

# Public Health Implications of Gene–Environment Interactions in Parkinson’s Disease: A Functional and Epidemiological Perspective

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*Abstract- Parkinson’s disease (PD) is a progressive neurodegenerative disorder, and we’re learning that its causes are tied to a complex mix of genetic factors and environmental influences. While we know that certain genetic mutations and harmful environmental agents can contribute to PD on their own, it’s the interplay between these factors known as gene–environment (G×E) interactions that gives us a fuller picture of the disease’s risk, variability, and progression. This review aimed at bringing together the latest findings on the molecular mechanisms and epidemiological trends related to G×E interactions in PD, highlighting their importance for real-world applications and public health. By analyzing data from influential functional genomics studies, epidemiological meta-analyses, and population-based cohorts, significant genetic markers (like SNCA, LRRK2, and GBA), environmental neurotoxins (such as pesticides and heavy metals), and new mechanistic pathways, including mitochondrial dysfunction, epigenetic changes, and disruptions in the gut–brain connection was delved into. Insights from precision medicine, biomarker development, and community-focused prevention strategies was woven together. Research showed that environmental factors like paraquat and organophosphates can work together with genetic weaknesses especially low-activity PON1 variants and LRRK2 mutations to speed up the onset and progression of PD. Epigenetic changes and inflammation driven by gut microbiota play crucial roles in these interactions. Epidemiological studies have pinpointed specific geographical and occupational risk clusters, and meta-analyses support the idea that G×E interactions have a causal impact. However, we still have a gap in data from low- and middle-income countries. Grasping the interactions between genes*

*and the environment in Parkinson’s disease opens up vital avenues for identifying risks early, tailoring prevention strategies, and implementing policies that aim to minimize environmental hazards. To truly enhance public health outcomes, future studies should focus on comprehensive, multi-omics methods and ensure fair access to these advancements across various global communities.*

*Indexed Terms- Parkinson’s disease, gene–environment interaction, public health, precision medicine, environmental neurotoxins, mitochondrial dysfunction, LRRK2, PON1, exposomics*

## I. INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta. This degeneration leads to classic motor symptoms like bradykinesia, rigidity, tremors, and postural instability, along with a range of non-motor features such as cognitive decline, sleep issues, and autonomic dysfunctions. PD is becoming an increasingly significant public health concern worldwide, with its prevalence nearly doubling over the last twenty years. Current estimates suggest that more than 10 million people are affected globally, and projections indicate that this number will continue to rise due to aging populations and better diagnostic methods [1,2]. While the exact cause of PD is still not fully understood, it’s clear that the disease arises from a complex interplay between genetic factors and environmental influences. Monogenic forms of PD, linked to mutations in genes like SNCA, LRRK2, PARK2, PINK1, and DJ-1, account for about 5–10% of cases, underscoring the

importance of inherited factors [3]. However, most PD cases are sporadic and are believed to result from the interaction of various genetic variants with modifiable environmental risk factors, such as exposure to pesticides, living in rural areas, drinking well water, and heavy metal toxicity [4,5]. The idea that gene-environment (G×E) interactions play a crucial role in PD is increasingly supported by both epidemiological and molecular research. For instance, individuals with the LRRK2 G2019S mutation may show different levels of disease severity depending on their environmental exposures, such as contact with neurotoxic substances like paraquat or rotenone, which can cause oxidative stress and mitochondrial dysfunction, mimicking the pathology of PD in experimental settings [6,7]. Additionally, epigenetic factors, including DNA methylation and histone modifications, are emerging as key players in how environmental factors influence gene expression related to PD, adding another layer of complexity to its pathogenesis [8].

