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The epidemiology of Parkinson's disease

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Abstract

The epidemiology of Parkinson's disease shows marked variations in time, geography, ethnicity, age, and sex. Internationally, prevalence has increased over and above demographic changes. There are several potential reasons for this increase, including the decline in other competing causes of death. Whether incidence is increasing, especially in women or in many low-income and middle-income countries where there is a shortage of high-quality data, is less certain. Parkinson's disease is more common in older people and men, and a variety of environmental factors have been suggested to explain why, including exposure to neurotoxic agents. Within countries, there appear to be ethnic differences in disease risk, although these differences might reflect differential access to health care. The cause of Parkinson's disease is multifactorial, and involves genetic and environmental factors. Both risk factors (eg, pesticides) and protective factors (eg, physical activity and tendency to smoke) have been postulated to have a role in Parkinson's disease, although elucidating causality is complicated by the long prodromal period. Following the establishment of public health strategies to prevent cardiovascular diseases and

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Contributors

YB-S and CT conceptualised the Series paper, which was then discussed with all authors and agreed upon. Each author led on various subsections of the Series paper, which were then collated and harmonised by YB-S. Each iteration of the Series paper was reviewed and discussed by all authors who all helped in drafting the response to the reviewers, revision, and approval of the final manuscript.

some cancers, chronic neurodegenerative diseases such as Parkinson's disease and dementia are gaining a deserved higher priority. Multipronged prevention strategies are required that tackle population-based primary prevention, high-risk targeted secondary prevention, and Parkinson's disease-modifying therapies for tertiary prevention. Future international collaborations will be required to triangulate evidence from basic, applied, and epidemiological research, thereby enhancing the understanding and prevention of Parkinson's disease at a global level.

Introduction

Over 65 years ago, Professor Jerry Morris, a founding father of epidemiology, stated, "One of the most urgent social needs of the day is to identify rules of healthy living that might reduce the burden of the metabolic, malignant and 'degenerative' diseases".[1] Epidemiology, complementing biological sciences, provides the scientific basis to monitor the secular patterns of disease to enable future disease projections, to undertake community diagnosis by measuring disease incidence and prevalence to enable health and social care service planning, and to search for risk or protective factors that could be addressed through individual and societal modifications and hence influence prevention strategies. Parkinson's disease is the second most common neurodegenerative disease, and is an important societal issue and global priority.[2,3] In the first paper in this Series, we review Parkinson's disease epidemiology and highlight what we know with confidence, what is less certain, and what we still do not know. We cannot, within the limits of this Series paper, discuss all potential risk factors in depth, so we have chosen those risk factors that we feel are of most interest based on the evidence, novelty, or potential for prevention. We hope this Series paper stimulates further discussion in academia and policy.

Parkinson's disease diagnosis

The International Parkinson and Movement Disorders Society (IPMDS) Task Force defined Parkinson's disease as "a core clinical motor syndrome (parkinsonism) accompanied by substantia nigra pars compacta neurodegeneration and synuclein deposition".[4] This clinicopathological entity has been impossible to verify pre-mortem, so diagnosis is based on typical parkinsonian motor features in the absence of indicators suggesting alternative diagnoses, such as atypical parkinsonian syndromes.[5] This diagnostic approach might change in the forthcoming years, as recent research shows that α-synuclein seed amplification assays can accurately distinguish Parkinson's disease from healthy controls and might also identify the stage of disease.[6] Because of these findings, novel biomarker-defined definitions of Parkinson's disease are currently being developed to diagnose preclinical Parkinson's disease on a biological basis.[7] However, the diagnostic value of biomarker assays to distinguish between Parkinson's disease and atypical parkinsonian syndromes requires further study.

The IPMDS Task Force proposed a separate clinicogenetic category in the definition of Parkinson's disease, so that individuals carrying highly penetrant mutations can be designated as having Parkinson's disease regardless of α-synuclein pathology. Seven genes are currently designated as monogenic causes,[8] four resulting in later onset, autosomal dominantly inherited disease (ie, *LRRK2, CHCHD2, VPS35*, and *SNCA*) and three in early

onset, autosomal recessively inherited disease (ie, *PARKIN, DJ1*, and *PINK1*). Variants in an eighth gene, *GBA*, are the most common genetic risk factor for Parkinson's disease, with penetrance up to 30%.[9] Genetic testing is not a cornerstone of Parkinson's disease diagnosis, but it helps to clarify prognosis and define risk for family members. The UK Brain Bank criteria[10] and the more recently updated Movement Disorder Society (MDS) clinical diagnostic criteria[11] are the most widely used criteria in clinical care and research to enhance diagnostic accuracy. The sensitivity of the UK Brain Bank criteria is high (>80%), tested against neuropathological assessment.[10] Standard neuropathological benchmarks do not yet exist for Parkinson's disease, and sensitivity might vary if tested against a different standard.[12] The 2015 MDS clinical diagnostic criteria for Parkinson's disease, based on the UK Brain Bank criteria, have been tested against clinical expert opinion with high accuracy (92·6%), exceeding the UK Brain Bank criteria's accuracy,[11,13] but clinicopathological validation studies are awaited. The MDS Task Force has also defined prodromal as a true stage of Parkinson's disease, recognising its earlier onset in non-dopaminergic neural structures.[14] Application of these criteria in prospective population-based studies shows high specificity for overt Parkinson's disease development (>98%).[15,16]

There are two types of possible diagnostic error in epidemiological studies. The first is misdiagnosis (false positives), which might result from misclassifying other neurodegenerative pathologies, secondary parkinsonism, and non-progressive Parkinson-like conditions, such as dystonic and essential tremor, as Parkinson's disease. The second possible diagnostic error is underdiagnosis (false negatives), which will occur if people with Parkinson's disease regard their symptoms as part of so-called normal ageing or do not present, or have no access, to health care, as highlighted from door-to-door surveys discussed later. Even when patients do present to healthcare settings, the diagnosis of Parkinson's disease might be missed when obscured by other comorbidities such as osteoarthritis, frailty, and depression.

Large epidemiological studies (eg, the Rochester Epidemiology Project[17]) frequently use record linkage and electronic health records. These methods can be very accurate if confirmed by specialist medical record review, although administrative codes can overestimate cases.[18] Often, studies rely solely on diagnostic codes or drug data without confirmation, using large databases (eg, insurance claims), or even relying on proxy report of Parkinson's disease,[19] at the cost of diagnostic accuracy.

Descriptive epidemiology

Time—With increasing survival into older age, the absolute number of people with Parkinson's disease has increased, and will continue to increase, labelled by some as a pandemic.[20] A systematic analysis of data from the 2016 Global Burden of Disease study estimated that while crude prevalence increased by around 74% between 1990 and 2016, the age-standardised prevalence increase, accounting for demographics, was less marked, at 22%.[21] The methods used to estimate global and country-specific mortality and prevalence are complex given the scarcity of high-quality, country-specific data. Given concerns of under-ascertainment of Parkinson's disease mortality, the highest mortality-to-prevalence

ratios from three high-income countries were used to extrapolate to all other countries, which might not have been generalisable.

