

Socioeconomic and Environmental Determinants of Parkinson's Disease

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ABSTRACT

PD is a major progressive neurological disorder. While research has underscored the role of genetic factors correlated with PD, very few cases display clear genetic foundations. As a result, it is crucial to understand the other key determinants involved in the pathogenesis of PD in order to more holistically understand its heterogeneous etiology. This literature review aims to explore the role that socioeconomic and environmental factors play in the development of PD through a literature review and qualitative thematic synthesis. The results of this review indicate that both socioeconomic and environmental factors were linked with PD. However, the strength of these associations diverged across studies and amongst factors. The most commonly identified socioeconomic contributors included occupational and lifestyle factors, education, and income and the most commonly identified environmental factors were pesticides and agricultural exposures and heavy metals. Other environmental factors, such as air pollution, solvents and industrial chemicals, and well-water exposure were also examined with emerging but tenuous evidence. Additionally, across both socioeconomic and environmental studies, consistent gender differences and occupational patterns are seen, suggesting connections between socioeconomic and environmental determinants. Overall, this review underscores the need for future research on how these factors influence PD and introduces possible clinical interventions that may address PD pathogenesis from these factors.

INTRODUCTION

Parkinson's Disease (PD), a major progressive neurological disorder in the world, affecting over 10 million people worldwide. (Luo et al.) Furthermore, it is designated as the most common serious movement disorder in the world, affecting around 1-3% of individuals over the age of 60. (Ball et al.; Samii et al.) PD is linked to the loss of dopaminergic neurons in the substantia nigra or the basal ganglia located in the midbrain. (Kalia and Lang) Symptoms of this disorder include both motor symptoms such as resting tremor, rigidity, bradykinesia, and postural instability, while also leaving non-motor symptoms like depression and constipation. (Di Monte et al.) The incidence of PD increases with age and is much more common in men than women. (*Parkinson Disease*) For instance, Caslake and colleagues, in their study, found that the age-adjusted male to female ratio was 1.87:1. (Caslake et al.)

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While research has underscored the role of genetic factors correlated with PD, very few cases display clear genetic foundations. (Kiebertz and Wunderle) In fact, while familial PD (PD caused by genetic mutations) accounts for 10-15% of all PD cases, the majority of cases are idiopathic and most likely develop due to other factors. (Ball et al.) As a result, it is crucial to understand the other key factors involved in the pathogenesis of PD in order to more holistically understand its heterogeneous etiology.

Research increasingly suggests that environmental and socioeconomic factors have critical roles in the onset and progression of PD (Atterling Brolin et al.; Ball et al.; Najafi et al.). Specifically, previous works have examined the risk of developing PD in regard to environmental factors including pesticides, industrial chemicals, heavy metals, and air pollution, and socioeconomic factors, including education, occupation/occupational exposures, healthcare access, and lifestyle. However, the extant literature lacks clear consensus on associations between environmental and socioeconomic factors on PD. Moreover, most current reviews examine the role of socioeconomic and environmental factors on PD separately. This, however, results in the inability to see interactions between socioeconomic factors and environmental factors and how they are interrelated. By integrating and combining these factors, this review aims to determine if socioeconomic factors cause exposure to environmental toxins, contributing to underlying differences in PD risk and progression. In other words, we aim to determine how these factors intersect to influence PD. This, in turn, will enable current researchers to better comprehend trends and identify gaps in current knowledge, allowing for future research on this topic. Even more, it will emphasize the need for public health interventions to reduce socioeconomic disparities and environmental neurotoxins that are affiliated with PD.

