

Parkinson's disease risk factors

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Atmospheric Particulate Matter and Parkinson's Disease

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[Atmospheric particulate matter](#) (PM) exacerbates Alzheimer's and [Parkinson's disease risk factors](#) (PD) by promoting the [alpha-synuclein](#) (α -syn) pathology in the brain.

Atmospheric particulate matter (PM) refers to a mixture of tiny particles and droplets in the air, including dust, dirt, soot, and smoke. PM is classified based on its size:

PM₁₀: Particles with a diameter of 10 micrometers or less. PM_{2.5}: Particles with a diameter of 2.5 micrometers or less. Ultrafine Particles: Particles with a diameter of less than 0.1 micrometers.

Mechanisms of PM Impact on Parkinson's Disease Neuroinflammation: Inhalation of PM can lead to systemic inflammation, including neuroinflammation, which can damage neurons and contribute to neurodegenerative diseases like Parkinson's.

Oxidative Stress: PM can induce oxidative stress, which damages cellular components, including lipids, proteins, and DNA. This oxidative damage is a known factor in the pathology of Parkinson's disease.

Direct Neurotoxicity: Ultrafine particles can cross the blood-brain barrier, potentially causing direct damage to brain tissues and neurons.

Transport of Toxic Compounds: PM can carry toxic substances, such as heavy metals and organic pollutants, into the body, which can then reach the brain and contribute to neurodegeneration.

Evidence from Studies Epidemiological Studies: Several studies have found associations between higher levels of PM exposure and increased incidence of Parkinson's disease. For example, long-term exposure to high levels of PM_{2.5} has been linked to a greater risk of developing Parkinson's.

Animal Studies: Experimental studies on animals have shown that exposure to PM can lead to Parkinson's-like symptoms and pathological changes in the brain, supporting the epidemiological findings.

Human Studies: Autopsy studies of individuals exposed to high levels of air pollution have found increased markers of neuroinflammation and oxidative stress in brain tissues, which are hallmarks of Parkinson's disease.

Conclusion While there is still much to learn about the exact relationship between atmospheric particulate matter and Parkinson's disease, current evidence suggests that PM exposure is a significant environmental risk factor for developing the condition. Reducing exposure to air pollution, particularly PM, may help lower the risk of Parkinson's disease and improve overall public health.

The molecular mechanisms of astrocytes involvement in α -syn pathology underlying the process remain unclear.

Li et al. in a study investigated PM with particle size <200 nm (PM_{0.2}) exposure-induced α -syn pathology in ICR mice and primary astrocytes, then assessed the effects of mammalian target of rapamycin inhibitor (PP242) in vitro studies. They observed the α -syn pathology in the brains of exposed mice. Meanwhile, PM_{0.2}-exposed mice also exhibited the activation of glial cell and the inhibition of autophagy. In vitro study, PM_{0.2} (3, 10 and 30 μ g/mL) induced inflammatory response and the disorders of α -syn degradation in primary astrocytes, and lysosomal-associated membrane protein 2 (LAMP2)-mediated autophagy underlies α -syn pathology. The abnormal function of autophagy-lysosome was specifically manifested as the expression of microtubule-associated protein light chain 3 (LC3II), cathepsin B (CTSB) and lysosomal abundance increased first and then decreased, which might both be a compensatory mechanism to toxic α -syn accumulation induced by PM_{0.2}. Moreover, with the transcription factor EB (TFEB) subcellular localization and the increase in LC3II, LAMP2, CTSB, and cathepsin D proteins were identified, leading to the restoration of the degradation of α -syn after the intervention of PP242.

The results identified that PM_{0.2} exposure could promote the α -syn pathological dysregulation in [astrocytes](#), providing mechanistic insights into how PM_{0.2} increases the risk of developing PD and

highlighting TFEB/[LAMP2](#) as a promising therapeutic target for antagonizing PM0.2 toxicity ¹⁾.

Genetic risk factors

Genetic risk factors have been identified, including monogenetic causes that are rare in unselected populations. Some genetic factor can be identified in 5-10% of the patients ²⁾.

Recent studies have shown that the activation of a neuroimmune response plays a key role in the development of PD. [Alpha-synuclein](#) (α -Syn), the primary pathological marker of PD, can gather in the SN and trigger a neuroinflammatory response by activating microglia which can further activate the dopaminergic neuron's neuroimmune response mediated by reactive T cells through antigen presentation. It has been shown that adaptive immunity and antigen presentation processes are involved in the process of PD and further research on the neuroimmune response mechanism may open new methods for its prevention and therapy. While current therapeutic regimens are still focused on controlling clinical symptoms, applications such as immunoregulatory strategies can delay the symptoms and the process of neurodegeneration ³⁾.

Some genetic forms such as [LRRK2](#)-associated Parkinson's disease. One of the most important genes associated with PD is [GBA1](#), as mutations in this [gene](#) are found in 5-20% of PD patients in different populations worldwide. Biallelic mutations in GBA1 may cause [Gaucher disease](#), a lysosomal storage disorder with involvement of the immune system, and other lines of evidence link GBA1 to the immune system and inflammation ⁴⁾.

Epigenetic influences mediating brain iron deposition, oxidative mitochondrial injury, and macroautophagy in Parkinson's disease and related conditions remain enigmatic ⁵⁾.

Sporadic PD is hypothesized to be a result of genetic susceptibility interacting with environmental insult. Epidemiological studies suggest that pesticide exposure is linked to higher PD risk, but there are no studies demonstrating SN changes with chronic pesticide exposure in human subjects.

The changes detected by MRI may mark "one of the hits" leading to PD, and underlie the increased risk of PD in pesticide users found in epidemiological studies. Further human studies assisted by these imaging markers may be useful in understanding the etiology of PD ⁶⁾.

Mitochondrial dysfunction has long been associated with Parkinson's disease (PD). Parkin and [PINK1](#), two genes associated with familial PD, have been implicated in the degradation of depolarized mitochondria via autophagy (mitophagy). Here, we describe the involvement of parkin and PINK1 in a vesicular pathway regulating mitochondrial quality control. This pathway is distinct from canonical mitophagy and is triggered by the generation of oxidative stress from within mitochondria. Wild-type but not PD-linked mutant parkin supports the biogenesis of a population of mitochondria-derived vesicles (MDVs), which bud off mitochondria and contain a specific repertoire of cargo proteins. These MDVs require PINK1 expression and ultimately target to lysosomes for degradation. We hypothesize that loss of this parkin- and PINK1-dependent trafficking mechanism impairs the ability of

mitochondria to selectively degrade oxidized and damaged proteins leading, over time, to the mitochondrial dysfunction noted in PD ⁷⁾.

Over the years [Genome-wide association study](#) (GWAS) have identified numerous [genetic risk](#) factors, however it is unclear whether genetics contribute to disease [Parkinson's disease etiology](#) in a sex-specific manner.

A study does not support the notion that common genetic variation on the [autosomes](#) could explain the difference in [prevalence](#) of PD between males and females at least when considering the current sample size under study. Further studies are warranted to investigate the genetic architecture of PD explained by [X](#) and [Y chromosomes](#) and further evaluate environmental effects that could potentially contribute to PD etiology in male versus females ⁸⁾.

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