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Air Pollution and the Risk of Parkinson's Disease A Review

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Abstract

Parkinson's disease, and other neurodegenerative disorders, are primarily characterized by pathological accumulation of proteins, inflammation, and neuron loss. Although there are some known genetic risk factors, most cases cannot be explained by genetics alone. Therefore, it is important to determine the environmental factors that confer risk and the mechanisms by which they act. Recent epidemiological studies have found that exposure to air pollution is associated with an increased risk of developing Parkinson's disease, although not all results are uniform. The variability between these studies is likely due to differences in what components of air pollution are measured, timing and methods used to determine exposures, and correction for other variables. There are several potential mechanisms by which air pollution could act to increase the risk of developing Parkinson's disease, including direct neuronal toxicity, induction of systemic inflammation leading to CNS inflammation, and alterations in gut physiology and the microbiome. Taken together, air pollution is an emerging risk factor in the development of Parkinson's disease. A number of potential mechanisms have been implicated by which it promotes neuropathology providing biological plausibility and these mechanisms are likely relevant to the development of other neurodegenerative disorders such as Alzheimer's disease. This field is in its early stages, but a better understanding of how environmental exposures influence the pathogenesis of neurodegeneration is essential for reducing the incidence of disease and finding disease-modifying therapies.

Graphical Abstract

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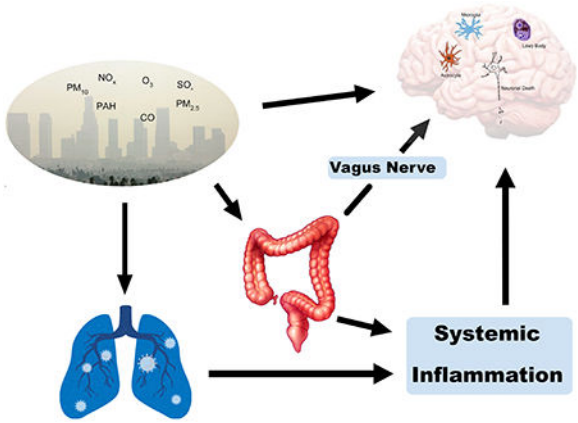

Air pollution is the leading environmental cause of mortality and is the fifth overall cause of mortality worldwide (World Health Organization 2016). There is evidence that air pollution exposure is linked with respiratory disease, heart disease, stroke, lung cancer, and diabetes[1]. Ambient air pollution, or outdoor air pollution, is primarily composed of gases such as ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide[2]. It also contains respirable particulate matter (PM), defined by its aerodynamic diameter (PM_{10}, <10 μm; $PM_{2.5}$ < 2.5 μm; ultrafine (UF), $PM_{0.1}$, < 0.1 μm). It has been well-established that $PM_{2.5}$ can move through the respiratory tract and reach the lung alveoli; $PM_{0.1}$ has been seen to pass through the alveolar-capillary membrane and enter the bloodstream, allowing it to access various organs[3]. According to data available in 2017, 92% of the world's population lived in areas that exceeded the WHO guideline for $PM_{2.5}$[1]. The ubiquitous nature of air pollution exposure necessitates further research regarding its effects on the brain and the role it plays in development of neurodegenerative diseases such as Parkinson's disease (PD).

Air Pollution and PD Risk

Although there is a large body of literature linking air pollution exposure to shortened life expectancy and cardiovascular disease, much less is known about the impact of air pollution on the brain. Recent studies suggest that air pollution can affect the brain in a variety of ways, resulting in an increased risk of neurodegenerative disease and stroke[4]. However, studying environmental influencers of neurodegenerative disease risk is challenging, particularly because of the likely relatively long latency period between disease initiation and diagnosis, and the difficulty with assessing individual exposure over a lifetime. For many neurodegenerative disorders including PD, pre-symptomatic disease initiation and diagnosis are thought to be separated by many years, or possibly decades[5,6]. Thus, it has been hypothesized that exposure to environmental contributors to disease risk occurs years prior to the disease diagnosis[7]. This concept is supported by observations with pesticide exposure and PD risk[8]. For example, paraquat and maneb exposure with a long lag time to diagnosis was associated with an increased risk of PD while short lag time was not[9]. It is also possible that environmental exposures can accelerate a disease process that is already established. Both of these possibilities need to be considered when interpreting associations with a chronic and progressive disorder such as PD.