From a public health perspective, grasping the interactions between genes and the environment in Parkinson's disease (PD) is incredibly important. For starters, it helps us pinpoint high-risk groups for early screening and intervention. Additionally, it guides environmental policy decisions like regulating pesticide use or tackling air pollution that could trigger PD in those who are genetically vulnerable. Moreover, it paves the way for precision medicine approaches that take into account a person's unique genetic background and environmental history for tailored treatments and preventive care. However, despite the importance of these interactions, many public health systems around the world still struggle to effectively combine genetic information with environmental risk assessments. There's a pressing need for thorough studies focused on gene-environment interactions, particularly in low- and middle-income countries where environmental risks are often overlooked and genetic testing is scarce. Closing this gap could transform our approach to PD from a reactive stance to a preventive one, ultimately enhancing patient outcomes and alleviating the economic strain associated with the disease. This review delves into the functional and epidemiological aspects of gene-environment interactions in Parkinson's disease, highlighting their practical significance for public health initiatives and policies.

By shedding light on the biological mechanisms and population trends that drive these interactions, we hope to contribute to future strategies aimed at reducing PD risk, facilitating early diagnosis, and ensuring fair access to healthcare.

## II. MOLECULAR AND FUNCTIONAL BASIS OF PARKINSON'S DISEASE

### 2.1 Pathophysiology of PD

Neuronal Degeneration and  $\alpha$ -Synuclein Pathology  
Parkinson's disease (PD) is mainly marked by the gradual loss of dopaminergic neurons in the substantia nigra pars compacta. This loss leads to a drop in striatal dopamine levels, which in turn causes motor symptoms like tremors, stiffness, slowness of movement, and issues with balance. The neurodegeneration doesn't stop there; it also affects non-dopaminergic systems, which can lead to non-motor symptoms such as cognitive decline, sleep problems, and autonomic dysfunction [12]. A key feature of PD at the neuropathological level is the buildup of misfolded  $\alpha$ -synuclein protein, forming Lewy bodies and Lewy neurites. These protein aggregates throw off cellular balance by disrupting synaptic function, hindering axonal transport, compromising mitochondrial health, and triggering inflammation mediated by microglia [13]. According to Braak's hypothesis, the pathology of  $\alpha$ -synuclein might spread from the enteric nervous system or olfactory bulb to the brainstem and neocortex in a manner similar to prion diseases [14].

### 2.2 Role of Genetic Mutations in Familial and Sporadic PD

While most PD cases are idiopathic, about 5–10% are familial, stemming from specific genetic mutations. Mutations in genes like SNCA, LRRK2, PINK1, PARK2 (parkin), and PARK7 (DJ-1) have been linked to both autosomal dominant and recessive forms of PD [15]. For example, duplications of the SNCA gene can lead to an overproduction of  $\alpha$ -synuclein, which is associated with early-onset PD that progresses quickly [16]. Additionally, genome-wide association studies (GWAS) have identified over 90 susceptibility loci related to sporadic PD, highlighting a significant polygenic influence. These genetic variants are involved in various pathways,

including vesicular trafficking, lysosomal degradation, and immune system regulation [17].

### 2.3 Key Genes Implicated in PD

SNCA, LRRK2, PINK1, PARK7, GBA SNCA is responsible for encoding  $\alpha$ -synuclein; mutations such as A53T and gene duplications lead to toxic protein buildup and early-onset PD [18].

### 2.4 Environmental Contributors

Pesticides, Heavy Metals, and Air Pollution Environmental factors significantly influence the development of Parkinson's disease (PD), especially when combined with genetic predispositions. Neurotoxic pesticides like paraquat, maneb, and rotenone disrupt mitochondrial complex I, leading to an increase in reactive oxygen species (ROS) and mimicking the loss of dopaminergic neurons [23]. People who work with these substances face a two- to three-fold higher risk of developing PD [24]. Heavy metals, including manganese, lead, and mercury, are also linked to the onset of PD. Chronic exposure to manganese, in particular, can trigger a syndrome similar to Parkinson's by causing oxidative stress and damaging structures in the basal ganglia [25]. Additionally, long-term exposure to fine particulate air pollution (PM<sub>2.5</sub>) has been associated with a heightened risk of PD, likely due to systemic inflammation and disruption of the blood-brain barrier [26].