There is marked heterogeneity in the observed temporal changes in prevalence and mortality both between and within regions, although most regions showed an increase. Much of the increase is projected to occur in low-income and middle-income countries. One suggested reason is increased longevity, with the decline in mortality risk from cardiovascular[22] and other chronic diseases resulting in patients with Parkinson's disease being more likely to live with their disease (increasing prevalence) and die of disease-related complications, as their disease can progress (increasing Parkinson's disease-specific mortality). Other possible reasons for the increase in prevalence and mortality include increased industrialisation, which might explain the largest increases in countries such as China, and the reduction in smoking, as smoking rates increased faster for men than women, with men being more likely to be smokers and to have quit smoking. This explanation is paradoxical because men also have a higher risk of Parkinson's disease. However, these explanations are unlikely to explain the very large differences reported for countries with similar geographical, demographic, and economic characteristics. For example, within Europe, the Netherlands has a predicted 7·5% decline in Parkinson's disease prevalence rates between 1990 and 2016, whereas Norway has an 87·1% predicted increase in the same time period.

These analyses did not examine the secular trends in incidence of newly diagnosed Parkinson's disease because data for this are still scarce. In general, studies using administrative or primary care records found either no increase or a decrease in Parkinson's disease incidence.[23,24] Two cohorts, a decade apart, from the population-based Rotterdam study found a similar relative decline in incidence across all age groups.[25] In contrast, the Rochester Epidemiology Project found a modest increase in Parkinson's disease incidence over a 30-year period, which was greater for men than women and for patients older than 70 years.[26] Age–period–cohort models suggested a birth cohort around 1920 for Parkinson's disease in men and predicted that incidence rates should decline in the future. A French cohort of women (E3N) also did not show any change in incidence over 27 years of follow-up.[27] Even less is known about incidence in low-income and middle-income countries (LMICs), although secondary analyses of the Global Burden of Disease study indicated modest increases in the annual percentage change in low (0·23%) and low-middle (0·31%) sociodemographic index countries.[28] This increase might reflect better ascertainment, or a true increase in incidence, or both.

Variations by geography, race, and ethnicity—Although variations in risk by geography, race, and ethnicity are typically discussed separately, in many parts of the world these characteristics might not be easily differentiated. In addition, racial or ethnic origins are sociopolitically defined and heavily influenced by differences in access to education, health care, socioeconomic status, and other factors.[29] Inequities across these groups complicate efforts to better explore biological and environmental effects on disparities in health status.

Incidence estimates are only available for few, usually high-income, regions. Prevalence estimates vary considerably across geographical regions.[21,30–36] Compared with Europe

and North America, the prevalence of Parkinson's disease has been estimated to be lower in Africa (particularly in sub-Saharan Africa),[37,38] similar[39,40] or lower in Asia,[2,21] and similar in Latin America.[36,41–46] There are a variety of potential, but unproven, explanations for the observed heterogeneity in prevalence, including geographical differences in genetic variations,[47] environmental factors, gene–environment interactions, access to health care, life expectancy, and study method. Occupational and passive exposure to pesticides might contribute to the rise in LMICs, whereas air pollution might be more important in industrialised high-income countries.

Some clues exist to the inter-relationship between genetic and environmental factors and Parkinson's disease risk. International, multi-ethnic genetic studies show that the frequency[48,49] and penetrance[50] of genetic risk variants of Parkinson's disease vary across ethnic groups and geographical regions, suggesting that genetic factors account for at least some of the heterogeneity. Migrant studies show that estimates of Parkinson's disease prevalence are considerably higher in people of African origin living in the USA than in Black Africans residing in sub-Saharan Africa.[51] Similarly, the prevalence and incidence of Parkinson's disease for Japanese-American men living in Hawaii are higher than for Japanese men living in Japan.[52] Such observations might be explained by differential exposure to a wide range of adverse exposures (eg, occupational or poverty-related) in migrant populations. Alternatively, the non-migrant population might have less awareness of the disease or access to health care, leading to underdiagnosis. Despite generally lower rates of parkinsonism in Black people compared with White people, two post-mortem studies found similar estimates of Lewy body pathology in White and Black individuals.[53,54] These findings suggest that subclinical disease risk might be similar, but either slower progression or worse access to health care results in less clinical diagnosis in Black people. Studies on ethnically diverse individuals living in the same area show that the incidence and prevalence of Parkinson's disease are higher in European White people than in Black people or Asian people.[30,55–58] A US study reported the incidence of Parkinson's disease to be higher among people of Hispanic ethnicity compared with non-Hispanic White people, Black people, or Asian people.[55] Another study in New York City noted higher incidence just in Black men compared with White and Hispanic men, but lower prevalence of Parkinson's disease in Black people than White people, although they did not differentiate White groups due to small numbers.[38] Whether these differences are real or due to bias in case ascertainment through differential access to health care is unclear.

Most of the aforementioned studies have been done in settings where health and social disparities among different race or ethnic groups could potentially bias the results. In addition, self-declared race or ethnicity has been used as a surrogate for genetic ancestry despite being more reflective of sociocultural conditions. Future studies will need to distinguish genetic and biological effects from environmental and social effects. Such an approach could provide valuable clues to modifiable environmental factors. For example, comparing the risk of Parkinson's disease in a large country such as India, which varies both geographically (eg, north and south) as well as by race and ethnicity, usually proxied by religion (eg, Hindu, Muslim, Jain, and Sikh), could be valuable, and has been studied with other major disease groups.[59]

Age—Increasing age is associated with increased Parkinson's disease risk, although whether this is a linear or exponential increase remains unclear. Unless individuals are screened, older individuals will be under-diagnosed to a greater degree than younger individuals. In the EUROPARKINSON study,[31] the percentage of undiagnosed screen-detected cases increased from 18% for individuals aged 65–70 years to 36% for those aged 80–85 years. This percentage further increased to over 50% of people older than 85 years in a sample of adults living in east Boston (MA, USA); the criteria used were two or more features of parkinsonism (ie, bradykinesia, gait disturbance, rigidity, or tremor) rather than clinically diagnosed Parkinson's disease.[60] This age pattern is similar to that seen for other neurodegenerative disorders and many cancers. Whether age-related cell death is an inevitable function of biological ageing or is secondary to chronic exposure to environmental toxins is unknown. In most cases, complex interactions among senescence-associated cellular changes, genetically determined processes, and environmental insults probably underlie the neurodegenerative process.[61]

Sex—The incidence, prevalence, and mortality risk of Parkinson's disease is higher in men than in women by a ratio of approximately 1·4:1.[62] The prevalence ratio estimate has remained stable for the past two to three decades,[21] whereas the incidence ratio might have increased over time: the Rochester Epidemiology Project found incidence in men increasing between 1976 and 1985 and 1996 and 2005, but remaining stable in women.[26] The reason for the higher incidence in men is not fully understood, but the observation that in *LRRK2*-associated Parkinson's disease there is a higher risk in women with the Gly2019Ser mutation as compared with other types of genetic mutations supports the role of environmental factors.[63] Hypotheses include greater exposure of men to adverse environmental risk factors and the protective role of female hormones. Unlike cardiovascular disease, where the male-to-female risk ratio disappears after 75 years, women appear to have lower risk at all ages. Few studies try to distinguish how biological sex might differ from sociocultural gender identity in terms of Parkinson's disease risk.

