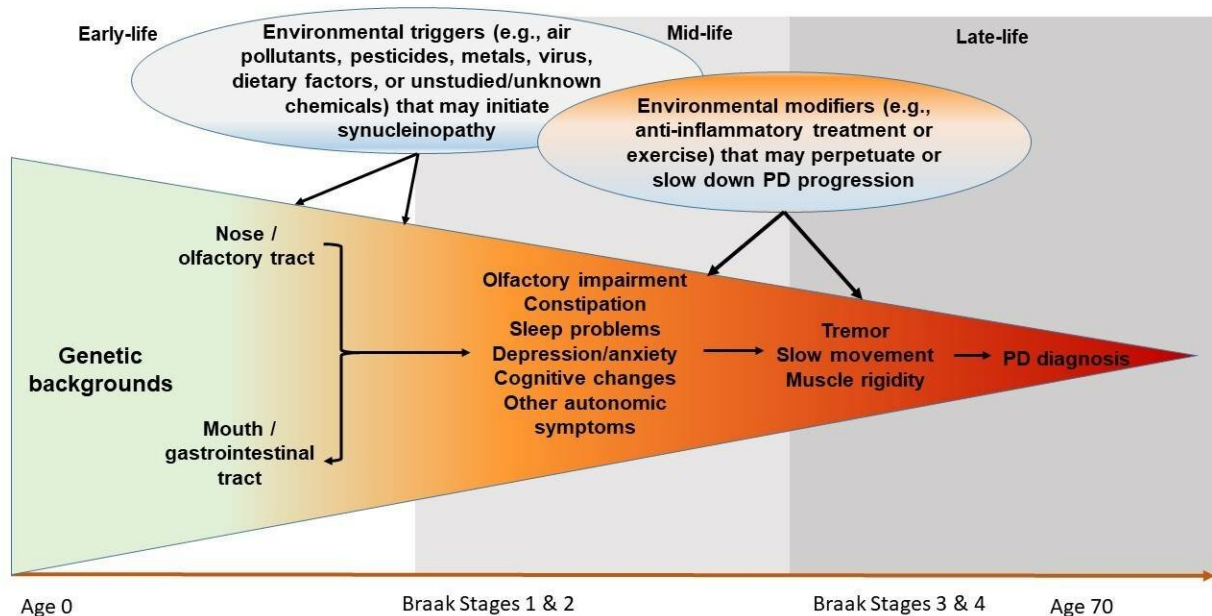


The search for environmental causes of Parkinson's disease moves forward

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Possible contributions of environmental factors to different Braak stages of PD and the PD prodrome. Credit: IOS Press

Environmental factors are widely believed to play a key role in the development of Parkinson's disease (PD), but little is known about specific environmental triggers. Writing in the *Journal of Parkinson's Disease*, scientists review novel research hypotheses and approaches that may help better define the role of environment in the development of

PD, especially before a diagnosis can be made based on the characteristic motor dysfunction for which PD is known.

PD is a slowly progressive disorder that affects movement, muscle control, and balance. Despite recent success in unveiling the [genetic basis](#) of late-onset sporadic PD, genetic findings may only explain a small portion of cases and cannot be easily extended to disease prevention. "The greatest risk factors for PD are likely environmental and not genetic," stated Honglei Chen, MD, Ph.D., of the Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing, MI, USA, and Beate Ritz, MD, Ph.D., of the Departments of Epidemiology, Environmental Health Sciences, and Neurology, Fielding School of Public Health, and Geffen School of Medicine, University of California Los Angeles, CA, USA. "Yet we know relatively little about environmental causes or triggers of PD onset and progression. Identifying these and defining ways to reduce their impact will be great research challenges for the coming two decades."

Late-onset sporadic PD takes decades to develop, and by the time of diagnosis, some of the neurodegenerative changes are too advanced to slow down, stop, or reverse. On the other hand, environmental factors that cause or trigger its development and modify its progression may come into play during the "prodromal phase," decades before specific signs and symptoms develop. "This prodromal stage is of major interest for prevention efforts," explained the authors. "Targeting factors that enter the body via the nose or gut has become even more important since the discovery that the alpha-synuclein protein-related Lewy pathology, which is characteristic of PD, was identified in the nervous systems of the olfactory pathway and the digestive tract."

During the past two decades, scientists have identified over a dozen environmental factors associated with the risk of developing PD, including pesticide exposures and traumatic brain injury. Other

environmental exposures that have been noted as potential risk factors include organic solvents, high-temperature cooked meats and heterocyclic amines, respiratory and gastrointestinal infections, and inflammation in general. There are also reports on inverse associations between PD and smoking, coffee consumption, vigorous exercise, ibuprofen use, and plasma urate.

The authors review the current research, suggest future directions and discuss the potential of novel tools and theoretical frameworks for scientists to design future studies, such as gene-environment interaction and epigenetic approaches.

Braak Hypothesis

The Braak hypothesis presents a unique hypothetical framework for PD development that allows scientists to better conceptualize different steps in the pathogenesis of the PD prodrome and manifest PD. This can also help define the contributions of environmental factors to the different stages of the pathogenic process. The Braak hypothesis states that PD is caused by a pathogen that enters the body via the nasal cavity and subsequently is swallowed and reaches the gut, initiating Lewy pathology in the nose and the digestive tract. According to this hypothesis, PD Lewy pathology develops in six sequential stages, starting in the olfactory bulb or enteric nerves (or both), years if not decades, before spreading to dopamine neurons in the substantia nigra in the brainstem.

Exposome Concept

Another concept described by the authors is the exposome, which represents the totality of human environmental exposures over an individual's lifetime. The authors propose that, together with the Braak hypothesis, the exposome concept provides a theoretical framework for

scientists to design future studies to decipher the environmental causes of PD and to develop early interventions that halt its progression to the characteristic motor and non-motor dysfunction in PD.

"We are at an exciting moment to unveil environmental contributions to PD development and progression by taking a life-course approach, considering prodromal stages of PD, and utilizing novel tools to assess environmental exposures," commented Dr. Chen and Dr. Ritz. "The lifelong contributions of [environmental factors](#) to PD are difficult to characterize because of the decades-long prodromal stage of the disease and the difficulty in assessing environmental exposures during this stage. We nevertheless believe it will be possible to assess long-term exposures through large-scale environmental monitoring and by using novel biomarkers that reflect the exposome."

More information: Honglei Chen et al. The Search for Environmental Causes of Parkinson's Disease: Moving Forward, *Journal of Parkinson's Disease* (2018). [DOI: 10.3233/JPD-181493](https://doi.org/10.3233/JPD-181493)

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