### 2.5 Cellular Mechanisms Linking Genes and Environment

Mitochondrial Dysfunction, Oxidative Stress, and Neuroinflammation A comprehensive model of PD indicates that both genetic and environmental factors converge on shared cellular mechanisms, especially mitochondrial dysfunction, oxidative stress, and inflammation. Several genes associated with PD, such as PINK1 and PARK2, play crucial roles in maintaining mitochondrial quality and regulating autophagy. When these genes malfunction, it leads to the buildup of faulty mitochondria and increased sensitivity to toxins like rotenone and paraquat [20,23]. Mitochondrial dysfunction results in excessive ROS production, which causes lipid peroxidation, protein misfolding, and DNA damage. These stressors kickstart and sustain the aggregation of  $\alpha$ -synuclein and the death of neurons [27].

Damaged neurons then release danger-associated molecular patterns (DAMPs), which activate microglia and astrocytes, prompting them to release pro-inflammatory cytokines like TNF- $\alpha$  and IL-1 $\beta$ , further worsening neurodegeneration [28,29].

### 2.6 Cellular Mechanisms Linking Genes and Environment

Mitochondrial Dysfunction, Oxidative Stress, and Neuroinflammation (continued) A comprehensive model of Parkinson's Disease (PD) suggests that both genetic and environmental influences come together on shared cellular pathways, particularly focusing on mitochondrial dysfunction, oxidative stress, and neuroinflammation. Key genes associated with PD, such as PINK1, PARK2, and DJ-1, play crucial roles in maintaining mitochondria and regulating reactive oxygen species (ROS). When mutations occur in PINK1 and PARK2, it disrupts the process of mitophagy, resulting in the buildup of damaged mitochondria and an increase in ROS production [27]. Environmental toxins like rotenone and paraquat can also hinder the activity of mitochondrial complex I, which further heightens oxidative stress and makes neurons more vulnerable. These toxins mimic PD-like symptoms in animal studies by causing the loss of dopaminergic neurons and the aggregation of  $\alpha$ -synuclein [28]. On top of that, oxidative stress leads to lipid peroxidation, protein misfolding, and DNA damage, all of which contribute to the ongoing neurodegeneration seen in PD [29]. Neuroinflammation is another significant mechanism that connects genetic factors and environmental exposures. When microglia are activated, they release pro-inflammatory cytokines (like TNF- $\alpha$ , IL-1 $\beta$ , and IL-6), creating a cycle of neuronal damage and immune response. This situation worsens with the presence of  $\alpha$ -synuclein aggregates, which act as danger-associated molecular patterns (DAMPs) and further provoke innate immune reactions [30]. Research from postmortem PD brains and studies of cerebrospinal fluid have confirmed the existence of chronic neuroinflammation and increased levels of cytokines [31]. Additionally, recent studies emphasize the importance of the gut-brain axis in PD, indicating that environmental factors might initiate  $\alpha$ -synuclein pathology in the gut, which then spreads to the brain through the vagus nerve. This process could be

influenced by the microbiome and its interactions with the host's immune system [32].

The interplay of mitochondrial dysfunction, oxidative stress, and immune system irregularities creates a crucial link between genetic vulnerability and environmental factors that lead to the development of Parkinson's disease (PD).

### III. GENE-ENVIRONMENT INTERACTIONS: MECHANISTIC INSIGHTS

#### 3.1 Models of G×E Interaction: Additive vs. Synergistic Effects

When we look at gene-environment (G×E) interactions in Parkinson's disease, they're mainly viewed as either additive where genetic and environmental risks simply add up or synergistic, where environmental factors amplify the impact of genetic predispositions in a more pronounced way. The synergistic models are especially important in PD, as individuals with certain genetic variants (like LRRK2 or GBA) show heightened sensitivity to neurotoxins, which can lead to an earlier onset or faster progression of the disease. This highlights the complex, non-linear nature of PD risk, making it crucial to combine insights from molecular genetics with environmental epidemiology.