Socioeconomic status—There are marked disparities between socioeconomic status and disease risk, with individuals of lower socioeconomic status having a higher risk of disease in general, reflecting greater exposure to a wide range of adverse experiences across the life course. Studies that have assessed the association between socioeconomic status and Parkinson's disease find inconsistent results, which is surprising because higher socioeconomic status in high-income countries is associated with a lower chance of being a current or previous smoker. Recent mendelian randomisation analyses found that genetic variants (single-nucleotide polymorphisms) that predict higher cognition were associated with increased Parkinson's disease risk,[64] the opposite to what is observed for Alzheimer's disease.[65] A consistent socioeconomic status gradient has not been found, which possibly suggests that people of lower socioeconomic status are often more likely to encounter neurotoxic exposures, countering the expected positive gradient.

Determinants of disease

In trying to identify causal determinants of disease, triangulation of knowledge obtained in basic and clinical science as well as epidemiological studies is important.[66] Disease

determinants can be intrinsic or extrinsic (figure 1). Possible extrinsic factors include environmental agents (eg, toxicants and infectious organisms), lifestyle behaviours (eg, diet), and physical factors (eg, trauma). Intrinsic factors include genetic predisposition, metabolic state (eg, elevated urate), and comorbidities (eg, diabetes). Intrinsic factors might result from, or interact with, extrinsic factors, including epigenetic changes, the microbiome, or other comorbidities. Some determinants might affect disease risk in men and women differently (table).

Most cases of Parkinson's disease result from the combined effects of environmental exposures and variation in genes regulating metabolic pathways, such as detoxification genes, which contribute to susceptibility.[67] Pathogenic variants in a number of genes are associated with familial Parkinson's disease, representing the minority of cases. For most of these variants, penetrance is incomplete, and other genetic or environmental factors probably determine if and when disease will manifest.

Concordance rates in monozygotic and dizygotic twins with lifelong follow-up estimated the heritability of Parkinson's disease to be only 30%, supporting a larger role of environmental and behavioural factors.[68] Because both genetic and environmental factors must be measured to assess gene–environment interaction, few studies have yet been performed, usually in small samples. One exception is UK Biobank, which examined interactions between a Parkinson's disease polygenic risk score and a very small range of risk factors.[19] This study found that the adverse effect of type 2 diabetes was stronger in those with less genetic predisposition to Parkinson's disease. This study illustrates how the contribution of extrinsic factors differs on the basis of genetic risk. Nearly all studies classify Parkinson's disease cases together or possibly stratify by known genetic variants, ignoring heterogeneity (known as clusters) in Parkinson's disease phenotype. Only one study has examined whether Parkinson's disease genetic risk score predicts variations in phenotype.[69] This study found that a more severe phenotype, previously shown to be associated with a pro-inflammatory profile, had a lower genetic risk than other clusters and might be more driven by extrinsic factors. This study requires replication, but has important methodological implications if such participants are less likely to be included in studies.

A recent review of meta-analyses and systematic reviews concluded that constipation (a well recognised prodromal feature of Parkinson's disease associated with Lewy pathology) and physical activity were the only factors providing class 1 evidence of association with Parkinson's disease risk.[70] Systematic reviews are useful in identifying associations easily measured in large populations, but will omit more novel risk factors with less published literature. Furthermore, many environmental factors proposed to be associated with Parkinson's disease are still difficult to measure at a large scale and thus will be under-represented in such reviews. Here, we briefly summarise some risk factors that might guide disease prevention strategies, if genuinely causal.

The most consistent association, recognised over five decades ago, is a reduced risk of Parkinson's disease in cigarette smokers and, in a few studies, other tobacco users, although this interpretation has remained controversial.[71] The association shows a dose–response effect, being stronger with increasing duration and frequency of tobacco use. Mendelian

randomisation studies, which avoid reverse causation and reduce confounding, support this association. Genetic variants that determine smoking liability are associated with lower risk of Parkinson's disease.[72] The mechanism of this association is not known. Nicotine might or might not play a central role, although no trial evidence exists of disease-modifying effects of the nicotine patches in patients with Parkinson's disease.[67] Coffee and tea drinking are also associated with a lower risk of Parkinson's disease, particularly in men.[73,74] Dietary dairy intake is associated with greater risk of Parkinson's disease, possibly due to toxicants bioconcentrated in milk,[75] while diets high in vegetables, fruits, and grains are associated with a reduced risk, although this might reflect residual confounding by other factors.[76] Anti-inflammatory drug use is associated with a decrease in risk of Parkinson's disease,[77] including that associated with *LRRK2*.[78] Inflammation is thought to contribute to Parkinson's disease pathogenesis in sporadic and familial disease. Physical activity and exercise are associated with lower risk of Parkinson's disease, and greater amounts and intensity of exercise are associated with greater risk reduction, although even modest levels reduce risk.[79] The combined effects of these lifestyle factors appear to be additive, suggesting an approach to disease prevention[76] analogous to cardiovascular disease.

Environmental toxicant exposures, including pesticides, solvents, and air pollution, are associated with higher risk of Parkinson's disease. Parkinson's disease risk is also increased in people with occupational pesticide use or those living near pesticide-treated fields, reducing recall bias.[80] Pesticides associated with Parkinson's disease, including paraquat, rotenone, 2,4-D, and several organochlorines, have biochemical effects, including mitochondrial dysfunction, inflammation, epigenetic methylation, and alterations of the microbiome that are thought to be important to Parkinson's disease, strengthening the possibility that these associations are causal effects.[61,80,81] This association is described in more detail in paper 2 of this Series.[82] Genetically determined impairment in handling of toxicants can increase the risk of Parkinson's disease due to pesticide exposure, whereas extrinsic factors, such as use of personal protective equipment when using pesticides and eating a healthy diet, can lower risk in those exposed. Chlorinated solvents (eg, trichloroethylene, perchloroethylene, and carbon tetrachloride) are associated with increased risk of Parkinson's disease in humans and cause parkinsonism-associated toxicity in animal models.[83] Many Parkinson's disease-associated toxicant chemicals are environmentally persistent, which is relevant given the long latency period between exposure and disease diagnosis. For example, in the USA, trichloroethylene can be detected in soil, air, food, human breastmilk, and nearly a third of drinking water supplies. Other toxicant exposures associated with Parkinson's disease include air pollution and occupational exposure to welding or certain metals.[84]

A meta-analysis of case control studies showed an association of head injury with Parkinson's disease,[85] but a record linkage study of hospital admissions, avoiding recall bias, and Parkinson's disease risk only found an association close to diagnosis, suggesting reverse causation.[86] In contrast, a high-quality retrospective cohort study with previous documented traumatic brain injury in the Veterans Health Administration database found a dose–response relationship with severity.[87] The sequelae of head trauma might also depend on genetic susceptibility, such as variants in the gene encoding α-synuclein.[88] Infectious agents, and particularly viral agents, might also serve as risk factors for Parkinson's disease,

although the evidence for this is not consistent. Such exposure, in susceptible individuals, might initiate an inflammatory process increasing vulnerability to other risk factors, or triggering a neuropathological cascade.[89]

Prevention of Parkinson's disease

Prevention strategies can be classified as primary, secondary, and tertiary (figure 2). Primary approaches are population-based, intervene for the whole population regardless of risk, and might operate before degeneration begins. They often require political or structural changes, such as banning a neurotoxic agent. Secondary interventions target people at greater risk of developing Parkinson's disease using either genetic risk markers or prodromal symptoms such as impaired olfaction, rapid eye movement (REM) sleep behaviour disorder, and constipation.[90] Intervention in the prodromal phase might either delay cellular degeneration or slow its rate of progression. Any pharmacological intervention will need to balance the cost and risk of any intervention, given the relatively high number of people who might be treated who will never develop clinical Parkinson's disease. Tertiary prevention treats people with established disease with disease-modifying therapies that slow or halt progression, and hence reduces future complications and mortality.