METHODS

Google Scholar was used as the primary search tool to identify peer-reviewed studies for this literature review. Articles were identified through an initial search using key words “Parkinson’s Disease and socioeconomic factors,” and “Parkinson’s Disease and environmental factors”. This allowed us to identify key factors and broad trends between these factors and PD. Following this initial search, a second search was conducted to identify additional studies that examined individual factors in relation to PD that were not well represented in the initial search, including search terms: “Parkinson’s Disease and pesticides”, “Parkinson’s Disease and heavy metals”, and “Parkinson’s Disease and Solvents and Industrial Chemicals”. To be included in this study, articles needed to be written in English and the research needed to be focused on human populations. Articles also had to examine an association between PD and at least one socioeconomic (education, income, occupation, socioeconomic status) or environmental (chemicals, heavy metals, air pollution, pesticides, rural/farming lifestyle) factor, with quantitative results to substantiate this association. Articles were excluded from the study if they consisted of solely genetic or racial focused research, used non-human populations in their study, did not have clear measurement variables and methods, or lacked any measurable statistical results. From this process, 14 articles were identified for our review, consisting of cohort, case-control, cross-sectional, and meta-analytic studies that all were centered on the role of socioeconomic/environmental factors on PD.

From this, we performed a qualitative thematic synthesis, comparing and integrating results from all studies in order to identify trends and interpret findings systematically. This was done by grouping studies based on its domain (socioeconomic or environmental). Following this, we took note of patterns between risk estimates in relation to specific factors (such as pesticide exposure). We then found common converging trends across studies as well as studies that act as outliers and did not exhibit these trends. This approach allowed us to capture the true character and variability of PD in relation to its association with socioeconomic and environmental factors, despite the heterogeneity of the studies.

While doing this, we took into consideration the limitations of each study and unique study attributes such as experimental design, using odds ratios, relative risk, hazard ratios, standard incidence ratios (SIRs), standard mortality ratios, incidence rates, prevalence rates, different models/regressions, types of stratification analyses (sex, socioeconomic status, or urban/rural), and population vs regional/local scale.

RESULTS

Overall, fourteen studies were identified as relevant and selected to be included in this literature review. The included studies consist of six primarily epidemiological studies- including population-based, case-control, and ecological designs (Caslake et al.; Frigerio et al.; Li et al.; Lix et al.; Najafi et al.; Rybicki et al.)- as well as eight meta-analyses or narrative reviews (Atterling Brolin et al.; Ball et al.; Di Monte et al.; Kieburtz and Wunderle; Luo et al.; Priyadarshi, Khuder, Schaub, and Shrivastava; Priyadarshi, Khuder, Schaub, and Priyadarshi; Vellingiri et al.). These studies were conducted across multiple different populations, including countries such as Sweden, Scotland, United States, Canada, and Iran.

Upon reviewing this literature, we found that both socioeconomic and environmental factors were linked with PD. However, the strength of these associations diverged across studies. This may be due to study variability as studies differed in many ways (the scale of their research, country/population, design, and variables/statistical measures used to quantitatively evaluate how their chosen socioeconomic and or environmental factors influenced PD). The most commonly identified socioeconomic contributors included occupational factors, education, and income and the most commonly identified environmental factors were pesticides and agricultural exposures and heavy metals. Other environmental factors, such as air pollution, solvents and industrial chemicals, and well-water exposure were also included with emerging but tenuous evidence.

DISCUSSION

Socioeconomic Determinants

Socioeconomic determinants are an important factor in PD pathogenesis. Associations between PD and socioeconomic determinants underscore possible disparities and access to healthcare and treatment for PD for those with lower income.

Occupational Factors

One key socioeconomic determinant examined in the literature was occupation. A nationwide study conducted in Sweden shed light on how occupation influences PD. Using SIRs to compare hospitalization rates, this study (Li et al.) found that men in manual labor occupations (typically falling in lower SES brackets) including farmers, wood workers, wall paperhangers and painters had increased hospitalization rates of PD among male occupations. This study also showed that some higher SES occupations (administrators, managers, sales agents, and teachers) had increased hospitalization rates of PD, possibly due to differences in lifestyle (e.g. stress levels, sedentary work) or due to greater healthcare access, leading to overrepresentation. Additionally, gender differences that were found as associations amongst females regarding their occupations were more tenuous compared to males. Overall, this trend observed in occupation displays the nuanced, intricate association between SES and PD is due to the interplay of a variety of factors that cause an individual to develop PD as a result. .