For this review, PubMed and the Cochrane databases were searched for English-language studies regarding air pollution and neurodegeneration through June 1, 2021, including epidemiological, basic science studies, meta-analyses, and reviews. Search terms included Parkinson's disease, air pollution, diesel, traffic, neurodegeneration, and inflammation. Most epidemiological studies examining the role of air pollution in neurodegenerative disease risk have been focused on PD and indicate an association between exposure to certain components of traffic- related air pollution and PD risk, although some studies have not found significant associations (recent studies since 2015 summarized in Table 1[10–22]).

One potential reason for the disparities is that the relative risk scores from the positive studies are relatively modest. For example, in the Ritz study, they found odds ratios (OR) of 1.08 for exposures in the 25-75th percentile and an OR of 1.22 (95%CI: 0.99, 1.51) above the 75th percentile for NO2 as compared to the <25th percentile. NO_2 exposures above the 95th percentile had the strongest association (OR=1.92). The effect size poses some important implications. 1) Since so many people are exposed to air pollution, it could account for a significant percentage of PD cases. For example, if we extrapolate the risk of PD in the Ritz study to the air pollution levels (i.e. NO_2, NO_x and CO levels) in Los Angeles, CA during the 1970s and 80s, air pollution could account for up to 70% of the cases[19]. 2) Small relative risk scores make it very challenging to document an effect in epidemiological studies of relatively rare disorders like PD.

The variability between studies could also be due to methodological differences. Some studies do not control for other factors known to associate with altered risk of PD. These include age, smoking history, pesticide exposure and time between exposures and disease onset. As mentioned previously, the pre-symptomatic lag time to disease is likely long, so exposures might need to be determined decades prior to diagnosis. The sources and composition of air pollution are often not considered, and the components measured vary considerably between studies. No one component can be used as a proxy for air pollution. For example, $PM_{2.5}$ is often used as a proxy for all particulate matter (PM), even though there are other sizes and chemical compositions that are not reflected by this one value. Furthermore, novel PM, trace metals and nanoparticles, which are not routinely measured, should be considered when studying the health effects of air pollution[23,24].

Despite these methodological challenges, recent meta-analyses support the association between air pollution exposure and risk of developing PD[25]. Since air pollution is generally associated with an urban environment, its association with PD would appear to contradict a widely-believed association of PD with rural living. The epidemiology of PD is likely more nuanced. For example, in a large registry in Thailand, elevated PD risk was associated with rural living primarily in regions where pesticides were heavily used, but was also associated with urban areas[26]. Furthermore, Wright Willis et al found that the prevalence and incidence of PD in urban counties were greater than in rural ones within the US[27]. Since associations do not necessarily indicate causality, animal and mechanistic studies are necessary to establish biological plausibility of a causal connection.

Modeling Air Pollution Exposure and Neurotoxicity

Altered risk of disease from environmental factors depends to some degree on the concentration of the toxicant, duration of exposure, and timing of exposure. Based on epidemiologic and animal studies, it is likely that long-term exposure to air pollution prior to diagnosis is necessary to alter risk of PD. Therefore, it is very difficult to model in animal and human studies. One approach to overcome this problem is to identify alterations in biological pathways that, over time, can lead to disease. This approach, referred to as "adverse outcome pathways (AOP)", utilizes molecular and biochemical endpoints as biomarkers to investigate disease pathogenesis[28]. The AOP approach has been extensively utilized in investigating the potentially causal link between environmental toxins and PD. For example, ziram, a fungicide, was identified to be an inhibitor of the ubiquitin proteasome system (UPS) in a screen and subsequently was found to increase the risk of developing PD[29–31]. In the context of air pollution, diesel exhaust has been shown to increase α-syn levels and induce neuroinflammation, both thought to be AOP for PD (see below)[32].

