Review

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Air pollution and Parkinson’s disease – evidence and future directions

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Abstract: Parkinson’s disease (PD) is a neurodegenerative disease of unknown etiology that is thought to be caused by a complex combination of environmental and/or genetic factors. Air pollution exposure is linked to numerous adverse effects on human health, including brain inflammation and oxidative stress, processes that are believed to contribute to the development and progression of PD. This review provides an overview of recent advances in the epidemiology of air pollution and PD, including evidence of the effects of various pollutants (ozone, PM\textsubscript{10}, PM\textsubscript{2.5}, PM\textsubscript{2.5-10}, NO\textsubscript{x}, NO\textsubscript{2}, CO, traffic air pollution, second-hand smoking) on PD risk. Based on this evidence, promising opportunities for future research are outlined, including: (1) studies of smaller particle sizes that cross the blood-brain barrier, (2) studies of the effects of air pollution on PD mortality and/or progression; (3) studies of interactions of air pollution with gene environment and other environmental factors.

Keywords: air pollution; epidemiology; Parkinson’s review; second-hand smoke.

Introduction

This article presents a review of recent epidemiologic literature on air pollution and Parkinson’s disease (PD), with an objective to summarize the available information about the associations of several air pollutants with PD. The recent years have seen a growing number of epidemiological studies on the association between air pollution and PD. There is a need for compilation and critical assessment of these results. Based on this assessment, this review also discusses some challenges and outlines several opportunities for future research in this direction.

Over one million Americans suffer from PD (1), which costs billions of dollars annually to the US economy (2). A neurodegenerative disease of unknown etiology, PD is thought to be caused by a complex combination of environmental and/or genetic factors. It is characterized by the depletion of dopaminergic neurons in the substantia nigra and the resulting progressive loss of normal motor function (1). The exact cause of neuronal depletion is unknown, but it may involve mitochondrial dysfunction (3), inflammatory reactions and oxidative stress (4). Exposure to pesticides (5), herbicides (6) and heavy metals (7) were shown to increase PD risk, whereas smoking (8–10), use of non-steroidal anti-inflammatory drugs (NSAIDs) (11), consumption of caffeine and high urate (12) are considered as protective factors.

Evidence of early PD pathology in the olfactory bulb of PD patients, which may precede brain pathology (13), suggests a potential role of inhaled toxins as a risk factor for PD. Exposure to elevated levels of air pollution is linked with numerous adverse effects on human health (14–17). In the last several years, an interest has grown in understanding whether air pollution might be a risk factor for PD. Air pollution exposure has been linked to brain inflammation and oxidative stress (18, 19), processes that are believed to contribute to the development and progression of PD (20). For example, residents of Mexico City, which is one of the most polluted metropolitan areas in the world, showed evidence of dangerous levels of neuroinflammation, an altered brain innate immune response, and early accumulation of alpha-synuclein (21). In a pilot study in Mexico city, 56% of randomly selected healthy children showed prefrontal white matter with hyper intense lesions (22). Air pollution is also thought to have neurotoxic effects on brain development (22). A role of inflammation in the pathogenesis of PD is supported by post-mortem, in-vivo and epidemiological studies (20). High plasma IL-6 concentrations were found to predict an increased PD risk in men (23). Plasma concentration of urate, a potent antioxidant, have consistently been associated with decreased PD risk and progression (24–27). Dietary urate intake is linked with lower risk of PD (12). Several epidemiological studies reported a protective

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effect of non-steroidal anti-inflammatory medications (NSAIDs) (11, 28, 29) on the risk of PD. Intake of vitamin E, a potent dietary antioxidant is also linked reduced PD risk (30). Intake of coffee and caffeine, also known for its antioxidant properties, were associated with a lower PD risk in numerous studies (31, 32).

Methods

The literature search for this review was conducted in PubMed between December 26, 2016 and January 6, 2017. Articles were accessed through PubMed using the terms “air pollution” and “Parkinson’s disease” (using both Parkinson’s disease and Parkinson disease as search terms) as well as “air pollution” and “second-hand smoking”. References of identified studies were reviewed for additional relevant literature. Studies were eligible for inclusion if the primary aim or outcome was PD and exposure of interest was either air pollution or second-hand smoking. Only articles in English were considered. We excluded all reviews and meta analyses, but used them to search for other relevant articles describing original research. Articles dealing with exposures other than air pollution or second hand smoking, and with outcomes other than PD, were excluded. We only included articles focusing on epidemiological research in humans, articles describing animal or other laboratory studies were excluded. Figure 1 presents a flow-chart of the literature search and review process.

