# Parkinson's Disease and Environmental Factors

The National Institute of Environmental Health Sciences (NIEHS) is one of the lead research agencies studying the environmental causes of Parkinson's disease, a neurodegenerative disease thought to be caused by the interaction of genes and environment. NIEHS works closely with other institutes and centers of the National Institutes of Health (NIH), as well as partners and researchers across the country, to look at every aspect of Parkinson's.

What is Parkinson's disease?

Parkinson's disease is a progressive neurodegenerative disease, the second most common disorder of this type after Alzheimer's disease. It progresses slowly as small clusters of dopaminergic neurons in the midbrain die. The gradual loss of these neurons results in reduction of a critical neurotransmitter called dopamine, a chemical responsible for transmitting messages to parts of the brain that coordinate muscle movement.

Studies have shown that the symptoms of Parkinson's usually appear when 50 percent or more of the dopamine neurons in the midbrain have been lost. Common motor symptoms are tremors or shaking in hands, arms, legs, jaw, and face; rigidity or stiffness of limbs and trunk; bradykinesia, or slowness of movement; and difficulties with balance, speech, and coordination. Symptoms begin gradually and typically worsen over time.

There is also a collection of nonmotor symptoms, such as poor sense of smell, constipation, depression, cognitive impairment, fatigue, and other impairments that also accompany Parkinson's. Some of these symptoms may develop years before the onset of motor problems.

Parkinson's patients have less dopamine
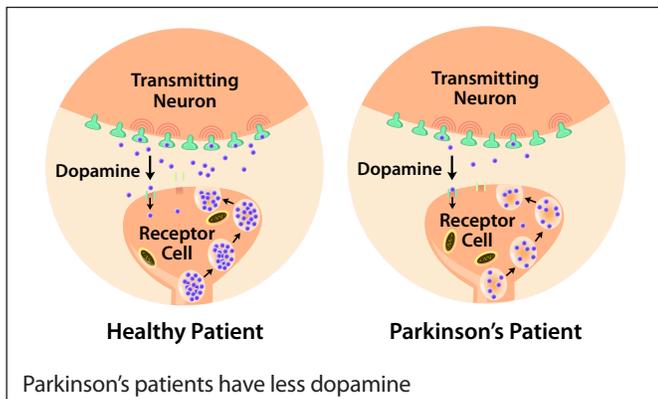
How many people are affected by Parkinson's disease?

It is difficult to know exactly how many people have Parkinson's disease, since there is no national registry, but it is estimated that at least 500,000 people in the U.S. currently have the disease.[1] The average age of onset is about 60, and prevalence is increasing as the population ages.

The majority of people diagnosed have late-onset sporadic Parkinson's, which does not have a clear genetic cause. About 10 percent have early-onset Parkinson's that often begins before the age of 50. There may be a genetic cause associated with many of these patients. Parkinson's strikes people of all races, ethnic groups, nationalities, and income levels. Actor Michael J. Fox, singer Linda Ronstadt, former U.S. Attorney General Janet Reno, and boxer Muhammad Ali, are among the celebrities living with Parkinson's.

What causes Parkinson's disease?

The exact cause of Parkinson's disease is unknown. Most researchers agree that the disease is caused by both genetic and environmental factors, and by interactions among these factors.

A full understanding of Parkinson's risk requires integrated efforts to study both genetic and environmental factors. If environmental exposures can be identified, it may lead to new targets for prevention and intervention.

What kind of research is NIEHS doing related to Parkinson's disease?

NIEHS is currently funding more than 30 grants focused on neurodegenerative diseases, including Parkinson's disease. There is also a very strong in-house research community working to understand the role of the environment, genes, and gene-environment interactions in the disease. The multidisciplinary teams of researchers at NIEHS and across the country are working toward ways to prevent Parkinson's disease or slow its progression.

A sampling of NIEHS-supported research

Pesticides

Accumulating evidence indicates that pesticide exposure is associated with an increased risk for developing Parkinson's disease. Many animal studies have provided evidence for this, and several human studies are beginning to reveal some specific pesticides and classes of pesticides that may be linked to Parkinson's.