The Pathophysiology of PD

The primary pathology in PD involves dopaminergic neuron loss, particularly in the substantia nigra, and inflammation. Most clinically defined PD patients have abnormally misfolded and aggregated α-synuclein (α-syn) in the form of Lewy Bodies at autopsy. Pathological α-syn aggregates appear to spread throughout the nervous system in a predictable manner which determines the clinical symptomology[33]. For example, the prodromal symptoms of constipation and olfactory dysfunction that can occur many years, or even decades, before disease diagnosis, likely reflect underlying α-syn pathology. This is supported by studies describing α-syn aggregates in the enteric nervous system of the gut and the olfactory bulb several years before motor symptoms develop, and it has been proposed that these aggregates can then spread to the CNS via the vagus nerve[33–37]. Later, the cardinal features of PD develop (e.g. tremor, rigidity etc.) when the substantia nigra becomes involved.

The molecular mechanisms by which these pathologies occur are still being uncovered, but aggregation and propagation of misfolded α-syn appear central to the pathogenesis of most PD cases[38]. Insight into the pathological pathways in sporadic PD have come from patients with relatively rare PD-associated gene mutations and include disrupted proteostasis, inflammation, and mitochondrial dysfunction[33]. Increased levels of α-syn can promote the formation of toxic oligomers and fibrils and can result from increased gene expression (e.g. SNCA gene duplication) or by reduced degradation[39,40,41]. Both the UPS and autophagy degrade α-syn and dysfunction in both processes has been implicated in the pathogenesis of PD through mutations in the Parkin and GBA genes[42,43].

In addition to alterations in proteostasis, mitochondrial dysfunction has also been implicated in PD and can lead to increased oxidative stress and neuronal loss[44]. Dysfunction of mitochondria promote the generation of reactive oxygen species that can result in α-syn aggregation or decreased α-syn degradation[45]. Aggregated α-syn can then bind to

mitochondria and further its dysfunction, creating a positive feedback loop[46]. This is supported by the fact that mutations in mitochondrial-associated genes (e.g. PINK1, Parkin) or exposure to mitochondrial toxins (e.g. rotenone, trichloroethylene) markedly increase the risk of PD[47,48].

Another pathway implicated in PD pathogenesis is inflammation. Neuroinflammation (e.g. microglial and astrocyte activation) is a universal pathological finding in PD brains and recent studies suggest that it contributes to neuronal damage and is not simply a response to injury[49]. Genetic alterations in several immune-related genes (e.g., DJ-1, leucine-rich repeat protein kinase-2 and HLA-DR) can markedly increase the risk of developing PD, and provide support for the hypothesis that inflammation contributes to the pathogenesis of sporadic PD[49].

Mechanisms by which Air Pollution May Increase the Risk of Developing PD

There are number of ways by which air pollution can affect the brain and contribute to the pathogenesis of PD and we hypothesize that it by disrupting proteostasis, injuring mitochondria, and/or inducing inflammation (Figure 1). Air pollution is a complex mixture of gases, PM, and smaller chemical moieties. Some of these components gain access to the brain via the bloodstream and/or by direct diffusion through the olfactory system (Fig 1A). Several potential mechanisms of toxicity have been proposed once these chemicals enter the brain. Air pollution may also affect brain health more indirectly through systemic mechanisms such as inducing the release of inflammatory cytokines or other chemicals from the lungs (Fig. 1B). Components of air pollution can also accumulate in the GI tract and alter gut mucosal physiology, promoting α-syn pathology (Fig 1C) and/or altering the microbiome (Fig. 1D), both of which have been implicated in the pathogenesis of PD. It is likely that multiple mechanisms are involved in altering the risk of PD and the evidence for each is reviewed below.

Neurotoxicity and Neuroinflammation by Air Pollution Components

Most mechanistic studies on air pollution to date have focused on inflammation[50]. CNS inflammation and oxidative stress are important findings in PD brains and air pollution appears to increase both. Observations from human autopsy studies and experiments in rodents support the hypothesis that air pollution increases inflammation in the CNS[51–53].

It is clear that many of the components of air pollution do reach the brain and therefore can contribute to the pathogenesis of PD by direct neurotoxicity and/or inducing neuroinflammation (Fig. 1A). Ultrafine particles can gain access to the brain either through the blood stream and/or through olfactory mucosa[57,58]. Of particular interest with regard to air pollution are the potent and biologically active compounds known as polycyclic aromatic hydrocarbons (PAHs), which can reach the brain through the circulation and accumulate in the CNS[59,60]. In fact, the levels of some PAHs found in human brains were very high and support the concept that components of air pollution can bioaccumulate in the nervous system, posing significant risk through direct toxicity[59]. Furthermore, exposure to

air pollution can weaken the integrity of the blood brain barrier (BBB)[61], making it more permeable to toxicants that enter circulation.