Air pollution and PD

This section of the review focuses on the observed effects of the individual pollutants on PD, including particulate matter (PM$_{10}$, PM$_{2.5}$ and PM$_{2.5-10}$), NO$_x$, NO$_2$, CO, “traffic air pollution”, ozone, airborne metals, gene-pollution interactions and second-hand smoking. Table 1 outlines the relationships between these pollutants and PD identified in the studies included in this review. Table 2 summarizes more detail of the association of second-hand smoking with PD discussed below, and Table 3 summarizes all the studies on air pollution and PD (exclusive of second-hand smoking), included in the review.

Particulate matter air pollution (PM)

In a nested case-control study within the National Institutes of Health (NIH) – AARP Diet and Health Study (34), Liu et al. (34) examined exposure to PM$_{10}$, PM$_{2.5}$ and NO$_2$ with relation to the odds of PD among 1556 self-reported PD cases and 3313 matched controls. Air pollution exposure
was estimated by using a nationwide fine-scale geostatistical model that incorporated roadway information and other geographic covariates. In their primary analyses, the authors reported no significant associations between an exposure to ambient PM$_{10}$, PM$_{2.5}$ and NO$_2$ and PD risk. However, in pre-planned and post-hoc stratified analyses, the authors observed positive significant associations between PM$_{10}$ and PM$_{2.5}$ and odds of PD among women \( OR = 1.65; 95\% \text{ CI: } 1.11–2.45; \text{ p-trend } = 0.02 \) comparing the top to bottom quintiles. Furthermore, odds of PD were elevated with exposure to PM$_{2.5}$ among never-smokers \( OR = 1.29; 95\% \text{ CI: } 0.94, 1.76; \text{ p-trend } = 0.04 \). For both PM$_{10}$ and PM$_{2.5}$, the risk of PD was elevated among female never-smokers \( OR = 1.79; 95\% \text{ CI: } 1.01, 3.17; \text{ p-trend } = 0.05 \) for PM$_{10}$ and \( OR = 2.34; 95\% \text{ CI: } 1.29, 4.26; \text{ p-trend } = 0.01 \).

Palacios et al. (35, 36, 42) conducted two prospective-cohort studies examining the association between PM air pollution exposure and risk of PD in men and women (Table 1). They examined the association between exposure to PM air pollution in the Nurses Health Study (NHS), a prospective cohort study of female nurses living throughout the US. Air pollution exposure was estimated by using spatio-temporal models that combined information from

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**Table 1:** Association of air pollutants with PD in the current literature.

<table>
<thead>
<tr>
<th>Pollutant type</th>
<th>Positive association</th>
<th>Inverse association</th>
<th>No association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozone</td>
<td>Kirrane et al. (33)$^a$</td>
<td></td>
<td></td>
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<tr>
<td>PM$_{10}$</td>
<td>Liu et al. (34)$^a$ (female never-smokers only)</td>
<td></td>
<td>Palacios et al. (35, 36)$^b$, Lee et al. (37)</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>Kirrane et al.$^a$, Liu et al.$^a$ (female never-smokers only), Lee et al. (37)$^a$ Zanobetti et al. (38)</td>
<td></td>
<td>Palacios et al. (35, 36)$^b$</td>
</tr>
<tr>
<td>PM$_{1.0-10}$</td>
<td>Lee et al. (37)$^a$</td>
<td></td>
<td>Palacios et al. (35, 36)</td>
</tr>
<tr>
<td>NO$_x$</td>
<td>Ritz et al. (39)$^a$, Lee et al. (37)$^a$</td>
<td></td>
<td>Liu et al. (34)$^a$</td>
</tr>
<tr>
<td>NO$_x$/traffic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manganese (Mn)</td>
<td>Finkelstein and Jerrett (40)$^a$, Willis et al. (41)$^b$</td>
<td></td>
<td>Palacios et al. (42)$^b$</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>Willis et al. (41)$^b$</td>
<td></td>
<td></td>
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<tr>
<td>Mercury (Hg)</td>
<td>Palacios et al. (42)$^b$</td>
<td></td>
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<tr>
<td>Gene-pollution interactions</td>
<td>Lee et al. (43)$^a$ (for IL1-b polymorphism)</td>
<td></td>
<td>Lee et al. (43)$^a$ (for TNF$\alpha$ polymorphism)</td>
</tr>
<tr>
<td>Second-hand smoking</td>
<td>O’Reilly et al. (44)$^b$; Searles Nielsen et al. (45)$^b$; Mellick et al. (46)$^b$</td>
<td></td>
<td>Tanaka et al. (47)$^a$</td>
</tr>
</tbody>
</table>

$^a$Case-control study. $^b$Prospective cohort study.