Income

Income was another socioeconomic factor assessed in the literature. A population-based study conducted in Manitoba, Canada (Lix et al.), compared age standardized prevalence (number of total cases) and incidence (the number of new cases) rates of PD across urban-rural areas. The authors found higher PD prevalence and, in urban areas, higher PD incidence, were most strongly linked to the quintile with the lowest area-level income, indicating that socioeconomic disparities may contribute to and exacerbate PD burden. In this study, differences in rates of PD among rural areas were smaller and not statistically significant.

Similarly, a study in Tehran, Iran (Najafi et al.), examined the role of income on PD. By comparing odds ratios computed from logistic regressions and measuring wealth based on an asset-based index, the authors found that individuals with lower wealth indexes had measurably higher PD risk, while intermediate and affluent groups had reduced PD risks. This study also used perceived SES (how people ranked their own social and economic status on a 10-step ladder) as a factor. Unexpectedly, authors found that the subjective measure of perceived SES had the strongest association with PD risk compared to the objective measures, such as wealth, income, education, and occupation in their study. Participants who ranked themselves as having intermediate or affluent SES had lower PD risk compared to others who had low self-perceived SES. This indicates that perception and attitude towards one's socioeconomic status plays a role in PD pathogenesis. This could be due to participants' ratings reflecting stress levels, which is commonly associated with neurodegeneration. Even more, this result might be due to perceived SES playing a role in the steps that one takes regarding one's health. However, because evidence is limited,

this result requires further research to understand perceived SES influence on PD more comprehensively. In sum, lower income is associated with higher risk of PD.

Education

Previous research has also examined the relationship between education and PD with mixed findings. A study conducted in Iran (Najafi et al.) grouped participants into three education groups (primary or below, secondary, and higher education) and performed logistic regressions while adjusting for confounding variables. Authors found that some groups with higher education displayed higher PD prevalence, likely as a result of diagnostic awareness. However, much more research needs to be done to better understand the role it plays. Education may act as a proxy for other factors influencing PD, such as greater diagnostic awareness, healthcare access, or occupational/lifestyle factors.

General SES

Some previous works use general SES to study the association with PD. Examining the relationship between PD and SES, the PINE study conducted in Scotland, used deprivation scores as a SES measure and compared incidence rates per 100,000 individuals. In this study, each potential case of PD was assessed by neurologists and supervised trainees, strengthening its methodology, making its contradictory findings surprising. The findings from this work show no significant relation between SES and PD incidence (Caslake et al.). This may be attributed to the large variability, creating a discrepancy in results.

Overall, SES is associated with PD burden, outcomes, and in some studies incidence. However, causal relationships have not been established. This research indicates that SES influences PD both directly (through education, income, perceived SES, occupation, etc.) and indirectly through environmental exposure and possible differences in accessing healthcare. Although lower SES was generally associated with higher PD risk, specific results amongst various socioeconomic factors in studies differ.

Environmental Determinants

Environmental exposures are one of the most prominent non-genetic factors that contribute to PD development. Pesticides, agricultural exposures, heavy metals exposures, air pollution, solvents and industrial chemicals, and well-water are examined as potential environmental contributors.

Pesticides and Agriculture Exposures

One of the most commonly studied sources of environmental exposure associated with PD development are pesticides and other agricultural exposures. Numerous previous works have sought to examine this relationship. For example, a population-based case control study in Minnesota (Frigerio et al.) investigated the influence of pesticides on PD. By calculating odds ratios, using logistic regression, and adjusting for confounding variables (age, sex, education, and smoking), the authors found that men with pesticide exposure had a significant association with PD with an odds ratio of ~2.4. Women showed no positive associations between pesticide exposure and elevated PD, highlighting gender differences.

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Frigerio and colleagues (2006) also estimated a population-attributable PD risk due to pesticides of 7% overall and 15% in men, suggesting that a significant amount of PD in men could be related to pesticide use. In addition, this calculated risk is important as it highlights the significance or severity of gender difference. The percentage of PD risk due to pesticides solely in men is estimated to be double that of both men and women combined, showing the scale of the gender difference and indicating that females are less susceptible to pesticides.