Organochlorine insecticides comprise the pesticide class most commonly associated with the disease. Most of these chemicals were banned in the 1970s and 1980s, but because their chemical structures resist breakdown, they can remain in the environment and food chain for a long time. The organochlorine class includes pesticides like DDT, used for mosquito control, and dieldrin, used for termites.[2]

A study published in 2011 by NIEHS researchers and collaborators at the Parkinson's Institute and Clinical Center in Sunnyvale, Calif., showed a link between the occupational use of two pesticides, rotenone and paraquat, and Parkinson's. People who reported use of either pesticide developed the disease 2.5 times more often than nonusers.[3]

Rotenone directly inhibits the function of mitochondria, the structures that create energy to run the cell, while paraquat increases production within cells of certain damaging oxygen derivatives. People who used other pesticides with a similar mechanism of action were also more likely to develop Parkinson's.

Researchers are trying to understand which people, exposed to specific pesticides, are most at risk of developing Parkinson's. For example, a recent study found that Parkinson's risk from paraquat use was particularly high in individuals lacking a certain metabolic enzyme known as GSTT1. The lack of this enzyme is very common, so more research is needed to determine if these individuals are more susceptible to certain pesticides.[4]

Other researchers are studying the combined effect of environmental exposures, like pesticides, and genetic susceptibility on Parkinson's risk. Studies conducted by

NIEHS-funded scientists at the UCLA School of Public Health have shown that the risk of developing Parkinson's in pesticide-exposed individuals was greater in those who had a gene variation that affected dopamine transport than in those who did not.[5]

Dietary factors

Both in-house researchers and grantees are continuing to explore the role that diet and lifestyle play in the onset, progression, and treatment of Parkinson's disease.

How much fat a person consumes in their diet is one area under study. Unfortunately, the findings over the years have been inconsistent. However, in a new study, NIEHS researchers and their collaborators discovered that some fats in a person's diet may be associated with lower risk for Parkinson's.

A 2013 study found that people who ate a diet high in polyunsaturated fatty acids and low in saturated fat had a lower risk of developing the disease.[6] Although the results need to be confirmed, they provide additional evidence that it can be beneficial to eat foods high in polyunsaturated fat.
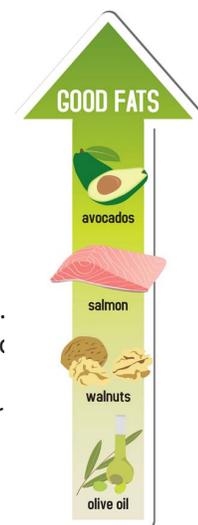
Researchers are also exploring the role of vitamin D deficiency in the development of Parkinson's.[7] Vitamin D, which can enter the body through food or sunlight, plays an important role in maintaining good balance and muscle strength, and in protecting the body from infections and diseases. Researchers are looking into the role that working outdoors may play in reducing the risk of Parkinson's.[8]
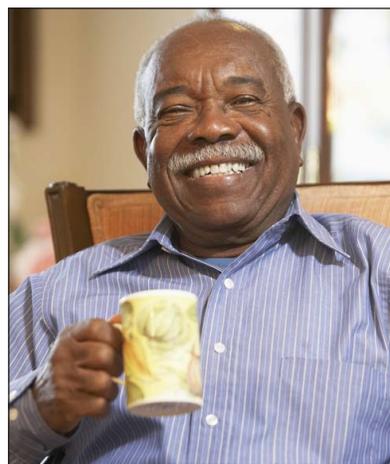
Another dietary component under study is the possible role of caffeine in the onset and progression of Parkinson's. Animal studies have shown that caffeine can protect the brain's dopaminergic neurons, indicating caffeine may reduce the risk of the disease. Researchers also looked at data from a large sample of older Americans, and found that higher caffeine intake was associated with lower risk of Parkinson's in both men and women.[9]

A collaborative study found that coffee consumption may be more protective among individuals with one genotype as compared to individuals with another genotype.[10]

Exercise

NIEHS in-house researchers have shown that there is at least one more reason to exercise on a daily basis—it may protect against Parkinson's disease. In a large population of U.S. older adults, higher levels of moderate to vigorous physical activity in midlife were associated with lower risk of Parkinson's.[11]

Exercise may also benefit patients with the disease, by improving balance and reducing depression, and increasing overall quality of life. For example, a recent study found that tai chi training in patients with mild to moderate Parkinson's improved balance and reduced falls.[12]

Nicotine

Despite the numerous adverse health effects of cigarette smoking, a large number of studies have consistently found that smokers have a lower incidence of Parkinson's disease than nonsmokers.

It is not clear why this occurs, but is likely related to the fact that nicotine interacts with receptors to protect dopamine neurons. Nicotine has also been shown to be neuroprotective in animal models.