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**Table 2:** Evidence for an association of second-hand smoking and PD.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Population</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Searles-Nielsen et al. (45)</td>
<td>Case-control</td>
<td>Newly diagnosed PD cases ( n = 154 ) from western Washington State and gender and age-matched neurologically normal controls ( n = 173 )</td>
<td>Reduced risk of PD among ever second-hand smokers only. Risk inversely associated with years exposed</td>
</tr>
<tr>
<td>Tanaka et al. (48)</td>
<td>Case-control</td>
<td>249 PD patient and 369 Controls in Japan</td>
<td>No association between second-hand smoking and PD</td>
</tr>
<tr>
<td>O’Reilly et al. (44)</td>
<td>Prospective cohort study</td>
<td>455 incidence PD cases in two prospective cohorts (Nurses Health Study: 26-year follow-up and health professionals follow-up study: 18 years follow-up)</td>
<td>Reduced hazard of PD among participant who reported that both parents smoked compared to those for whom none of the parents smoked</td>
</tr>
<tr>
<td>Mellick et al. (46)</td>
<td>Case-control</td>
<td>151 Australian PD patients recruited from a neurology clinic and 151 matched controls</td>
<td>No statistically significant protective associations with (1) ever having lived with a smoker, (2) years lived with a smoker, (3) ever worked in a smoky workplace and (4) years worked in a smoky workplace, including among never-smokers</td>
</tr>
<tr>
<td>Study</td>
<td>Popn.</td>
<td>Size</td>
<td>Design</td>
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<tr>
<td>Finkelstein and Jerrett (40)</td>
<td>Residents of Toronto and Hamilton, Canada</td>
<td>332 PD cases identified via admin. Database linkage</td>
<td>Case-control</td>
</tr>
<tr>
<td>Willis et al. (41)</td>
<td>29 million Medicare beneficiaries in the year 2003</td>
<td>35,000 incident PD cases</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Palacios NHS PM, (36)</td>
<td>NHS, a prospective cohort of 115,767 US nurses living through the continental US</td>
<td>508 incident PD cases</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Palacios NHS Metals, (42)</td>
<td>Nurses Health Study, prospective cohort of 94,430 US women</td>
<td>425 incident PD cases</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Kirrane et al. (33)</td>
<td>Farmers and their spouses enrolled in Agricultural Health Study</td>
<td>301 PD cases (104 in NC and 195 in IA)</td>
<td>Case-control</td>
</tr>
<tr>
<td>Zanobetti et al. (38)</td>
<td>Medicare enrollees &gt;65 years old</td>
<td>40,496 PD hospitalizations</td>
<td>Multi-site case-crossover</td>
</tr>
<tr>
<td>Ritz et al. (39)</td>
<td>Danish hospital registries</td>
<td>1696 PD cases from Danish hospital registries diagnosed 1996–2009 and 1800 population controls matched by gender and year of birth</td>
<td>Case-control</td>
</tr>
</tbody>
</table>
the Environmental Protection Agency (EPA) Air Quality System (AQS) as well as data from several other sources including the Interagency Monitoring of Protected Visual Environments (IMPROVE) network and a number of Harvard-based studies. They did not find associations between PM$_{10}$, PM$_{2.5}$ and PM$_{2.5-10}$ and PD risk in women. In a separate study, Palacios et al. (35) examined exposure to PM$_{10}$, PM$_{2.5}$ and PM$_{2.5-10}$ in the Health Professionals Follow-up Study (HPFS), a prospective cohort study of men living throughout the continental US (35). They followed over 50,000 men in the HPFS, between 1988 and 2007, estimating air pollution via a spatio-temporal model that linked each participant’s time-varying address to address-specific PM levels throughout the study. As in the previous study in women, this study in men reported no significant association between PM air pollution and PD, and the results tended towards a protective effect of air pollution on PD risk hazard ratio comparing the top to bottom quintile of PM exposure was 0.85 95% CI: (0.63, 1.15) for PM$_{10}$, 0.97 95% CI: (0.72, 1.32) for PM$_{2.5}$ and 0.88 95% CI: (0.64, 1.22) for PM$_{2.5-10}$. In their studies, Palacios et al. conducted sensitivity analyses restricting to participant who did not move during the studies, as well as analyses stratified by smoking.