Similarly, a nationwide hospitalization study in Sweden (Li et al.) examined occupations that were associated with exposures to environmental toxins as a proxy for pesticide exposure to investigate associations between these occupation-based toxins and PD. Using SIRs for PD hospitalization, the results suggest that farmers, painters, and woodworkers (occupations high in pesticide exposure), had elevated risk, further indicating that pesticides (and other factors) are associated with PD.

To examine this association further, a meta-analysis (Priyadarshi, Khuder, Schaub, and Priyadarshi) pooled together odds ratios from case-control studies in which 11-19 studies were randomly selected per exposure. Examining the influence of farming, rural residence, well water, pesticides, and farm animals on PD risk, results found odds ratios were greater in farming areas, rural living regions, and with pesticide exposure. Pesticide exposure had the highest odds ratio (1.85), followed by rural living (1.56), and then farming/farm animal exposure (1.42). Moreover, epidemiological works have also shown that long-term exposure to pesticides makes the odds of developing PD 1.5-2.5 times higher than that of a person who is unexposed (Priyadarshi, Khuder, Schaub, and Shrivastava). This is another important factor to consider with the increasing use of pesticides in today's agriculture. With a strong association with PD, this could pose a severe issue.

Together these works show that exposure to pesticides has one of the strongest and most consistently observed environmental associations with PD. This connection may have a mechanical explanation as pesticides are hypothesized to contribute to mitochondrial dysfunction, oxidative stress, and α -synuclein aggregation which can cause loss of dopaminergic cells, as seen in PD pathogenesis.

Heavy Metals

Heavy metals, including iron, copper, manganese, mercury, nickel, cobalt, and chromium, have also been linked to PD across several studies. To examine exposure effects, a Michigan-based study sought to examine the association between industrial exposures and PD mortality. This study (Rybicki et al.), was conducted across 83 counties and used age-adjusted PD mortality rates from the 1980 United States standard population (calculated from death certificates) linked with the 1987 County Business Patterns database in order to evaluate the relation between these exposures and PD. Using Standard Industrial Code (SIC) classifications, researchers were able to link specific heavy metals to specific industries (manufacturing of iron, paper, and chemicals). Overall, the authors found that counties with at least one industry associated with the use of heavy metals had 20-32% higher PD mortality rates compared to counties without these industries. Iron-associated industries had the strongest relationship with PD mortality. This association was further supported when looking at the mean death rate among individuals diagnosed with PD. Counties with no industries had 16.3 deaths per 100,000 people; counties with one or

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more of these industries had 26.9 deaths per 100,000 people; and counties with two or more of these industries had 25.7 deaths per 100,000 people, indicating that more than one industry does not have a greater association with PD risk.

Review and epidemiological studies (Rybicki et al.; Vellingiri et al.) further indicate that heavy metal exposure through one's occupation, such as mining and welding, is associated with elevated PD risk. This is supported mechanistically as the association between heavy metals and PD is hypothesized to be due to heavy metals causing dopaminergic neuron loss, α -synuclein aggregation, oxidative stress, and more, all of which are biological symptoms of PD (Vellingiri et al.).

Air Pollution

Air pollution is another environmental factor assessed in regard to impacting PD development. While little research has been conducted examining this relationship, it is an emerging factor. Biologically, air pollution has been found to cause oxidative stress and neuroinflammation, both of which are associated with PD.

A review (Atterling Brolin et al.) evaluated air pollution and found that PM 2.5 (fine particulate matter with a diameter of $\leq 2.5\mu\text{m}$), in several cohort studies, was linked to trace increases in PD risk. This suggests that exposure to air pollutants, such as fine particulate matter (PM 2.5), is associated with PD. This association, however, was smaller compared to other environmental factors. The authors suggested that policy interventions may aid in the mitigation of the impact of these exposures on PD. While more research needs to be done to further explore this relationship, these findings indicate that PD has an association with air pollution.

