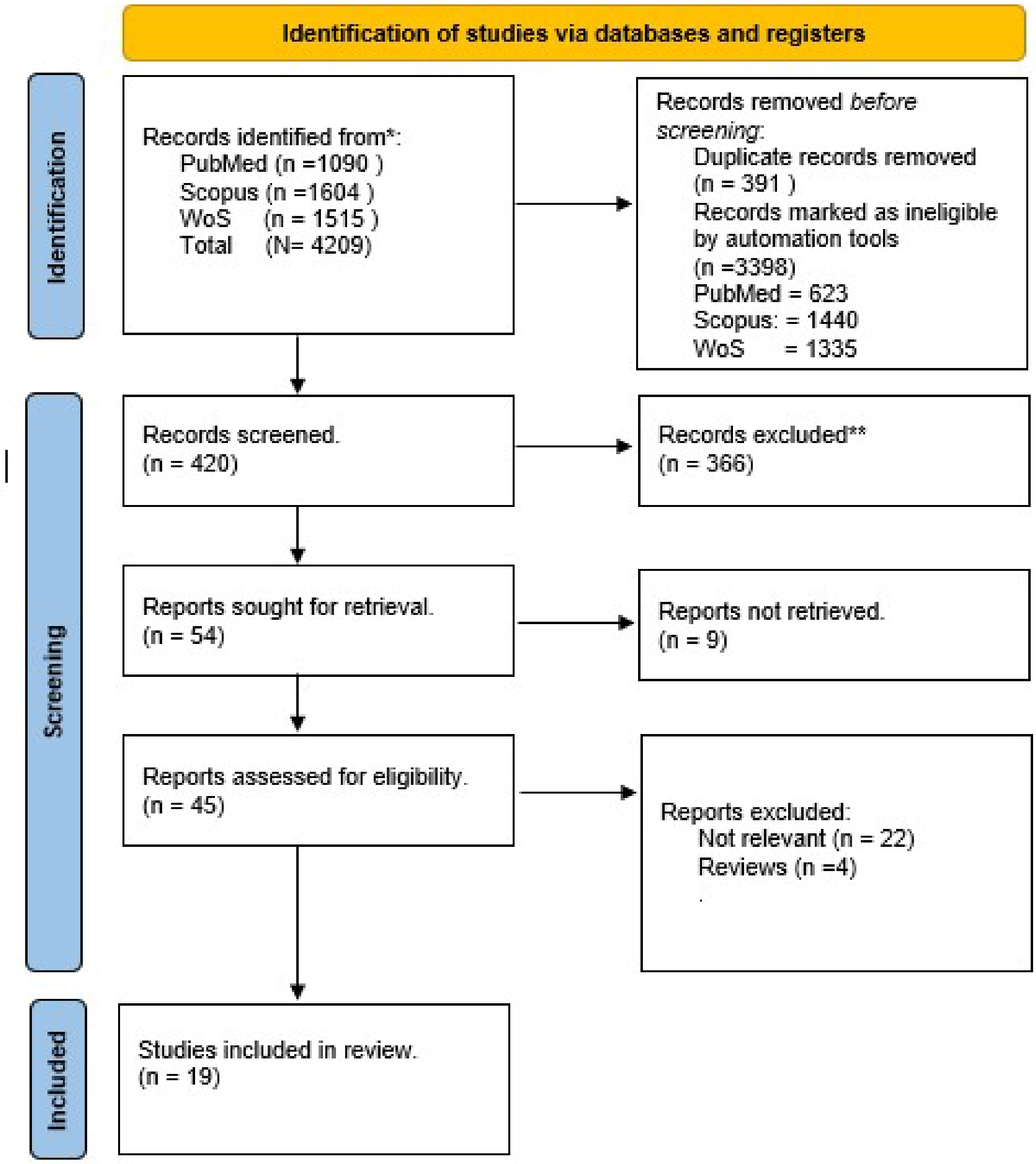

Figure 1 Prisma flow for the study selection

Table 2 Summary of the study included in the review

Bil	Year	Authors	Country	Study design	Environmental factors
1	2022	(Achbani et al. 2022)[22]	Morocco	Case- control	• Spring water • Pesticides
2	2022	(Góngora-Alfaro et al. 2022)[5]	Mexico	Case-control	• Organic solvent exposure and the years of exposure
3	2022	(Belingheri et al. 2022)[23]	Italy	Cross-sectional	• Agrochemical exposure • Metals exposure
4	2022	(Rosales et al. 2022)[14]	Philippines	Cross-sectional	• Insecticides usage • Water from deep well
5	2022	(Xu et al. 2022)[15]	China	Cross-sectional	• Pesticides
6	2021	(Kim et al. 2021)[16]	South Korea	Case report	• Pesticide
7	2021	(Andrew et al. 2021)[24]	England	Case control	• Lead
8	2021	(Fleury et al. 2021)[29]	Switzerland	Case-control	• NO_2 • PM_{10}
9	2021	(Rhew et al. 2021)[27]	USA	Cross-sectional	• $PM_{2.5}$
10	2021	(Schwartz & Williamson 2021)[25]	USA	Cross-sectional	• Lead
11	2021	(Cagac 2020)[26]	Turkey	Case-control	• Well water • Heavy metal
12	2021	(Jo et al.2021)[30]	Korea	Cohort	• NO_2
13	2020	(Belvisi et al. 2020)[21]	Italy	Case-control	• Pesticides • Solvents
14	2020	(Schneider Medeiros et al. 2020)[17]	Brazil	Cohort study	• Pesticides
15	2020	(Shi et al. 2020)[28]	USA	Cohort	• $PM_{2.5}$
16	2019	(Illes et al. 2019)[31]	Hungary	Case report	• Drug abuse
17	2019	(Gamache et al. 2019)[18]	Canada	Cohort	• Pesticides
18	2018	(Caballero et al. 2018)[19]	USA	Cross-sectional	• Pesticides (Paraquat and Glyphosate)
19	2018	(Rösler et al. 2018)[20]	Egypt	Case- control	• Pesticides

DISCUSSION

Pesticides exposure

Pesticides are a class of chemicals which are designed to kill, repel or prevent the reproduction of pests, which can be classified as insecticides, herbicides, rodenticides, and fungicides. There were nine studies that found an association between pesticide exposure and PD in this review.[14–22] A study done in Philippines found insecticides usage among the respondent.[14] Meanwhile, a study by Xu et al. in the Chinese population found higher serum levels of organochlorine pesticides, including α-hexachlorocyclohexane (α-HCH) and propanil levels, which were associated with the risk of PD.[15] Exposure to pesticides can be either direct or indirect. An example of direct exposure is in a case study of PD involving a greenhouse worker in South Korea, who works without adequate personal protective equipment (PPE).[16] Meanwhile, consumption of pesticide-exposed agricultural products such as vegetables and fruits is an example of indirect exposure, as reported in the study by Belingheri et al in Italy.[23]