In vitro, DE particles (DEP) are toxic to dopaminergic neurons, but this is less evident when animals are exposed to DE *in vivo.* Block et al reported that DEP caused selective dopaminergic neurotoxicity in primary mesencephalic cultures. They demonstrated that toxicity of DEP was dependent on microglial activation and 2^0 phagocytosis[54]. They later showed that phagocytosis of the particulate was responsible for activating microglia and was necessary for neurotoxicity[62]. Particles clearly activate microglia, but only very small quantities reach the brain[63]. DE exposure for weeks *in vivo* does not result in dopaminergic neuron loss, but does result in an increase in α-syn levels in the midbrain and enhanced dopaminergic toxicity of LPS[54–56]. Accumulation of α-syn is an important AOP in the pathogenesis of PD and this evidence further implicates air pollution in the disruption of α-syn proteostasis.

Inhaled moieties that are soluble in organic solvents, such as PAHs, reach the brain much more readily than particulate matter[57]. Therefore, many researchers utilize organic extracts of DE (DEPe) for experiments where inhalation is not the primary means of exposure. We have utilized zebrafish to study direct neurotoxicity of DEPe containing concentrations of PAHs similar to those found in human brains[59,64]. A brief exposure to DEPe resulted in abnormal swimming and loss of dopaminergic neurons, although the neuronal loss was not selective[64]. Importantly, there was an accumulation of zebrafish synuclein in this model, which appeared to be caused by dysfunction of neuronal autophagic flux, and stimulation of autophagy was neuroprotective. We also exposed zebrafish embryos to DEPe and performed proteomic and transcriptomic analyses on brain tissue to identify altered pathogenic pathways. DEPe treatment altered several AOPs relevant to PD and other neurodegenerative disorders, including xenobiotic metabolism, phagosome maturation, and amyloid processing[65]. Others have reported CNS inflammation in rodent models similar to that seen in human PD brains. Of interest are the findings that DE increases expression of some inflammatory genes in the olfactory bulb (OB) of mice, a brain region where PD pathology is seen very early in the disease[55,56,66]. Inflammatory changes are also seen in the brains of dogs and people living in urban areas, as compared to those living in rural areas, and the authors speculated that these changes are due to high levels of air pollution[51–53]. There are clear limitations in many of these studies, but they support a causal link between air pollution and increased risk of PD through direct neurotoxicity and/or neuroinflammation.

The Air Pollution-Lung-Brain Connection

In addition to direct particle translocation, exposure of the airway to air pollution also leads to peripheral or systemic inflammation, which in turn, can affect the CNS (Fig. 1B). Epithelial cells lining the airway can physically block larger inhaled particles and can secrete cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), which promote synthesis of other cytokines and chemokines and results in immune cell activation[67]. Peripheral inflammation from the lungs and other tissues is thought to contribute to CNS neuroinflammation[68,69]. The BBB is weakened by

systemic inflammation-derived pro-inflammatory cytokines and chemokines, which can allow inflammatory cells and pro-inflammatory cytokines to pass into the brain. Once in the brain, these factors from the periphery, along with brain-derived cytokines, chemokines, β-amyloid, α-syn, and amyloid precursor proteins can activate CNS immune cells and lead to downstream effects such as neuronal injury[69,70]. Air pollution exposure is well-accepted as a significant risk to pulmonary health and contributor to systemic inflammation, but its downstream effects on the brain may be important mechanisms by which it increases the risk of developing PD and neurodegenerative diseases.

Systemic inflammation, which has been observed in PD patients, may contribute to CNS neuroinflammation. Blood cytokines representing a proinflammatory state (e.g. TNF-α, IL-1β, IL-2 and −6, CRP) are elevated in PD patients, and are associated not only with an increased risk of developing PD[71] also with faster progression[72]. There is strong evidence in animal models that systemic inflammation can lead to neuroinflammation and loss of dopaminergic neurons, especially in combination with elevated α-syn levels[73]. Taken together, air pollution induces a systemic inflammatory response that may lead to neuroinflammation and an elevated risk of developing PD (Fig 1B).