Solvents and Industrial Chemicals

Several studies also describe the potential association between solvents/industrial chemicals and PD. A study conducted in Sweden found that male painters and varnishers, who typically are frequently exposed to organic solvents, paint thinners, and degreasers through their occupation, had higher SIRs for PD (Li et al.). Similarly, a review (Atterling Brolin et al.) underscored a specific industrial degreaser, Trichloroethylene (TCE), as an emerging risk factor of PD. To investigate this association, the authors included case reports of workers exposed to TCE who developed PD later in their life. In addition, results supported this mechanistically with animal models that exhibited selective dopaminergic neuron loss and other PD biological symptoms. Contradicting this, the study conducted in Minnesota (Frigerio et al.) found that while pesticides were associated with PD, no chemical products- including paints, cleaning agents, petroleum products, printing products, and glues- had any significant association with PD. Overall, literature indicates that solvents and industrial chemicals have a positive association. However, one study diverges from this, highlighting the need for further research on how they influence PD.

Well Water Usage

Lastly, reviews considering well water as a potential environmental exposure increasing PD risk displayed overall weak results. Priyadarshi and colleagues (2001) found that well water use showed the smallest association with increased PD risk, compared to all other environmental factors (rural living, exposure to

farming/farm animals, and pesticides). In addition, while having an odds ratio of 1.26, the association between well water and PD risk was overall not significant (Priyadarshi, Khuder, Schaub, and Priyadarshi). Authors emphasized, however, the possibility of well water serving as an indicator of other exposures in rural and farming environments. Another study (Rybicki et al.), was conducted across 83 counties in Michigan and used age-adjusted PD mortality rates from the 1980 United States standard population (calculated from death certificates) linked with the 1987 County Business Patterns database in order to evaluate the relation between these exposures and PD. Authors identified a negative association between well water use and PD as counties with higher well water use had lower PD mortality rates. Across studies, mixed findings were seen in regards to well-water usage having an association with elevated PD risk. More studies need to be done in order to understand this possible association better.

Overall, many environmental exposures have been strongly associated with PD. Together these works highlight relationships between some environmental exposures such as pesticide and heavy metals with PD risk. Additionally, exposures to air pollution, solvents and industrial chemicals, as well as to well water are emerging determinants that have relatively small associations and mixed findings, and as a result, need to be further studied.

Interaction Between Socioeconomic and Environmental Determinants

Gender Differences

Across studies of both socioeconomic and environmental factors, consistent differences were found in the strength of certain associations with PD risk between genders. For example, associations with PD risk and exposures among women were frequently less substantial or non-significant compared to associations among men, whose PD risk exhibited stronger associations to SES and occupational factors. In fact, one study found that men are 1.5-2 times more likely to develop PD than women when considering risk factors (Kiebertz and Wunderle). This may be due to differences in occupational exposures as men may more commonly work in professions that have greater exposure to factors that contribute to PD. For instance, men are more likely to be farmers and to work in the industrial setting and as a result may have more exposure to environmental determinants, such as pesticides and industrial metals, that are associated with PD risk. Another possible explanation is hormonal protection in women. Estrogen may protect neurons from being damaged, helping to reduce PD in women as PD is mechanistically caused through a loss in dopaminergic cells (Ball et al.). Finally, women may have key differences in their lifestyle or access to healthcare that could contribute to reduced risk or protective factors. By contrast, one study found that female nurses had elevated PD risks compared to females in other professions. This may be attributed to chemical exposure and stress in their occupation (Li et al.). In both socioeconomic and environmental studies, more research needs to be conducted to understand the divergences between men and women in these associations.

Occupation Patterns

Occupation patterns were also common between environmental and socioeconomic studies. While seen as a socioeconomic factor, these patterns show the interplay of social determinants with environmental factors as many of the lower SES occupations that exhibit higher PD risk involve consistent exposure to neurotoxins and environmental factors seen to be associated with PD. For instance, as mentioned

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previously, farmers exhibit higher PD risk and also have long-term exposure to pesticides through their profession.