NIEHS researchers looked at data from a large study to see if they could determine the characteristics of smoking behavior that decreased Parkinson's risk. They found that more years of smoking, rather than increased number of cigarettes smoked per day, was linked closely to lowering risk of Parkinson's among smokers.[13] NIEHS researchers are also investigating whether genetic factors modify the associations between smoking and Parkinson's.[14]

Head injuries

Numerous studies over the years have looked at the role that head injuries may play in Parkinson's disease. This is a reasonable area to explore, since brain injuries involve inflammation, oxidative stress, and possible disruption of the blood-brain barrier, all of which may play a contributing role in neuronal degeneration and Parkinson's.

Recent studies involving NIEHS researchers further found that the association between head injury and Parkinson's may be affected by genetic factors. For example, researchers found that certain variations of a key Parkinson's gene, SNCA, might modify the association between head injury and Parkinson's disease risk.[15]

Moving forward with promising research areas

Identifying premotor symptoms before disease sets in

One new area of research that NIEHS is pursuing is the premotor symptoms that may occur years before some of the classic muscular deficits surface. By thinking of Parkinson's as a systemic illness that takes decades to develop, researchers will be better poised to understand the cause of the disease and its initial progression. Some of the early warning indicators were discussed at a 2012 NIEHS symposium on premotor symptoms, including constipation, loss of smell, excessive daytime sleepiness, mood or anxiety disorders, and sleep disorders. Many of these symptoms may occur years before Parkinson's disease is diagnosed. Although it is difficult to identify a single early symptom that is specifically tied to the disease, researchers are working to identify whether a combination of symptoms may help characterize high-risk populations.[16]

Some of the risk factors and premotor symptoms that may be involved in Parkinson's
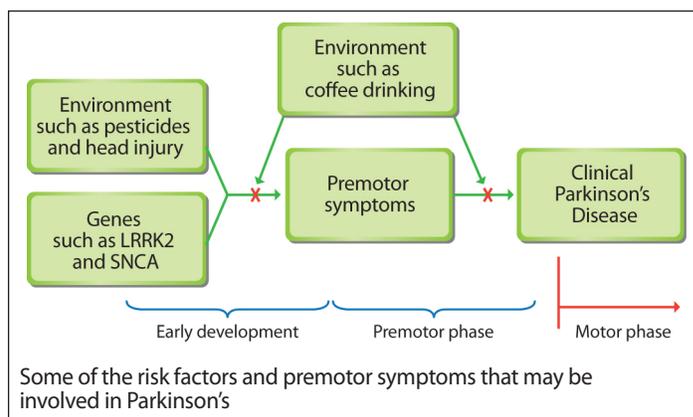
Air pollution

Researchers are beginning to explore the role that air pollution may play in the development and progression of brain diseases, such as Parkinson's disease. Much of the previous research on air pollution has been focused on heart and lung diseases, rather than neurodegenerative diseases. A 2012 NIEHS workshop brought researchers from across the country together, to look at what is known about outdoor air pollution and brain health.[17] The researchers called for more studies to identify how air pollution affects brain health, with the ultimate goal of identifying early markers of disease and developing approaches for prevention and intervention.

Taking advantage of new tools

NIEHS plans to take advantage of the new tools and technologies that will be coming out of the president's Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative, launched in 2013. The initiative aims to accelerate work on technologies that give a dynamic picture of how individual cells and complex neural circuits interact. The ultimate goal is to enhance understanding of the brain and improve prevention, diagnosis, and treatment of brain diseases, such as Parkinson's disease.

NIEHS will also continue to support basic research on Parkinson's, in order to find new approaches and models to advance our understanding of the disease.

For the past few decades, the development and use of animal models have provided valuable insight into the classical motor symptoms of Parkinson's. These models will continue to shed new light on the pathophysiology of Parkinson's. Understanding the mechanisms that account for the selective loss of dopamine neurons may provide important clues to explain how Parkinson's develops, so that therapies can be developed to slow or reverse disease progression. For example, some researchers are beginning to use stem cells that can be induced to develop into dopamine neurons, in order to test new cell-based therapies for central nervous system disorders such as Parkinson's.[18] Other researchers are using animal models, such as zebrafish, to look at the role that some chemicals may play in the brain, and to better understand how neurodegeneration occurs.[19]

Brain imaging techniques and genome-wide association studies are providing us with additional insight into the molecular causes of Parkinson's. Since no one can predict which paths of study will provide major breakthroughs, NIEHS will continue to support diverse research, involving experts from a wide range of disciplines.

> For more information on the National Institute of Environmental Health Sciences, please go to our website at:
> **http://www.niehs.nih.gov/**

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