In the Agricultural Health Study (AHS), Kirrane et al. (33) conducted a case-control study of PM$_{2.5}$ with relation to PD risk in Iowa and North Carolina. These authors used a hierarchical Bayesian model to predict 4-year ambient PM$_{2.5}$ levels based on geocoded addresses among AHS participants. The authors reported significant positive associations with PM$_{2.5}$ (OR = 1.34; 95% CI: 0.93, 1.93) in North Carolina, but not in Iowa (33).

Lee et al. (37) studied the relation between exposures to PM$_{10}$ and PD in 11,117 incident PD cases diagnosed between 2007 and 2009 and 44,468 age- and gender-matched population controls from the Taiwan’s National Health Insurance Research database. These authors did not report significant associations between PM$_{10}$ and PD (Table 1).

### NO$_x$, NO$_2$, CO, and “traffic air pollution”

In a nationwide case-control study in Denmark, Ritz et al. (39) examined the associations between traffic-related air pollution (represented by NO$_x$) and PD. These authors analyzed exposures to NO$_x$, NO$_2$, and CO but focused the analysis on NO$_x$ because of the high inter-correlation between the pollutants and NO$_2$ being a commonly studied air pollutant. This study had a long exposure period (1971 to index date) and a large sample size. The authors observed...
a 9% increase in PD risk (95% CI: 3%–16%) per interquartile range increase (2.97 μg/m³) in NO₂. This study also reported an effect modification by urbanity. The participants who lived in Copenhagen had the highest increase in PD risk (OR = 1.21; 95% CI: 1.11–1.31). For those living in provincial towns, the increase in PD risk was lower (OR = 1.10; 95% CI: 0.97–1.26), and no association was observed in rural towns. The study was stratified by gender and smoking status and noted no effect modification by gender. When stratified by smoking status, significant associations were observed among former and current smokers, but not among never-smokers. This observation was somewhat contrary to the finding by Liu et al. (34), who observed an effect of PM among never-smokers and female never-smokers. However, Liu et al. (34) also noted no significant effect of NO₂ among the rural and urban subgroups. Thus, difference suggests that whether one can observe an effect in never-smokers may depend on the type of pollutant under investigation (Table 1), highlighting the need for larger studies with the ability to examine subgroups and interactions.

Lee et al. (37) used 11,117 incident PD cases diagnosed between 2007 and 2009 and 44,468 age- and gender-matched population controls from the Taiwan’s National Health Insurance Research database to estimate the odds of PD associated with ambient concentrations of NO₂, SO₂, CO, O₃, and PM₁₀. Pollution exposure was estimated by using quantile-based Bayesian maximum-entropy models. The authors reported significant positive associations with the exposure to NO₂ (OR = 1.37; 95% CI = 1.23–1.52) and CO (OR = 1.17; 95% CI: 1.07–1.27). Interestingly, significant effects were seen only in multi-pollutant, but not in single-pollutant models. To the author’s knowledge, this is the only study to compare single-pollutant to multi-pollutant models in the context of air pollution and PD, and all of the other studies used single-pollutant models as the exposure. An improved understanding of the inter-relationship between multiple pollutants, and more studies utilizing multi-pollutant models would be useful.

Ozone

Kirrane et al. (33) examined the relationship between air-pollution and PD in a rural population by using the AHS. In a case-control study, these authors related levels of ozone (and PM₁₀ as discussed above) to PD risk in Iowa and North Carolina. These authors used a hierarchical Bayesian model to predict 4-year ambient ozone levels based on geocoded addresses among AHS participants. The authors reported significant positive associations of the warm season (April to November) ozone (OR = 1.39; 0.98–1.98) in North Carolina, but not in Iowa. Kirrane et al. (33) reported no significant associations with year-round ozone exposure (Table 1).