Air Pollution and Gut α-Syn

Evidence from animal and human studies supports the hypothesis that pathological forms of α-syn can accumulate in the gut, spread to the brainstem via the vagus nerve, and eventually lead to neuronal loss in the substantia nigra (SN; Fig. 1C). This ordered progression of α-syn pathology was first described in autopsy specimens[33] and later supported by the finding that α-syn aggregates are present in colonic biopsy specimens years before PD diagnosis[34]. Furthermore, prior vagotomy is associated with a reduced risk of developing PD[35,36]. In animals, α-syn preformed fibrils (PFFs) injected into the duodenum results in α-syn spread into brainstem nuclei and eventually to the SN[37]. Vagotomy blocked this spread, as well as dopaminergic neuron loss. Relevant to this review, environmental toxins administered into the GI tract can lead to the formation of pathological α-syn in the gut that spreads to the CNS and induces dopaminergic neuron loss[74,75]. There is little direct evidence that air pollution can induce α-syn aggregates in the gut that spreads to the CNS, but there is an increasing body of literature demonstrating that it can induce changes in the gut mucosa that are thought to promote α-syn pathology. Air pollution exposure has been reported to induce gut inflammation and leakiness and alters the risk of developing inflammatory bowel disease (IBD)[76]. It has been hypothesized that gut inflammation and increased permeability may be the trigger for α-syn aggregation, which eventually spreads to the CNS. Interestingly, IBD has also been associated with an increased risk of developing PD[77]. It is unclear how air pollution exerts these changes in the gut, but it may act, in part, by altering the microbiome.

Air Pollution, the Microbiome, and the Brain

The microbiome is an emerging topic of interest related to human health. Its role and importance in the development of neurodegenerative disease is not well-understood, but recent studies in rodents and PD patients raise the possibility that alterations in the gut

microbiome may be an important means by which the environment can alter risk of developing CNS diseases. This is particularly relevant for PD, since α-syn pathology may first appear in the GI system in close proximity to the gut microbiome (Fig. 1D)[78–80]. Studies in rodent models of PD have reported dramatic changes in behavior and CNS pathology resulting from alterations in the microbiome[81]. Several groups have found altered microbiota in PD patients, further supporting its pathogenic role in the development of PD[82].

Exposure to air pollution has recently been linked to alterations in the microbiome, but primarily in animals. “Gut leakiness”, a result of imbalances in the microbiome leading to disruption of the epithelial barrier of the gut, can allow various bacterial metabolites and virulence factors to travel through the intestinal lining, into the bloodstream, and subsequently across the BBB[83–85]. Some examples of molecules that can be produced, suppressed, and overused by strains of microbiota include synaptogenic proteins, short-chained fatty acids, L-DOPA, GABA, serotonin and dopamine, Such changes can have a direct effect on neurological function[86]. Mice exposed to ambient $PM_{2.5}$ exhibited significant changes in gut microbial diversity. Significant increases were found in *Bacteriodales* which likely involve degradation of the mucus layer and increased gut permeability, as well as the depletion of *Lactobacillus*, a strain known to help maintain homeostasis in the gut[87]. Furthermore, PM_{10} exposure in mice led to changes in microbiota composition and an intestinal inflammatory response[88]. These findings have not been reproduced in all studies, and the mouse microbiome is very different from the human microbiome.

Alterations in the microbiome in PD patients have been reported by several investigators[89]. Although some changes are common among these studies, there are significant inconsistencies and few controls for confounds, such as constipation. Some studies have investigated the effect of air pollution on the microbiome in humans and they have found associations between air pollution and changes in gut microbiome, but there are several potential confounds. Taken together, these studies raise the possibility that air pollution might alter disease risk by changing the microbiome, but this field is in very early stages.

Conclusions

The etiology of PD is complex, but undoubtedly involves a combination of genetic and environmental factors. Air pollution is emerging as an important risk factor for many diseases including PD, and may account for a significant percentage of cases worldwide. Recent epidemiological studies support an association of PD and air pollution and investigations are beginning to determine if this association is causal. There are several potential mechanisms by which air pollution may promote neurodegeneration and it is likely that several disease-related pathways are involved. A better understanding of this field is important given the number of people affected worldwide and the fact that many pathological pathways implicated are likely common to other disorders, such as Alzheimer’s disease. Ultimately, determining the pathogenesis of PD and the factors that alter risk can inform efforts to lower incidence and improved therapies targeted at underlying causes.