Many chronic diseases and ageing phenotypes are increasingly recognised to have both developmental and degenerative phases, and should be viewed within a life course framework[91] (figure 2). The possible developmental origins of Parkinson's disease have been understudied,[92] and there is currently an absence of neuropathological evidence as to whether Parkinson's disease pathology is already present subclinically in early life. Possible causal factors that might act in the healthy phase include childhood infections, neurotoxic exposure, smoking behaviour, and developmental factors (eg, height and weight gain). Understanding the timing of any toxic exposures might be particularly important in relation to any critical or sensitive periods whereby the brain might be susceptible to any adverse impact. Delineating the prodromal or latency period is also important to determine whether exposures either reflect reverse causation secondary to the existing pathophysiology, or accelerate the manifestation of clinical disease after onset of pathology, rather than initiating it.

The need for secondary prevention trials—Interventions in the prodromal phase of Parkinson's disease might be more effective than agents targeting disease mechanisms after disease has become established. To date, these interventions have been disappointing, similar to those seen with therapeutic trials for Alzheimer's disease.[93] The Michael J Fox Foundation has recently announced plans to assess therapeutics in individuals who have clinical, imaging, and biomarker characteristics of prodromal Parkinson's disease who are participating in the longitudinal Parkinson's Progression Markers Initiative study.[94]

One promising non-pharmacological intervention is promotion of physical activity in people with prodromal features of Parkinson's disease, such as idiopathic REM sleep behaviour disorder. Converging evidence suggests that intense physical activity might have disease-modifying properties in Parkinson's disease, while the risk of side-effects and costs are low.[95] A serious challenge, however, will be to sustain compliance with any exercise

intervention given the highly variable latency period between the onset of REM sleep behaviour disorder and Parkinson's disease, which might span more than a decade.[96] New digital technologies enable a cost-effective way to deliver a self-directed intervention, using gamification, as well as remote measurement of intermediate endpoints and Parkinson's disease phenoconversion.

Applying such an approach at a population level could lead to large benefits, preventing 14·5% of all current cases given the following assumptions: first, that the lifetime risk of Parkinson's disease is approximately 5%; second, that the summary risk ratio for Parkinson's disease comparing those with moderate to vigorous physical activity versus those with low levels is 0·71,[97] reflecting a causal effect; third, that 50% of the general population do not meet the WHO recommended standard for moderate to vigorous physical activity;[98] and fourth, that societal interventions could abolish low activity levels. Whether or not these conditions are achievable in the real world, the concept shows the large prevention potential of a population-based approach. Albeit an extreme example, the US embargo of Cuba between 1990 and 1995 was associated with an increase in the proportions of people who were physically active, from around 30% to 80%, as well as a decline in daily calorie intake from 3200 kcal to 2400 kcal per capita, with a corresponding population-wide weight loss of 5·5 kg and a 33% decline in diabetes incidence (1·8 per 1000 people to 1·2 per 1000 people).[99]

Conclusions

We have attempted to summarise what we do and do not know about the epidemiology of Parkinson's disease, how to prevent it, and the future research needs. A recent special communication by a WHO task force similarly highlighted the need for better quality epidemiological data with equitable representation (by race, ethnicity, geography, sex, and gender) and for harmonised risk reduction and prevention strategies.[100] In LMICs, there is also a need to enhance research infrastructure, offer better training and support, enhance appropriate governance procedures, and create greater inclusion of civil society organisations and people with Parkinson's disease. Even in high-income countries too many silos remain between basic, clinical, and epidemiological researchers, who often view each other as competitors for scarce funding. We welcome initiatives such as Aligning Science Across Parkinson's, which aims to foster collaboration and encourage data sharing to promote new discoveries with programmes such as the Global Parkinson's Genetics Program, although its focus is around genetics. We hope future endeavours will aim to measure global environmental factors and use natural experiments to promote evidence-based prevention strategies.

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References

1. Smith GD. The uses of 'uses of epidemiology'. Int J Epidemiol 2001; 30: 1146–55. [PubMed: 11689538]
2. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2014; 29: 1583–90. [PubMed: 24976103]
3. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007; 68: 384–86. [PubMed: 17082464]
4. Berg D, Postuma RB, Bloem B, et al. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord 2014; 29: 454–62. [PubMed: 24619848]
5. Kalia LV, Lang AE. Parkinson disease in 2015: evolving basic, pathological and clinical concepts in PD. Nat Rev Neurol 2016; 12: 65–66. [PubMed: 26782330]
6. Siderowf A, Concha-Marambio L, Lafontant DE, et al. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study. Lancet Neurol 2023; 22: 407–17. [PubMed: 37059509]
7. Chahine LM, Merchant K, Siderowf A, et al. Proposal for a biologic staging system of Parkinson's disease. J Parkinsons Dis 2023; 13: 297–309. [PubMed: 37066922]
8. Lange LM, Gonzalez-Latapi P, Rajalingam R, et al. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society task force - an update. Mov Disord 2022; 37: 905–35. [PubMed: 35481685]
9. Anheim M, Elbaz A, Lesage S, et al. Penetrance of Parkinson disease in glucocerebrosidase gene mutation carriers. Neurology 2012; 78: 417–20. [PubMed: 22282650]
10. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181–84. [PubMed: 1564476]
11. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015; 30: 1591–601. [PubMed: 26474316]