Airborne metals

The first epidemiological study of air pollution and PD known to the author of this review was performed by Finkelstein and Jerrett (40) in Hamilton and Toronto, Canada. Finkelstein and Jerrett (40) related modeled traffic pollution and airborne manganese (Mn) exposure at the participant’s residence locations, recorded using the postal code as one proxy and proximity to road as another proxy, with relation to PD risk. Mn is a metal used extensively in steel production, and previously linked to Parkinsonism, although this link remains controversial. The investigators noted a slight elevation in PD risk with Mn exposure, reporting about a 3% increase in the risk of PD [relative risk (RR) of 1.034 (95% confidence intervals (CI) 1.00–1.07)] for each 10 ng/m³ increase in Mn concentration (40), as well as a somewhat earlier onset of PD, in Hamilton, but not in Toronto. In this study, markers of traffic-derived air pollution did not predict increased PD risk.

In a large study using data on 29 million Medicare beneficiaries, Willis et al. (41) identified over 35,000 incident PD cases and performed county-level analyses of exposure to airborne copper (Cu), Mn and lead (Pb), with relation to PD risk. They used model-based publically-available air-pollution data provided by the EPA, which they linked to the Medicare database. In this study, counties with high Mn and/or Cu release had significantly elevated incidences of PD [RR = 1.78, 95% CI: 1.54, 2.07 for Mn and 1.1, 95% CI: 0.94, 1.31 for Cu] compared to counties with no or low release of these metals. This study focused on participants living in urban areas, designated as counties with population of 250,000 people or greater. This study benefited from a very large size but was limited by imprecise exposure (tract-level modeled metal release) and outcome (registry-based PD ascertainment). Because this study focused on densely populated areas, the results may also be confounded by easier access to healthcare and more active healthcare-seeking behavior among the participants. For example, due to differences in socioeconomic status, population density, physician availability, or other variables, participants in counties with higher metal emissions might be more likely to see a physician and receive a diagnosis of PD.
In a prospective cohort study, the NHS, Palacios et al. (42) the association between exposure to these HAPS, including antimony (Sb), arsenic (As), cadmium (Cd), chromium (Cr), Pb, Mn, mercury (Hg) and nickel (Ni) and the future risk of PD (Table 1). These authors linked county-level EPA data on Hazardous Air Pollutant (HAPS) to the NHS participants, and examined prospectively the association between exposure to the above airborne metals and the future risk of PD. They found some evidence of an association between an exposure to airborne mercury and risk of PD, particularly among never-smokers and among the participants living in counties with high population density (in access of 250,000 persons per county) (42).

Gene-pollution interactions

To the author’s knowledge, the only study of gene-environment interactions in the context of air pollution and PD was conducted within the PASIDA study using data from the Danish National Hospital Register (43) (Table 1). These authors genotyped two polymorphisms in the tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1β) genes and examined the interaction between these polymorphisms and exposure to NO₂ air pollution. They found a 3-fold elevation in risk of PD among participants with high NO₂ exposure who were carriers of the AA genotype of IL-1β, compared to those with lower NO₂ exposure and the GG genotype of the same gene (p-int: 0.01). The authors did not report significant interactions with the TNF-α polymorphisms. These findings were intriguing and merit further investigations and they also may suggest that the effect of air pollution on PD risk can be seen only among those with a genetic predisposition. More work is needed to study the relation between polymorphisms related to inflammation as well as other polymorphisms, and PD risk.

Hospitalization for PD

Zanobetti et al. (38), linked data from the Medicare beneficiary denominator file from the centers for Medicare and Medicaid services (CMS) to data on PM₂.₅ from the US EPA’s Air Quality Transfer Network to study the association between short-term (2-day average) air pollution exposure and risk for hospitalization for several chronic conditions including PD (identified via ICD-9 codes). They report an increased (3.23%, 1.08, 5.43) increased risk for hospitalization for PD for a 10 μg/m³ increase in the 2 days’ average PM₂.₅. They also examined whether hospitalization for PD modified the association between PM₂.₅ exposure and all-cause mortality (which was significantly associated with short term PM₂.₅ exposure) and did not find significant evidence of such effect modification.

Second-hand (passive) smoking

Second-hand smoking is a type of indoor air pollution. Interestingly, one of most consistently observed associations with PD is the inverse association between (personal) smoking and PD (48–52). Among participants who smoke themselves, the risk of PD is approximately half of that in non-smokers (49, 50). Several studies examined whether the persons regularly exposed to second-hand smoking but are not smokers themselves may be at a reduced risk of PD (Table 2).