#### 3.2 Pesticide Exposure and Genetic Susceptibility (e.g., PON1, LRRK2)

A well-known example of G×E synergy is the relationship between pesticide exposure and variations in the PON1 gene, which produces paraoxonase-1, an enzyme that helps detoxify harmful substances. People with low-activity PON1 alleles (like Q192R) struggle to break down organophosphates and face a significantly higher risk of developing PD when exposed to pesticides. Similarly, those carrying the LRRK2 G2019S mutation show varying degrees of disease manifestation, indicating that environmental factors like rotenone or paraquat could trigger symptoms in individuals who are genetically predisposed.

#### 3.3 Epigenetic Regulation: DNA Methylation and Histone Modification

Environmental factors can influence gene expression without altering the DNA sequence itself, through

epigenetic processes such as DNA methylation, histone modifications, and microRNA activity. For example, exposure to air pollutants and pesticides has been linked to reduced methylation of the SNCA gene promoter, which results in increased production and aggregation of  $\alpha$ -synuclein, a protein associated with PD. Epigenetic marks are reversible, which opens up exciting possibilities for therapeutic targets and biomarkers when assessing environmental risks [38].

#### 3.4 Microbiome and the Gut-Brain Axis in G×E Context

The gut-brain axis has become a vital link for understanding G×E interactions in Parkinson's disease (PD). Factors from our environment, like what we eat, the use of antibiotics, and exposure to toxins, can change the composition of our gut microbiota. This shift can influence neuroinflammation and the aggregation of  $\alpha$ -synuclein through immune signaling and vagal pathways [39]. Research involving mice that overexpress  $\alpha$ -synuclein has demonstrated that an imbalance in gut bacteria can worsen motor deficits and activate microglia, highlighting the microbiome's significant role in G×E dynamics [40].

#### 3.5 Limitations of Current Mechanistic Models and Future Directions

Even with advancements, our understanding of G×E interactions in PD is still hampered by several limitations: Many studies depend on animal models or snapshot data from humans, which restricts our ability to draw causal conclusions. Environmental exposures are frequently not well-measured or are based on retrospective self-reports. G×E studies seldom consider interactions across multiple genetic loci or the cumulative effects of lifelong exposures. To truly grasp the intricate interplay of G×E, future research needs to adopt multi-omics strategies, longitudinal studies, and integrated exposomics platforms. These improvements are essential for pinpointing modifiable risk factors, creating early biomarkers, and shaping precision public health initiatives.

#### IV. EPIDEMIOLOGICAL EVIDENCE OF GENE-ENVIRONMENT INTERACTIONS IN PARKINSON'S DISEASE

##### 4.1 Population-Based Cohort and Case-Control Studies

Epidemiological research has played a crucial role in uncovering how genetic factors and environmental influences come together in Parkinson's disease (PD). Through case-control and population-based cohort studies, strong links have been established between pesticide exposure, rural living, and an elevated risk of developing PD, particularly in individuals with specific genetic variants. For example, research conducted in California's Central Valley found that people with low-activity PON1 alleles who were exposed to organophosphates faced up to a 2.5-fold increase in PD risk. Longitudinal studies, such as the Nurses' Health Study and the Agricultural Health Study, have further reinforced these findings, allowing researchers to assess the timing of exposure in relation to disease onset.

##### 4.2 Biomarker-Driven Epidemiology and Exposure Assessment

The traditional approach of relying on self-reported exposure data is being challenged by biomarker-based methods that offer a more objective way to quantify environmental toxins. By measuring pesticide, heavy metal, and air pollutant levels in blood or urine, alongside genotyping, researchers can more accurately stratify risk. Biomarkers like paraoxonase-1 activity and mitochondrial DNA copy number are being investigated to connect exposure with biological responses, providing real-time insights into gene-environment interactions.