Clinical Implications

The growing evidence of the influence of socioeconomic and environmental determinants on PD reveals several important clinical implications. Primarily, because certain factors, such as pesticides and heavy-metal exposure, are consistently related to elevated PD risk across several studies, clinicians should examine environmental exposure histories of patients through their occupation and daily life. This comprehensive review of environmental exposures may contribute to better identification of high-risk populations. Additionally, while there are no current environmental protocols, this evidence could lead to mitigation strategies and policy interventions for environmental determinants. For instance, the use of protective material when working in agricultural and industrial work could, and should be implemented, to reduce exposure and PD risk. Furthermore, with policy changes, using these materials could be limited or more highly regulated through greater management of pesticides and agricultural chemicals to reduce exposure and risk. Finally, because some studies show lower SES is associated with higher PD incidence, the results of this review emphasizes a need for greater resources in underserved areas, indicating that steps need to be taken to address said disparities.

Limitations

Several limitations are present in this review, which are important to consider when interpreting results. Firstly, across many environmental studies, assessment of exposure was reliant on self-reporting. For instance, Frigerio (2006) used telephone interviews and an established questionnaire to collect data on participants' exposures, introducing participant recall bias into their study as participants may not accurately remember or give correct information (Frigerio et al.). Additionally, several studies were reliant on occupation titles as a proxy to quantify exposure rather than directly measuring exposure to factors (Li et al.). As a result, these studies assessing only job titles do not adjust for lifestyle confounding factors, which means that other exposures that are not being considered are playing a role in the results. Another important limitation to consider is the role of confounding variables due to the intertwinement between socioeconomic, environmental, and lifestyle factors. While some studies try to adjust for these, it is likely that researchers were not able to account for these completely. This makes it harder to attribute higher risk to an individual factor. Finally, the heterogeneity between studies is a key limitation as the included studies differed geographically, temporally, and methodologically. The research included in this review consisted of different study designs and were conducted across different countries and time periods. Likewise, researchers used different measurements to determine results, making it difficult to compare results and generate reliable findings. Despite these limitations, this review still works to provide a holistic understanding of current research being done in the study of the impact of socioeconomic and environmental exposures on PD.

Future Directions

Current literature reveals several gaps that future research should work to address. Through this future work, we can increase our knowledge on the role these factors play in PD pathogenesis. For example, in

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order to more effectively find consistent associations, larger longitudinal studies need to be conducted. This will allow for more generalizable results that can be compared and viewed across time periods and populations. Additionally, future studies need to be conducted in more diverse and underserved communities in order to understand the disparities present in PD for these socioeconomic and environmental determinants. Future research should also focus on emerging determinants: solvents, air pollution, and well-water and their role contributing to PD. Additionally, future works should utilize objective measures of environmental exposure (e.g., blood tests) in addition to subjective self-report. Finally, research should be conducted to examine the relationship interplay and compounded impacts of socioeconomic and environmental factors. Patterns, such as gender difference and high risk in occupation, are interconnected to both socioeconomic and environmental factors. As a result, it is important to research if socioeconomic conditions increase environmental exposure to possible PD risk factors, and if so, what the mechanism behind this relationship is.

CONCLUSION

In conclusion, when examining the influence of socioeconomic factors on PD, research suggests that lower socioeconomic status is often associated with higher PD burden and mortality, although associations with incidence are not consistent. Through this examination, several common patterns emerge between occupation and PD risk such that men with lower-skilled occupations that require more manual labor exhibited higher PD incidence and women's PD risk is not typically significantly associated with occupation. The role of education was also less strongly related to PD risk, while still demonstrating a positive association. Environmental exposures, especially pesticides and heavy metals, have been consistently associated with elevated PD risk as well. Longer exposures to pesticides as well as high levels of exposure at once were associated with strongest risk; however, causal relationships have not yet been established. Similarly, exposure to heavy metals was related to greater PD incidence and mortality. Additionally, PD risk was elevated in areas with industrialization and rural farming. Finally, while not well established, urban air pollution has been seen as a factor contributing to PD risk, with emerging but less consistent evidence. Across socioeconomic and environmental studies, researchers emphasized gender differences and the role of occupations demonstrating that multiple factors contribute to PD pathogenesis. In sum, the result of these studies indicate the role of socioeconomic and environmental factors on PD risk. These exposures should be considered when developing PD prevention and treatment plans.

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