In a case-control study in western Washington State, Searles-Nielsen et al. (45) considered 154 cases newly diagnosed with idiopathic PD and 173 neurological normal controls unrelated to these cases. These authors assessed whether, among never-smokers, second-hand smoking was related to a risk of PD. Smoking history was assessed via an in-person questionnaires containing questions regarding second-hand smoking (such as “ever lived with someone who smoked daily” and “ever worked with people who smoked daily”). The questionnaires also assessed the duration of exposure to second-hand smoking. These authors reported a reduced risk of PD in those who had ever been exposed to second-hand smoking and were not smokers themselves (OR=0.34, 95% CI: 0.17–0.73).

Mellick et al. (46) examined the association between second-hand smoking and the odds of PD among 151 Australian PD patients recruited from a neurology clinic and 151 matched controls. They reported protective, although not statistically-significant associations between the exposures to second-hand smoke at work and at home, including among never-smokers.

O’Reilly et al. (44) used data from two large prospective epidemiological studies, the NHS and the HPFS, and posed the question whether parental smoking during childhood was linked to PD risk. They found a significant reduction in PD risk among the offspring whose parents smoked while they were young compared to participants whose parents did not smoke. In sensitivity analyses restricted to non-smokers, no association between parental smoking and PD in offspring was observed, which the authors suggest is because the effect of parental smoking is mediated through smoking in study participants themselves. The authors suggest that their findings serve to
refute a reverse causation or the influence of a common third factor as potential explanations for the smoking-PD relationship.

In the only study that does not confirm a relationship between second-hand smoking and PD, Tanaka et al. (48) examined active and second-hand smoking exposure in 249 PD patients and 369 controls in Japan. While reporting a significant protective effect of former and current smoking, these authors found no association between second-hand smoking and the odds of PD (48).

With the exception of the study by Tanaka et al. (48) above, most evidence suggests a protective relationship between second-hand smoking and PD. At the same time, most studies of air pollution and PD found a harmful or no effect of air pollution on PD risk (Table 1). Second-hand smoke includes hundreds of compounds (53), many of which are known as potential carcinogens and some of which overlap with ambient airborne air pollutants. Why would second-hand and personal smoking be opposite to other types of air pollution and related to reduced risk of PD remains controversial? In studies of twins, which control the genetic factors as well as shared environment, smoking remains protective for PD (49, 50, 54). Therefore, an explanation of this contradiction based on a purely genetic common factor is unlikely. There also are some possibilities for residual confounding by personal and second-hand smoking in studies or air pollution and PD. For example, Lee et al. (37) found significant associations with pollution exposure among non-smokers, which were not seen in smokers. However, in their prospective cohort studies, Palacios et al. (35, 36, 42) found no significant associations between air PM air pollution and PD in stratified analyses or interactions with smoking. None of the studies of air pollution and PD to date considered second-hand smoking in the absence of personal smoking. In view of these controversies, it would be useful to consider second-hand smoking as a potential confounder and/or effect modifier in future studies of air pollution.

**Future directions**

To date, epidemiological investigations of air pollution and PD have covered a wide variety of sizes and types of pollutants, geographical locations, populations and other factors. However, a number of important questions remain unanswered, and new challenges become revealed. Several challenges and opportunities for future research on air pollution and PD are outlined below.

**Relevant exposure window**

There is an agreement that PD diagnosis is preceded by a long pre-motor and pre-clinical latent period. Therefore, a study addressing air pollution as a risk factor for PD requires measurements of air pollution exposure prior to the onset of the disease process. The relevant window of exposure is hitherto unknown and may precede the diagnosis of PD by over 10 years. Studies of air pollution and PD reviewed in the preceding section (Tables 1 and 2) are particularly sensitive to this limitation, as routine reporting and modeling of air pollution started only recently in most populations and countries. Of the existing studies, Ritz et al. (39) had the longest exposure window of 31 years and reported a significant association between exposure to ambient NO\textsubscript{2} and PD risk. Studies that did not observe an association between air pollution and PD had the shorter exposure windows. More investigations, especially those using a prospective-cohort design with long follow-up, would be useful.