##### 4.3 Geographic and Occupational Risk Patterns

Geospatial epidemiology has uncovered regional clusters of PD that align with agricultural activity, industrial pollution, and the use of well water. For instance, rural residents living in areas with heavy pesticide use show significantly higher rates of PD compared to those in urban settings. Similarly, studies on occupational exposure have pointed to farm workers, metal welders, and miners especially those with mutations in genes like SNCA, LRRK2, or GBA—as being at a greater risk for developing PD

##### 4.4 Meta-Analyses and Systematic Reviews

**Evidence Synthesis** A number of meta-analyses have provided strong quantitative support for the gene-environment (G×E) hypothesis in Parkinson's disease (PD). A recent systematic review highlighted a significant interaction between PON1 polymorphisms and pesticide exposure, showing an odds ratio of 1.96 (95% CI: 1.40–2.74) [46]. Similarly, the combined impact of GBA mutations along with exposure to solvents or industrial chemicals has been linked to an earlier onset of PD [47]. These collective analyses bolster causal inference and highlight the necessity of multi-variable models in the study of PD epidemiology.

##### 4.5 Gaps in G×E Epidemiological Research in LMICs

While there's an increasing body of evidence from high-income countries, data from low- and middle-income countries (LMICs) is still quite limited. This is particularly alarming given the prevalent use of pesticides, inadequate occupational safety measures, and the lack of genetic screening infrastructure in many LMICs, especially in Sub-Saharan Africa and parts of Asia. Additionally, ethnic-specific genetic variants could influence susceptibility profiles but are often overlooked in global G×E studies [48]. Bridging this gap is essential for effective PD prevention and ensuring equitable healthcare planning worldwide.

#### V. PUBLIC HEALTH IMPLICATIONS

##### 5.1 Risk Stratification and Population Screening Programs

Grasping the gene-environment (G×E) interactions in Parkinson's disease (PD) paves the way for better risk stratification and the early identification of high-risk groups. By combining genetic profiling particularly for variants in LRRK2, GBA, and PON1 with environmental exposure histories, we can create predictive models to pinpoint individuals who are at greater risk [49]. Implementing these stratification frameworks in public health could lead to more targeted screening, timely interventions, and lifestyle counseling focused on modifiable risk factors.

### 5.2 Environmental Policy and Exposure Mitigation Strategies

A key public health response to our understanding of gene-environment interactions (G×E) is the regulation of environmental neurotoxins. For instance, the connection between paraquat and rotenone and Parkinson's disease (PD) has led some countries to limit their use. However, many low- and middle-income countries still use these substances widely, often without sufficient regulatory oversight [50]. By implementing surveillance systems that combine environmental toxin monitoring with geospatial risk mapping, we can better guide community-level interventions aimed at reducing exposure, especially in rural and agricultural areas.

### 5.3 Genetic Counseling and Ethical Considerations

As genomic data related to PD continues to grow, there's a rising focus on genetic counseling and the ethical implications that come with it. It's crucial to provide counseling for individuals at risk particularly those who are asymptomatic carriers of mutations like LRRK2 G2019S or GBA to help them navigate psychological impacts, potential discrimination, and informed decision-making [51]. Public health policies need to strike a balance between providing access to genetic information and protecting against its misuse, ensuring that ethical and legal standards are upheld worldwide.

### 5.4 Health System Preparedness and Resource Allocation

With the expected increase in PD cases due to aging populations and ongoing environmental risks, it's essential to plan proactively for health system needs. Resources should be directed not just toward clinical management but also toward community-based prevention, education, and rehabilitation initiatives. Health systems in at-risk regions must focus on training the workforce, building biomonitoring infrastructure, and fostering collaborations across sectors to weave G×E insights into broader strategies for tackling non-communicable diseases [52].

### 5.5 Disease Prevention through Integrative Genomic Surveillance

New advancements in public health genomics and exposomics are opening up exciting possibilities for preventing Parkinson's disease (PD). Tools like

polygenic risk scoring (PRS), tracking environmental risk exposures, and utilizing multi-omics datasets can help us keep a close eye on PD risk patterns in real-time. These innovative systems support a more personalized approach to prevention, enabling public health responses that are tailored to both genetic predispositions and modifiable environmental factors [53]. However, it's essential to ensure that these advancements are accessible to everyone. Many low- and middle-income countries (LMICs) still struggle with the necessary infrastructure for genetic testing and environmental toxicology assessments. To prevent widening health disparities in this genomic age, international public health initiatives need to tackle these inequalities head-on [54].