12. Dickson DW, Braak H, Duda JE, et al. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. Lancet Neurol 2009; 8: 1150–57. [PubMed: 19909913]
13. Postuma RB, Poewe W, Litvan I, et al. Validation of the MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2018; 33: 1601–08. [PubMed: 30145797]
14. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015; 30: 1600–11. [PubMed: 26474317]
15. Marini K, Seppi K, Tschiderer L, et al. Application of the updated Movement Disorder Society criteria for prodromal Parkinson's disease to a population-based 10-year study. Mov Disord 2021; 36: 1464–66. [PubMed: 33729608]
16. Pilotto A, Heinzel S, Suenkel U, et al. Application of the Movement Disorder Society prodromal Parkinson's disease research criteria in 2 independent prospective cohorts. Mov Disord 2017; 32: 1025–34. [PubMed: 28509336]
17. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ 3rd. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. Mayo Clin Proc 2012; 87: 1202–13. [PubMed: 23199802]
18. Petersen BJ, Rocca WA, Bower JH, Savica R, Mielke MM. Identifying incident Parkinson's disease using administrative diagnostic codes: a validation study. Clin Park Relat Disord 2020; 3: 100061. [PubMed: 34164614]
19. Jacobs BM, Belete D, Bestwick J, et al. Parkinson's disease determinants, prediction and gene-environment interactions in the UK Biobank. J Neurol Neurosurg Psychiatry 2020; 91: 1046–54. [PubMed: 32934108]
20. Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. J Parkinsons Dis 2018; 8: S3–8. [PubMed: 30584159]
21. Dorsey ER, Elbaz A, Nichols E, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018; 17: 939–53. [PubMed: 30287051]
22. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999; 353: 1547–57 [PubMed: 10334252]
23. Akushevich I, Kravchenko J, Ukraintseva S, Arbeev K, Yashin AI. Time trends of incidence of age-associated diseases in the US elderly population: Medicare-based analysis. Age Ageing 2013; 42: 494–500. [PubMed: 23482353]
24. Horsfall L, Petersen I, Walters K, Schrag A. Time trends in incidence of Parkinson's disease diagnosis in UK primary care. J Neurol 2013; 260: 1351–57. [PubMed: 23263597]
25. Darweesh SK, Koudstaal PJ, Stricker BH, Hofman A, Ikram MA. Trends in the incidence of Parkinson disease in the general population: the Rotterdam Study. Am J Epidemiol 2016; 183: 1018–26. [PubMed: 27188952]
26. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Time trends in the incidence of Parkinson disease. JAMA Neurol 2016; 73: 981–89. [PubMed: 27323276]
27. Canonico M, Artaud F, Degaey I, et al. Incidence of Parkinson's disease in French women from the E3N cohort study over 27 years of follow-up. Eur J Epidemiol 2022; 37: 513–23. [PubMed: 35286513]
28. Ou Z, Pan J, Tang S, et al. Global trends in the incidence, prevalence, and years lived with disability of Parkinson's disease in 204 countries/territories from 1990 to 2019. Front Public Health 2021; 9: 776847. [PubMed: 34950630]
29. Cerdeña JP, Grubbs V, Non AL. Racialising genetic risk: assumptions, realities, and recommendations. Lancet 2022; 400: 2147–54. [PubMed: 36502852]
30. Wright Willis A, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: a population-based study of US Medicare beneficiaries. Neuroepidemiology 2010; 34: 143–51. [PubMed: 20090375]
31. de Rijk MC, Tzourio C, Breteler MM, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study. European community concerted action

on the epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry 1997; 62: 10–15. [PubMed: 9010393]

32. Kasten M, Chade A, Tanner CM. Epidemiology of Parkinson's disease. Handb Clin Neurol 2007; 83: 129–51. [PubMed: 18808913]
33. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Influence of strict, intermediate, and broad diagnostic criteria on the age- and sex-specific incidence of Parkinson's disease. Mov Disord 2000; 15: 819–25. [PubMed: 11009185]
34. Alves G, Forsaa EB, Pedersen KF, Dreetz Gjerstad M, Larsen JP. Epidemiology of Parkinson's disease. J Neurol 2008; 255 (suppl 5): 18–32. [PubMed: 18787879]
35. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016; 15: 1257–72. [PubMed: 27751556]
36. Llibre-Guerra JJ, Prina M, Sosa AL, et al. Prevalence of parkinsonism and Parkinson disease in urban and rural populations from Latin America: a community based study. Lancet Reg Health Am 2022; 7: 100136. [PubMed: 35300390]
37. Okubadejo NU, Bower JH, Rocca WA, Maraganore DM. Parkinson's disease in Africa: a systematic review of epidemiologic and genetic studies. Mov Disord 2006; 21: 2150–56. [PubMed: 17044056]
38. Mayeux R, Marder K, Cote LJ, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. Am J Epidemiol 1995; 142: 820–27. [PubMed: 7572958]
39. Muangpaisan W, Hori H, Brayne C. Systematic review of the prevalence and incidence of Parkinson's disease in Asia. J Epidemiol 2009; 19: 281–93. [PubMed: 19801887]
40. Zhang ZX, Roman GC, Hong Z, et al. Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. Lancet 2005; 365: 595–97. [PubMed: 15708103]
41. Barbosa MT, Caramelli P, Maia DP, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambuí study). Mov Disord 2006; 21: 800–08. [PubMed: 16482566]
42. Nicoletti A, Sofia V, Bartoloni A, et al. Prevalence of Parkinson's disease: a door-to-door survey in rural Bolivia. Parkinsonism Relat Disord 2003; 10: 19–21. [PubMed: 14499202]
43. Melcon MO, Anderson DW, Vergara RH, Rocca WA. Prevalence of Parkinson's disease in Junin, Buenos Aires Province, Argentina. Mov Disord 1997; 12: 197–205. [PubMed: 9087978]
44. Sánchez JL, Buriticá O, Pineda D, Uribe CS, Palacio LG. Prevalence of Parkinson's disease and parkinsonism in a Colombian population using the capture-recapture method. Int J Neurosci 2004; 114: 175–82. [PubMed: 14702206]
45. Chouza C, Ketzoian C, Caamaño JL, et al. Prevalence of Parkinson's disease in a population of Uruguay. Preliminary results. Adv Neurol 1996; 69: 13–17. [PubMed: 8615121]
46. Giroud Benítez JL, Collado-Mesa F, Esteban EM. Prevalence of Parkinson disease in an urban area of the Ciudad de La Habana province, Cuba. Door-to-door population study. Neurología 2000; 15: 269–73 (in Spanish). [PubMed: 11075574]
47. Correia Guedes L, Ferreira JJ, Rosa MM, Coelho M, Bonifati V, Sampaio C. Worldwide frequency of G2019S LRRK2 mutation in Parkinson's disease: a systematic review. Parkinsonism Relat Disord 2010; 16: 237–42. [PubMed: 19945904]
48. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009; 361: 1651–61. [PubMed: 19846850]
49. Healy DG, Falchi M, O'Sullivan SS, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol 2008; 7: 583–90. [PubMed: 18539534]
50. Shu L, Zhang Y, Sun Q, Pan H, Tang B. A comprehensive analysis of population differences in *lrrk2* variant distribution in Parkinson's disease. Front Aging Neurosci 2019; 11: 13. [PubMed: 30760999]
51. Dotchin C, Msuya O, Kissima J, et al. The prevalence of Parkinson's disease in rural Tanzania. Mov Disord 2008; 23: 1567–672. [PubMed: 18581482]