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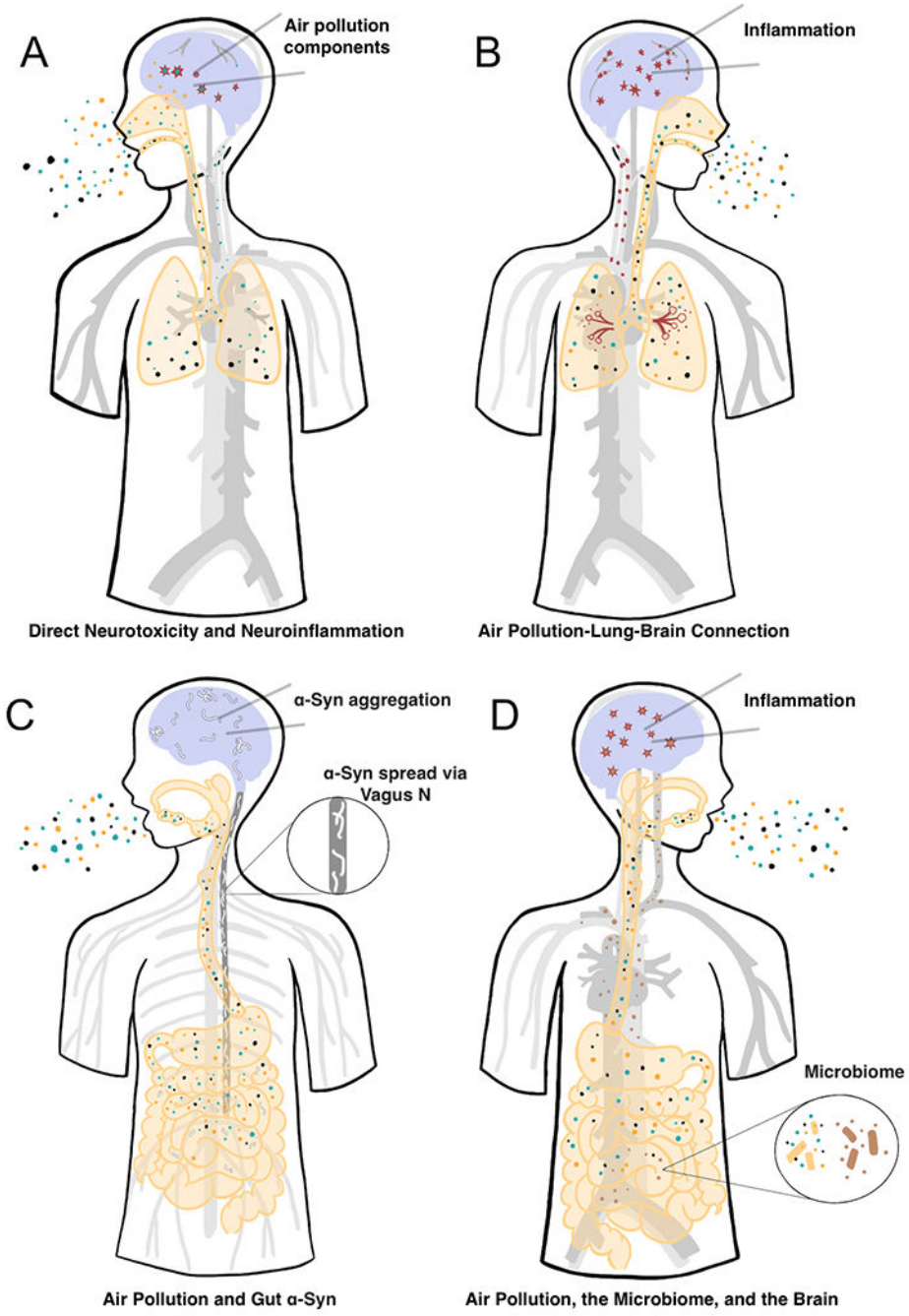

Figure 1. Proposed mechanisms by which air pollution may promote Parkinson's disease pathology.