## VI. TRANSLATIONAL AND CLINICAL PERSPECTIVES

### 6.1 Precision Medicine in PD: Challenges and Opportunities

The intersection of genetic susceptibility and environmental factors in Parkinson's disease (PD) has sparked a growing interest in precision medicine. By combining genomic data—like mutations in LRRK2, GBA, and PINK1 with individual environmental histories, we could enhance personalized risk assessments, enable earlier diagnoses, and tailor treatments more effectively [55]. Yet, we still face hurdles, such as the complex and varied nature of PD, incomplete exposure histories, and differences in gene expression across populations. Moreover, the lack of ethnic diversity in genomic databases limits the applicability of precision medicine strategies to diverse global populations [56].

### 6.2 Potential for Early Diagnostic Tools Based on G×E Profiling

Identifying biomarkers that reflect gene-environment interactions—like DNA methylation patterns,  $\alpha$ -synuclein aggregates found in peripheral tissues, and metabolomic profiles—shows great potential for diagnosing PD in its early stages [57]. By combining these molecular signatures with digital exposure tracking tools like wearable sensors and exposomic apps we could pave the way for dynamic risk modeling and early therapeutic interventions. This approach has the potential to transform the clinical

landscape from a focus on diagnosing symptoms to proactively intercepting risks.

### 6.3 Lifestyle Modifications in Genetically At-Risk Populations

Research from both epidemiological and experimental studies indicates that lifestyle changes—such as cutting down on pesticide exposure, boosting antioxidant intake, and increasing physical activity might help delay or lessen the onset of Parkinson's disease (PD) in those who are genetically predisposed [58]. For instance, moderate exercise has been found to influence neuroinflammation and enhance mitochondrial resilience in preclinical models of PD, serving as a valuable non-drug option for high-risk individuals [59]. Being aware of genetic risks can empower people to take charge of their health by avoiding certain exposures, especially for those working in high-risk environments like agriculture or industry, or living in areas with elevated risks. This highlights the importance of preventive neurology as a vital extension of precision healthcare in public health.

### 6.4 Public Health Genomics and Community-Based Interventions

To effectively integrate G×E-informed strategies into public health initiatives, we need to focus on community involvement, health literacy, and fair access to genomic resources. Large-scale projects like All of Us (USA) and the UK Biobank are collecting multi-omic data that can help us spot trends and vulnerabilities at the community level [60]. In areas with limited resources, community-driven programs that include genetic education, efforts to reduce environmental hazards, and culturally relevant messaging are crucial for translating G×E insights into real-world benefits. These initiatives should also be supported by ethical, legal, and social frameworks that promote inclusivity and respect individual autonomy when implementing G×E-based clinical applications [61].

## CONCLUSION

Parkinson's disease is a complex neurodegenerative disorder, and its development is influenced by a mix of genetic factors and environmental influences. Recent research shows that these elements don't

work in isolation; instead, they come together through shared molecular pathways—like mitochondrial dysfunction, oxidative stress, and neuroinflammation—that contribute to the onset and progression of the disease. This blend of functional and epidemiological insights into gene-environment (G×E) interactions in Parkinson's disease has important implications for public health. From a practical perspective, understanding G×E interactions lays the groundwork for precision medicine, early diagnostic tools, and tailored lifestyle changes. The data from epidemiological studies highlight the urgent need for policy responses, especially in regulating neurotoxic exposures and addressing occupational hazards in at-risk communities. However, there are still significant gaps, particularly in underrepresented populations where genetic information is limited, environmental exposures are high, and healthcare resources are lacking. Closing these gaps requires a concerted effort to weave G×E-informed strategies into global public health initiatives making sure that the advantages of precision neurology are available, fair, and ethically sound. By harnessing integrative genomics, exposomics, and community-driven interventions, public health can shift from a reactive approach to a more predictive and preventive strategy in tackling Parkinson's disease. Future research should focus not only on unraveling the complex mechanisms of G×E interactions but also on turning that knowledge into practical policies and actions that lessen the disease burden across various populations.

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