52. Morens DM, Davis JW, Grandinetti A, Ross GW, Popper JS, White LR. Epidemiologic observations on Parkinson's disease: incidence and mortality in a prospective study of middle-aged men. Neurology 1996; 46: 1044–50. [PubMed: 8780088]
53. Jendroska K, Olasode BJ, Daniel SE, et al. Incidental Lewy body disease in black Africans. Lancet 1994; 344: 882–83.
54. Nag S, Barnes LL, Yu L, et al. Association of Lewy bodies with age-related clinical characteristics in Black and White decedents. Neurology 2021; 97: e825–35. [PubMed: 34088871]
55. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 2003; 157: 1015–22. [PubMed: 12777365]
56. Dahodwala N, Siderowf A, Xie M, Noll E, Stern M, Mandell DS. Racial differences in the diagnosis of Parkinson's disease. Mov Disord 2009; 24: 1200–05. [PubMed: 19412929]
57. Troiano AR, Micheli FE, Alarcón F, Teive HA. Movement disorders in Latin America. Parkinsonism Relat Disord 2006; 12: 125–38. [PubMed: 16503410]
58. Pitcher TL, Myall DJ, Pearson JF, et al. Parkinson's disease across ethnicities: a nationwide study in New Zealand. Mov Disord 2018; 33: 1440–48. [PubMed: 30035822]
59. Dandona L, Dandona R, Kumar GA, et al. Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. Lancet 2017; 390: 2437–60. [PubMed: 29150201]
60. Bennett DA, Beckett LA, Murray AM, et al. Prevalence of parkinsonian signs and associated mortality in a community population of older people. N Engl J Med 1996; 334: 71–76. [PubMed: 8531961]
61. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol 2022; 22: 657–73. [PubMed: 35246670]
62. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 2004; 75: 637–39. [PubMed: 15026515]
63. Chen W, Yan X, Lv H, Liu Y, He Z, Luo X. Gender differences in prevalence of LRRK2-associated Parkinson disease: a meta-analysis of observational studies. Neurosci Lett 2020; 715: 134609. [PubMed: 31698024]
64. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 2019; 18: 1091–102. [PubMed: 31701892]
65. Anderson EL, Howe LD, Wade KH, et al. Education, intelligence and Alzheimer's disease: evidence from a multivariable two-sample mendelian randomization study. Int J Epidemiol 2020; 49: 1163–72. [PubMed: 32003800]
66. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol 2016; 45: 1866–86. [PubMed: 28108528]
67. Marras C, Canning CG, Goldman SM. Environment, lifestyle, and Parkinson's disease: implications for prevention in the next decade. Mov Disord 2019; 34: 801–11. [PubMed: 31091353]
68. Goldman SM, Marek K, Ottman R, et al. Concordance for Parkinson's disease in twins: a 20-year update. Ann Neurol 2019; 85: 600–05. [PubMed: 30786044]
69. Lawton M, Tan MM, Ben-Shlomo Y, et al. Genetics of validated Parkinson's disease subtypes in the Oxford Discovery and Tracking Parkinson's cohorts. J Neurol Neurosurg Psychiatry 2022; 93: 952–59. [PubMed: 35732412]
70. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism Relat Disord 2016; 23: 1–9. [PubMed: 26739246]
71. Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. Arch Neurol 2007; 64: 990–97. [PubMed: 17620489]
72. Larsson SC, Burgess S. Appraising the causal role of smoking in multiple diseases: a systematic review and meta-analysis of mendelian randomization studies. EBioMedicine 2022; 82: 104154. [PubMed: 35816897]

73. Ross GW, Abbott RD, Petrovitch H, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. JAMA 2000; 283: 2674–79. [PubMed: 10819950]
74. Palacios N, Gao X, McCullough ML, et al. Caffeine and risk of Parkinson's disease in a large cohort of men and women. Mov Disord 2012; 27: 1276–82. [PubMed: 22927157]
75. Park M, Ross GW, Petrovitch H, et al. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. Neurology 2005; 64: 1047–51. [PubMed: 15781824]
76. Kim IY, O'Reilly EJ, Hughes KC, et al. Integration of risk factors for Parkinson disease in 2 large longitudinal cohorts. Neurology 2018; 90: e1646–53. [PubMed: 29643081]
77. Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. Neurology 2011; 76: 863–69. [PubMed: 21368281]
78. San Luciano M, Tanner CM, Meng C, et al. Nonsteroidal anti-inflammatory use and LRRK2 Parkinson's disease penetrance. Mov Disord 2020; 35: 1755–64. [PubMed: 32662532]
79. Yang F, Trolle Lagerros Y, Bellocco R, et al. Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. Brain 2015; 138: 269–75. [PubMed: 25410713]
80. Tanner CM, Goldman SM, Ross GW, Grate SJ. The disease intersection of susceptibility and exposure: chemical exposures and neurodegenerative disease risk. Alzheimers Dement 2014; 10 (suppl): S213–25. [PubMed: 24924672]
81. Goldman SM. Environmental toxins and Parkinson's disease. Annu Rev Pharmacol Toxicol 2014; 54: 141–64. [PubMed: 24050700]
82. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH. The pathogenesis of Parkinson's disease. Lancet 2024; 403: 293–304. [PubMed: 38245249]
83. Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med 2020; 36: 1–12. [PubMed: 31733690]
84. Murata H, Barnhill LM, Bronstein JM. Air pollution and the risk of Parkinson's disease: a review. Mov Disord 2022; 37: 894–904. [PubMed: 35043999]
85. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol 2012; 72: 893–901. [PubMed: 23071076]
86. Rugbjerg K, Ritz B, Korbo L, Martinussen N, Olsen JH. Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. BMJ 2008; 337: a2494. [PubMed: 19074944]
87. Gardner RC, Byers AL, Barnes DE, Li Y, Boscardin J, Yaffe K. Mild TBI and risk of Parkinson disease: a Chronic Effects of Neurotrauma Consortium study. Neurology 2018; 90: e1771–79. [PubMed: 29669907]
88. Goldman SM, Kamel F, Ross GW, et al. Head injury, α-synuclein Rep1, and Parkinson's disease. Ann Neurol 2012; 71: 40–48. [PubMed: 22275250]
89. Smeyne RJ, Noyce AJ, Byrne M, Savica R, Marras C. Infection and risk of Parkinson's disease. J Parkinsons Dis 2021; 11: 31–43. [PubMed: 33361610]
90. Ross GW, Abbott RD, Petrovitch H, Tanner CM, White LR. Pre-motor features of Parkinson's disease: the Honolulu-Asia Aging Study experience. Parkinsonism Relat Disord 2012; 18 (suppl 1): S199–202. [PubMed: 22166434]
91. Ben-Shlomo Y, Cooper R, Kuh D. The last two decades of life course epidemiology, and its relevance for research on ageing. Int J Epidemiol 2016; 45: 973–88. [PubMed: 27880685]
92. Miller DB, O'Callaghan JP. Do early-life insults contribute to the late-life development of Parkinson and Alzheimer diseases? Metabolism 2008; 57 (suppl 2): S44–49. [PubMed: 18803966]
93. Aisen PS, Jimenez-Maggiora GA, Rafii MS, Walter S, Raman R. Early-stage Alzheimer disease: getting trial-ready. Nat Rev Neurol 2022; 18: 389–99. [PubMed: 35379951]
94. Berg D, Crotty GF, Keavney JL, Schwarzschild MA, Simuni T, Tanner C. Path to Parkinson disease prevention: conclusion and outlook. Neurology 2022; 99 (suppl 1): 76–83. [PubMed: 35970586]
95. de Vries NM, Darweesh SKL, Bloem BR. Citius, Fortius, altius-understanding which components drive exercise benefits in Parkinson disease. JAMA Neurol 2021; 78: 1443–45. [PubMed: 34724528]

96. Hu MT. REM sleep behavior disorder (RBD). Neurobiol Dis 2020; 143: 104996. [PubMed: 32599063]

97. Fang X, Han D, Cheng Q, et al. Association of levels of physical activity with risk of Parkinson disease: a systematic review and meta-analysis. JAMA Netw Open 2018; 1: e182421. [PubMed: 30646166]

98. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020; 54: 1451–62. [PubMed: 33239350]

99. Franco M, Bilal U, Orduñez P, et al. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends. BMJ 2013; 346: f1515. [PubMed: 23571838]

100. Schiess N, Cataldi R, Okun MS, et al. Six action steps to address global disparities in Parkinson disease: a World Health Organization priority. JAMA Neurol 2022; 79: 929–36. [PubMed: 35816299]

Search strategy and selection criteria

We searched the PubMed and Embase electronic databases from database inception to June 18, 2023, using the following terms and keywords: (Parkinson Disease OR parkinsonism) AND (epidemiology or incidence or prevalence) AND (mortality OR distribution OR sex OR gender OR race OR racial OR socioeconomic OR sociodemographic OR inequality OR disparity OR risk factor OR “protective factor” OR environment OR genetics OR gene–environment OR toxicant OR prevention). Priority was given to reviews published within the past 5 years, supplemented with key articles from the bibliographies of those reviews. The original search, which ran until April 30, 2022, was conducted in subgroups of two or three authors per topic. SD later updated the search on June 18, 2023. The selection of reviews and original articles was proposed by two or three authors per topic. Disagreements were resolved through consensus via video call and email.

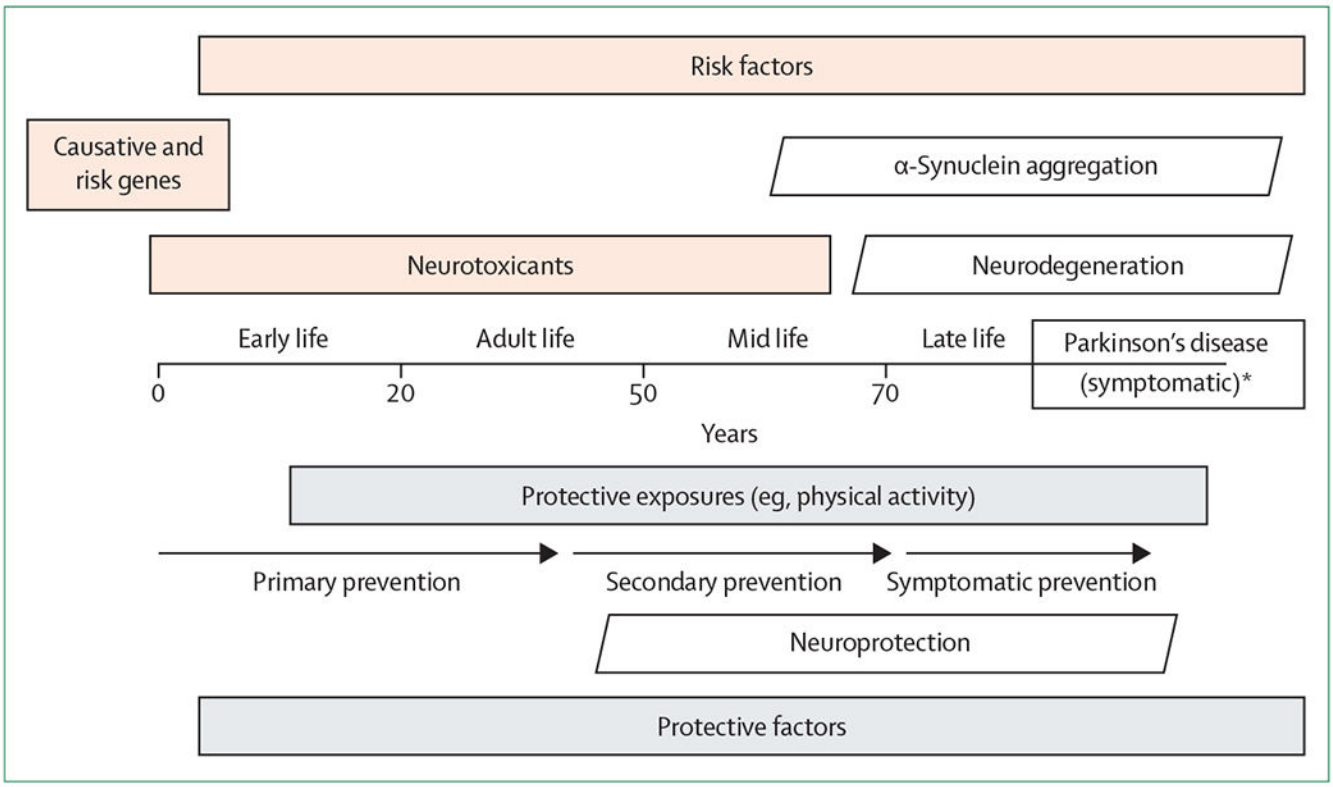

Figure 1: Simplified schematic of how risk and protective factors might determine neuropathology and the development of Parkinson's disease

*While Parkinson's disease is shown as developing in later life, the age of onset is variable and cases can develop disease at much younger ages.