PD patients with a history of occupational pesticide were found to have worse symptoms, graded by Unified Parkinson's Disease Rating Scale III (UPDRSIII).[17] Besides that, Gamache et al in their study in Canada reported that patients that had prior exposure to pesticides had a significantly earlier age-at-onset (AAO) compared to the control group.[18] Besides earlier AAO, PD patients with pesticide exposure also have twice the mortality risk than their unexposed PD counterparts,[17] as well as higher odds of premature mortality if the pesticides were Glyphosate and Paraquat.[19]

The interaction of pesticides with genetic factors may also determine the susceptibility of a person to develop PD. An example is single nucleotide polymorphisms (SNPs) in candidate genes which are involved in detoxification or neuronal uptake of pesticides and alter pesticide exposure. K variant of butyrylcholinesterase (BCHE) which is defined by SNP rs1803274, interacted significantly with pesticide exposure and increased the risk of PD only in those pesticide-exposed individuals.[20] This is because the presence of the gene reduces the serum activity of butyrylcholinesterase, a bioscavenger for pesticides. Hence, when exposed to pesticides, individuals with the K variant of BCHE appear to be at increased risk for PD.[20]

Heavy metal and organic solvent exposure

There were six studies in this review which found exposure to heavy metals and organic solvent as a risk factor for PD.[23–26] Study in Italy by Belingheri et al identified respondents with at least one exposure to heavy metals in their employment life. Among the metals included were aluminium, mercury, and lead. The study found that exposure to any of the metals was significantly associated with PD.[23] Participation in lead-containing activities was also associated with a 2.7-fold increased risk of Parkinson's disease.[24] One of the sources of lead exposure may come from lead service lines, which is the underground pipes that link the housing area to the municipal water source. Fall of acid rain corrodes the pipes which exposed lead to drinking water.[25] In rural areas, heavy metals exposure may be found in well water.[26] Organic solvent exposure also increases PD risk. Solvents are compounds that present in fuels, paints, glues, lubricants, degreasers, and cleaning solutions, and they have all been related to an elevated risk of PD.[5,21] An example is Trichloroethylene (TCE), which is a chlorinated solvent that was once widely used as a metal degreaser and as an ingredient in some consumer products.[32] A case study of a 47-year-old woman exposed to TCE for seven years in the 1990s first identified TCE as an environmental risk factor for PD.[33] Further studies in rodents confirmed that TCE treatment resulted in the demise of dopaminergic neurons in the midbrain and recapitulated other features of PD, such as neuroinflammation and -synuclein accumulation.[10] A recent study in the Finnish population examining the risk of PD due to occupational exposure to solvents also concluded that the risk of PD was significantly associated with employment using chlorinated hydrocarbon solvents.[34]