Imprecision in the assessment of air pollution, either due to the overall modeling approach for residential exposure or because air pollution was modeled on the tract or other level, is a potential concern in the studies discussed in this review. Furthermore, the reviewed studies focused on modeled outdoor air pollution, while elderly PD patients, are likely to spend most of their time indoors, which could cause a misclassification of the exposure. With rapid development of wearable personal monitoring and telecommunication technology, we may foresee future possibilities for more precise, inexpensive and accurate personal monitoring or air pollution. Such technology could greatly benefit studies of air pollution and human health health, including PD.

**Particle sizes and types**

Another question is whether the types of air pollutants examined to date, including the traffic-related pollutants, are the right ones to study with regard to PD. In particular, it is unclear what is the relationship between particle size and their impact on PD. For example, do ultra-fine particulates present a greater risk than larger particles? Are the particles (PM\textsubscript{10} and PM\textsubscript{2.5}) studied to date too large to be related to PD risk and should we be focusing future studies on smaller, including ultrafine particles? PM\textsubscript{15} is the smallest of the particles studied so far, and to the author’s knowledge, no studies to date have examined the exposure to ultrafine pollutants or to ultra-fine particles with regard to the risk of PD.
Air pollution is generally linked to increased mortality from all causes (14) and in particular from respiratory, cardiovascular and cerebrovascular diseases (55). However, no studies to date have examined exposure to air pollution with regard to mortality specifically from PD. Also, no work known to us examined the association between air pollution and progression of PD. There is some evidence that factors related to PD incidence may also affect progression. For example, in a recent clinical study (27), urate, an antioxidant that has been linked with lower PD incidence, was also found protective for PD progression.

Interactions with other environmental factors, gene-environment interaction and the gut microbiome

Exposure to air pollution is likely to affect vulnerable subgroups more than others. Thus, studies sufficiently powered to examine the effects of air pollution on PD risk and progression in specific subgroups, such as non-smokers, gender-specific groups, and other subgroups relevant to PD are needed. The PAGE study by Liu et al. (34) (Table 1), reported significant positive associations between PM$_{10}$ and PM$_{2.5}$ and the risk of PD in female never-smokers, highlighting the importance of stratified and interaction analyses. Few of the studies included in this review stratified their analyses by gender or smoking [e.g. Finkelstein and and Jerrett (40), Ritz et al. (39), and Palacios et al. (35, 36, 42) stratified by smoking]. In future studies, it would be important to examine the potential interactions between pollutant exposure and gender, smoking, as well as other exposures, such as antioxidants, caffeine, use of NSAID, and other factors.

Along the same note, more studies of gene-environment interaction with air pollution are also needed. Only one study to date [Lee et al. (43)] reported on the potential implications of gene-environment interactions on the air pollution to PD relationship. This study reported a 3-fold increase in PD risk with joint exposure to the AA genotype of the IL1-$eta$ gene and high NO$_2$ levels. It would be interesting to examine such interactions with other pro-inflammatory genes. More research on gene-environment interactions in this field is needed.

Finally, the involvement of the human gut microbiome and PD (56–60) is an exciting emergent area of research. It is possible that larger particles such as PM$_{10}$, PM$_{2.5}$ and PM$_{2.5-10}$, although being too large to cross the blood-brain barrier, could still enter the body via another route. Upon being inhaled, these particles could be swallowed and end up in the gut. Even if they are still too large to pass the blood brain barrier, the particles could then induce systemic inflammation, or interact with the gut bacteria in other ways, thus potentially impacting PD risk. Thus, future studies could explore the interaction between the human gut microbiome and exposure to air pollution with regard to PD risk.

Summary

The recent studies outlined in this review have contributed greatly to our understanding of the relationship between air pollution and PD, but many questions remain and more work is needed to understand the complexities of this relationship. Most of the studies to date were case-control, and only three prospective-cohort studies have been conducted. More prospective studies on the relationship between air pollution and PD are warranted. Furthermore, studies have focused on a heterogeneous mix of air pollutants. Our understanding of the relationship between air pollution and PD will improve in the coming years as more investigations are performed and more reproducible findings reported. Several opportunities for novel investigation, particularly with relation to exposure assessment, a potential look at smaller particles, more focus on interactions with genes, as well as other predisposing factors, such as the gut microbiome, as well as an examination of the impact of air pollution on the progression and survival in PD are noted.

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References