1A: *Neurotoxicity and Neuroinflammation by Air Pollution*. Components of air pollution reach the brain either through the blood stream and/or through olfactory mucosa. Once in the brain, some moieties are neurotoxic and cause neuroinflammation. 1B: *The Air Pollution-Lung-Brain Connection*. Air pollution induces pulmonary and systemic inflammation, which induces CNS inflammation. 1C: *Air Pollution and Gut α-Syn.* Air pollution causes gut inflammation and leakiness, which promotes local accumulation of α-syn. α-Syn (white) can then spread to the brainstem via the vagus nerve (enlarged). 1D: *Air Pollution, the*

Microbiome, and the Brain. Air pollution alters gut microbiome (enlarged), which can lead to systemic inflammation, release of neuroactive molecules and neuroinflammation.

Table 1.

Recent Epidemiological Studies Investigating the Association of PD and Air Pollution

Author	Study Design	Population	Exposure Range	Length of Exposure/Lag time to Ds	OR	Strengths	Weaknesses
Kirrane 2015[14]	Case-Control	301 cases in US	**O_3** (ppb): • IA mean: 39.0, max: 41.5 • NC mean 40.6, max 46.5 **$PM_{2.5}$** (μg/m^3): • IA mean 8.9, max 11.5 • NC mean 12.6, max 17.7	4 years	**O_3**: OR = 1.39 (.98-1.98) **$PM_{2.5}$**: OR = 1.34 (.93–1.93)	Adjusted for multiple variables including pesticides	Short exposure time, small population
Ritz 2016 [19]	Case-Control	1696 PD cases in Denmark	**NO_2**: 9.8-43.26 ug/m^3 **NO_x**: 13.46-181.55 ug/m^3 **CO**: 0.36-2.34 mg/m^3	31 years	**NO_2**: 1.09 per 2.97 μg/m of exposure **NO_x**: 1.06 per 7.10 ppb of exposure **CO**: 1.13 per 0.12 ppm of exposure	Large population, long exposure, adjusted for multiple variables	Low air pollution in Denmark
Lee 2016 [15]	Case-Control	11,117 incident PD cases in Taiwan	**PM_{10}**: 29.3-86.8 ug/m^3 **NO_x**: 5.2-77.6 ppb **O_3**: 19.0-39.2 ppb **CO**: 0.2-1.5 ppm	11 years	**CO:** OR = 1.37 (1.23–1.52) **Multi-pollutant models**: OR = 1.17 (1.07–1.27)	Large population, adjusted for age, year of Dx	Short exposure time, adjusted for only a few variables
Lee 2016 [16]	Case-Control	408 incident PD cases in Denmark (subset of Ritz 2016)	**NO_2**: 9.8-43.26 ug/m^3 **NO_x**: 13.46-181.55 ug/m^3 **CO**: 0.36-2.34 mg/m^3	31 years	**AA allele of the interleukin-1β) gene with high NO exposure**: OR = 3.1	Long exposure, adjusted for multiple variables, gene interaction with air pollution	Small population, low air pollution in Denmark,
Liu 2016 [17]	Case-Control	1,556 cases in US	Quintiles **$PM_{2.5}$** (μg/m^3): • Q1:4.4- < 10.8 • Q2: 10.8- < 12.3 • Q3: 12.3- < 13.8 • Q4: 13.8- < 15.4 • Q5: 15.4–26.9 **PM_{10}** • Q1:4.3- < 22.9 • Q2: 22.9- < 25.1 • Q3: 25.1- < 27.9 • Q4: 27.9- < 33.8 • Q5: 33.8–65.4 **NO_2** (ppb): • Q1: 1.0- < 7.7 • Q2: 7.7- < 10.4 • Q3: 10.4- < 13.1 • Q4: 13.1- < 16.6 • Q5: 16.6–34.2	Average of 1990 and 2000, very short to no lag to disease onset.	**$PM_{2.5}$**: OR = 1.02 per 3.8 μg/m^3 **PM_{10}**: OR = 1.02 per 8.4 μg/m^3 **NO2**: OR = 1.01 per 7.3 ppb of exposure Female: **PM10**: Q5 vs. Q1: OR = 1.65 Never smokers: **$PM_{2.5}$**: Q5 vs. Q1: OR = 1.29	Adjusted for multiple variables, large population. Preplanned subgroup analysis	Short exposure time, little to no lag time