Drug abuse

Drug abuse , has been associated with an increased risk of developing PD. Certain substances, when abused over a long period of time or taken in high doses, have been found to damage dopamine-producing neurons in the brain, a crucial aspect of the pathogenesis of PD. Cocaine is one of these illegal substances found in this review.[31] Cocaine cause overexpression of alpha-synuclein in dopaminergic neurons which may increase the risk of degenerative changes in dopaminergic neurons. Besides cocaine, methamphetamine or other amphetamine type drugs have also shown to increase risk of PD.[38]

Air pollutants

There are four studies that found association of air pollution with PD in this review. [27–30] Air pollutants are caused by a mixture of different pollutants, including Nitrogen dioxide (NO_2) and particulate matter (PM). NO_2 is a reactive gas produced by combustion processes and is a major component of smog. It can irritate the eyes, nose, and throat and has been linked to an increased risk of respiratory diseases such as asthma and bronchitis.[39] A retrospective cohort study in Korea by Jo et al. found that statistically significant association between NO_2 exposure and PD risk.[30]

Meanwhile, PM or particle pollution refers to microscopic solid and liquid particles suspended in the air and is originated from primary and secondary sources. Primary sources generate PM themselves (e.g., wood stoves, forest fires), while secondary sources emit gases that can form particles (e.g., power plants and coal).[40] PM_{10} and $PM_{2.5}$ are often used as measures of particulate matter in the atmosphere because they represent particles less than or equal to 10 micrometres (μm) and 2.5 micrometres in diameter, respectively. Because particles in this size range are small enough to be inhaled into the lungs, they can have negative health effects, especially for people with heart or lung disease.

PM in the air, even at low concentrations, has been linked to reduced human health and life expectancy. It is known that the complex dose and duration of a person's environmental exposure to certain metals and toxins in particulate matter can lead to inflammation, neurodegeneration and other chronic disease processes.[27] A study conducted in North Carolina tested the hypothesis that residents exposed to chronically elevated levels of airborne $PM_{2.5}$ were at greater risk of dying or being hospitalized from neurodegenerative diseases and found that mortality rates and risk of hospitalization for Parkinson's were higher among residents of the southern Piedmont area of North Carolina, which is exposed to airborne $PM_{2.5}$ levels above the WHO standard.[27] A study done among the American Medicare population also found that PD patients exposed to annual mean $PM_{2.5}$ in the USA were significantly associated with first hospital admission.[28] Meanwhile, another study conducted in the canton of Geneva found a significant positive association between PD clusters and atmospheric NO_2 and PM_{10} concentrations, highlighting clusters of high and low risk of PD in the spatial distribution of PD in the region.[29]

Source of water

Several studies in this review reported possible association of water sources such as springs and well with PD.[14,22,26] For example, Rosales et al in the Philippines found that one of two individuals diagnosed having PD obtained water from deep well, which was not regulated by the Philippines authority.[14] Another study in Morocco also found association of spring water consumption with PD.[22] However, a meta-analysis of fifteen observational studies found no association between well water consumption and the risk of PD, [35] which may actually indicate that these water sources are actually safe, but may be contaminated with agrochemicals or heavy metals which had been proved to be linked to PD.[36] A study in the USA, examining groundwater from public supply wells across the country, found six pesticide compounds and 1.6% of wells had concentrations approaching levels of potential concern (individual or summed benchmark quotients (BQs) or estimated benchmark quotients (BQE) > 0.1)[37] Meanwhile, a study by Cagac in Iğdır province found that levels of heavy metals and anions such as iron, lithium, manganese and nitrate levels were significantly higher in well water.[26]

CONCLUSION

In conclusion, PD is a complex neurological disorder that involved multiple environmental risk factors. These include exposure to pesticides, heavy metals and organic solvents, as well as drugs abuse. Furthermore, air pollutants such as $PM_{2.5}$, PM_{10} and NO_2 have also been linked to the development of PD.

RECOMMENDATION

It is crucial to understand the role that these environmental factors play in the development of PD to develop effective prevention and treatment strategies. More research is needed to fully understand the interplay between these risk factors and the underlying mechanisms of PD but identifying and reducing exposure to these environmental factors could have a significant impact on the future incidence of this debilitating condition.

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