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Author	Study Design	Population	Exposure Range	Length of Exposure/Lag time to Ds	OR	Strengths	Weaknesses
Palacios 2017 [18]	Prospective	N =50,352 550 PD cases in US	**$PM_{2.5}$**: 3.1-29.2 ug/m^3 **PM_{10}**: 7.4-81.3 ug/m^3	9 years	0.99 (0.96-1.01)	Prospective, Adjusted for age, tobacco	Short exposure time to disease.
Chen 2017 [13]	Case-Control	1060 incident PD cases in Taiwan	**PM_{10}** Tertiles (μg/m^3): • T1 ≤ 54 • 54 < T2 ≤ 65 • T3 > 65 SO_2, O_3, CO, NO_x, NO, NO_2, THC, CH_4, and NMHC not specified.	1-18 years	**PM_{10}** T3 v T1: OR = 1.35 (1.12-1.62) Others increased only with comorbidity	Large population of incident cases. Considered comorbid conditions.	Variable exposure and lag time. Did not have data on $PM_{2.5}$. Adjusted for age and gender only.
Shin 2018 [21]	Population-based cohort	38 745 incident cases in Ontario, Canada	**$PM_{2.5}$**: 1.3-20.0 ug/m^3 **NO_2**: 2.2-53.2 ppb **O_3**: 24.3-64.1 ppb	2, 5 and 10 year lag.	**$PM_{2.5}$**: 4% increase risk per interquartile increment of 3.8 ug/m^3 Similar results for NO_2 and O_3.	Large population, Considered comorbid conditions.	Relatively short exposure lag, did not adjust for smoking, physical activity or pesticide exposure.
Cerza 2018 [12]	Prospective cohort	13,104 cases in Rome, Italy	**$PM_{2.5}$**: 9.8-31.4 ug/m^3 **PM_{10}**: 29.6-58.2 ug/m^3 **NO_2**: 13.2-84.9 ug/m^3 **NO_x**: 14.3-173.4 ug/m^3 **O_3**: 54.5-112.8 ug/m^3	0-3 year lag	**PM abs, NO_2:** HR = 0.97 per 10 μg/m^3 increase **NO_x:** HR = 0.97 per 20 μg/m^3 increase **O_3:** HR = 1.02 per 10 μg/m^3 increase	Large prospective study. Adjusted for gender and age	Short to no lag time, Did not adjust for other exposures, occupation, limited adjustment for smoking.
Salimi 2019 [20]	Cross sectional	1,428 cases in New South Wales, Australia	**$PM_{2.5}$**: 0.1-10.3 ug/m^3 **NO_2**: 4.21-71.2 ug/m^3	0-2 year lag	**$PM_{2.5}$**: OR = 1.01 per 1 ug/m^3 **NO2**: OR = 1.03 (all) and 1.11 (past smokers) per 5 ug/m^3	Adjusted for multiple potential confounds including smoking	Short to no lag time, Self-reported cases. Limited statistical power. Relatively low range $PM_{2.5}$ range.
Yuchi 2020 [22]	Database Cohort	4,201 cases in Vancouver, Canada	**$PM_{2.5}$**: 0.1-10.4 ug/m^3 **NO_2**: 12-57.7 ppb **NO**: 8.2-101.0 ppb	5-9 years	**$PM_{2.5}$**: HR = 1.09 per interquartile range (IQR) **NO2**: HR = 1.12 per IQR **NO:** HR = 1.03 per IQR	Large number of cases. Multiple co-variants reported.	Relatively low range $PM_{2.5}$ range. Did not adjust for smoking or other behavioral risks.
Jo 2021 [10]	Retrospective cohort study	338 newly diagnosed cases in South Korea	**$PM_{2.5}$**: 18.0-44.4 ug/m^3 **PM_{10}**: 41.0-79.0 **NO_2**: 0.026-0.045 ppm **O_3**: 0.013-0.025 ppm **SO_2**: 0.0036-0.0074 ppm **CO**: 0.40-0.82 ppm.	5 years	**NO_2:** HR = 1.41 highest v lowest quartile. No significance for other measures	Measured several pollution components, Adjusted for multiple co-variants.	Low number of cases. Relatively low range $PM_{2.5}$ and PM_{10} range. Short lag.

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