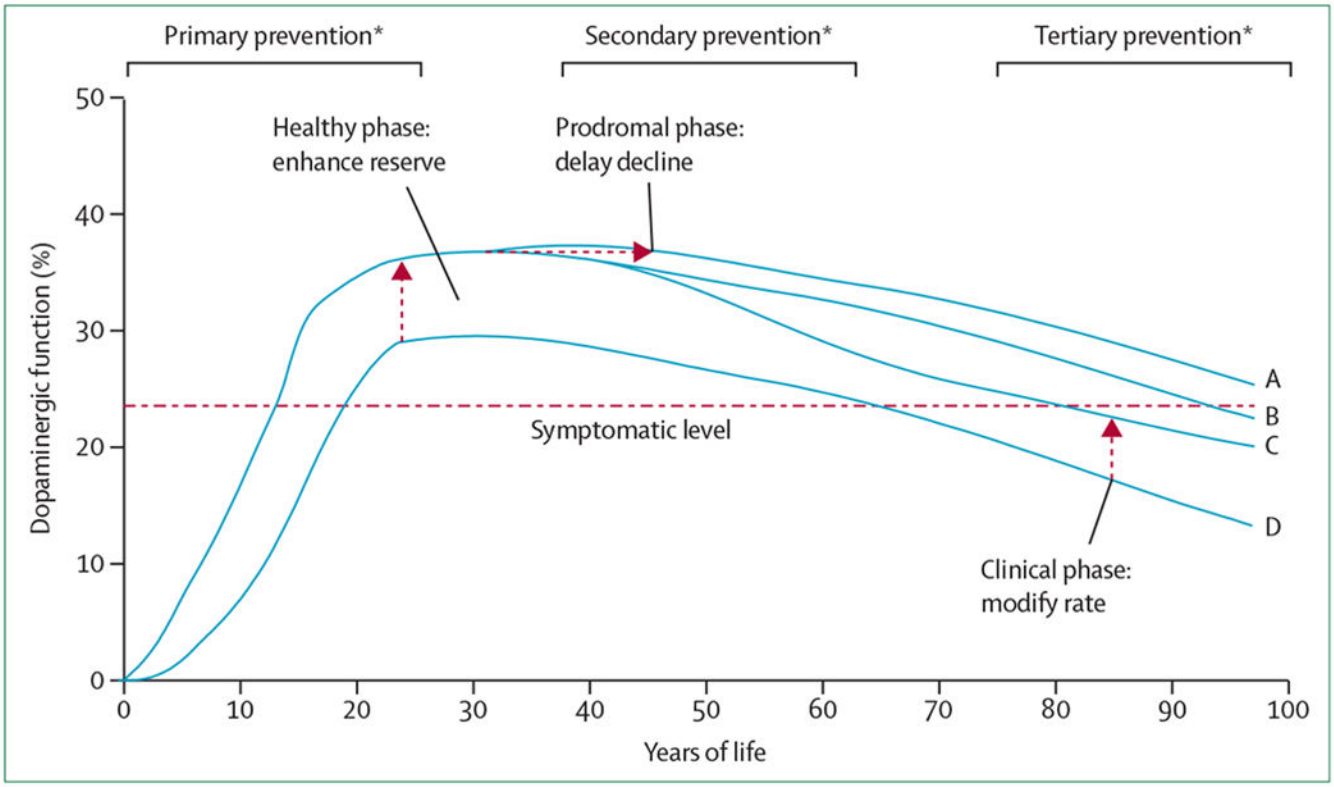

Figure 2: Hypothetical primary, secondary, and tertiary strategies to prevent, slow the onset of, and slow the progression of Parkinson's disease across the life course

The horizontal line indicates a hypothetical threshold whereby decline in function is sufficiently severe to lead to a clinical diagnosis. (A) Normative trajectory of function that never results in clinical disease. (B) Extended plateau phase; decline is delayed and disease is diagnosed later in life. (C) Normative developmental phase, but rapid decline phase with earlier disease diagnosis. (D) Suboptimal developmental phase (lower plateau) followed by normative decline, leading to earlier disease diagnosis. *No assumptions have been made about the relative effectiveness of each strategy.

Table:

The epidemiology of Parkinson's disease

	What we know	What is less certain	What we do not know	Future research needs
Diagnosis	UK Brain Bank criteria have high accuracy *vs* neuropathology; MDS Parkinson's disease criteria have high accuracy vs clinical experts	How diagnostic errors differ by demographic characteristics	Validity of MDS Parkinson's disease criteria *vs* neuropathology	Neuropathological studies validating MDS Parkinson's disease diagnostic criteria; search for systematic diagnostic errors by demographic groups
Prevalence	The marked increase in worldwide prevalence is partly due to demographic changes, but also other factors	To what degree the increase reflects a reduction in other competing causes of death or other extrinsic factors	The reasons for the increase in prevalence, and how they differ for HICs and LMICs	High-quality simulation modelling to examine role of possible reasons for increasing prevalence; improved disease surveillance
Incidence	Incidence appears to be stable in many HICs, particularly for women	Whether incidence is stable in all HICs; what the incidence trends are over time in LMICs	Why incidence is stable despite changes in certain Parkinson's disease risk factors at a population level	High-quality standardised worldwide data on incidence over time
Geography	There are marked variations in prevalence across HICs and LMICs	To what degree these differences reflect genetic, environmental, or methodological factors	Whether there are ethnic differences in Lewy body pathology	Better quality migration studies and studies of admixed populations with adjustment for age, sex, SES, and occupational factors
Sex	Men have a higher incidence and prevalence of Parkinson's disease	Whether in certain rare populations, the male preponderance might not be observed (ie, some forms of monogenic Parkinson's disease)	What explains the sex difference, and to what degree it is biological (ie, due to genetic or environmentally determined pathophysiology) or the result of measurement error (eg, differences in access to or use of health care)	Improved Parkinson's disease surveillance; cohort studies with data to explore male–female differences in Parkinson's disease risk; laboratory studies investigating sex-related pathophysiological mechanisms
Race and ethnicity	There appear to be differences in Parkinson's disease risk by race and ethnicity	Whether there is a mismatch between racial and ethnic differences in Lewy body pathology and clinical features	How much of this difference reflects geographical variations in environment, access to or use of health care, or method	Studies of similar populations with markedly different ethnic subgroups; studies of racial and ethnically similar populations with different environments (eg, comparing same racial or ethnic groups but in different countries or continents, or with very different social, occupational, or behavioural exposures)
Age	Parkinson's disease increases with increasing age	Whether this association is linear or exponential	What aspects of ageing underlie this association; time-dependent factors; age-related neuronal vulnerability	Epidemiological, clinical, and pathological studies comparing younger with older Parkinson's disease to identify differences in exposures, behaviours, and genotype; laboratory studies of Parkinson's disease models comparing older with younger animals to determine age-related effects
Socioeconomic status	We do not know definitively if there is or is not a socioeconomic gradient	That SES has not been consistently associated with Parkinson's disease risk	Why, despite the obvious social patterning of exposures such as smoking behaviour and toxic exposures, there is no clear SES gradient	International studies with uniform protocols to assess the role of SES in Parkinson's disease; studies to examine different SES associations with risk factors
Risk factors—genetic	Parkinson's disease can be associated with specific genetic variants; in most monogenic Parkinson's disease, penetrance is	The genetic and environmental determinants of penetrance	How genetic mechanisms operate and interact with other risk factors	Investigation of environmental and genetic determinants of Parkinson's disease in the same populations, with high-quality

	What we know	What is less certain	What we do not know	Future research needs
	generally low, suggesting additional genetic or environmental factors			genotyping and exposure assessment
Risk factors—non-genetic	Extrinsic factors directly associated with Parkinson's disease or Lewy pathology in observational studies and that replicate Parkinson's disease-like pathology in animal models are likely causative, including specific pesticides (eg, paraquat, rotenone, maneb, benomyl, and organochlorines) and chlorinated solvents; associated with greater Parkinson's disease risk are occupations with associated toxicant exposure (eg, farming or welding), high dietary intake of dairy products, and reduced oestrogen status in women (eg, early surgical menopause); cigarette smoking, caffeine intake, greater physical activity, and higher serum urate are inversely associated with Parkinson's disease, suggesting protective effects but possibly reflecting residual confounding	Other non-genetic risk factors—eg, head injury (which might occur in early undiagnosed Parkinson's disease due to balance changes and falls, but might also independently initiate pathogenic changes such as blood–brain barrier disruption and inflammatory processes); potential interactions such as combinations of gene × environment, gene × gene, and environment × environment	As the complex interactions of genetic predisposition, age, sex, race, ethnicity, and multiple extrinsic and intrinsic factors are largely undefined, what combinations of determinants are the primary ones, and what corresponding pathophysiological determinants must be established	More studies with high-quality measures of Parkinson's disease, prodromal features, comorbid conditions, and environmental and genetic factors in the same individuals; laboratory studies of genes and non-genetic factors to elucidate the mechanisms of neuronal injury
Prevention	Prevention in those at risk for Parkinson's disease due to genetic or environmental causes might be more effective than trials in people with established Parkinson's disease	Whether there are periods in the life course that are more sensitive to environmental exposure	The correct time in the disease course to implement a trial, and the preferred intervention	To undertake high-quality secondary prevention trials and use population-based natural experiments to test hypotheses around primary and secondary prevention

HICs=high-income countries. LMICs=low-income and middle-income countries. MDS=Movement Disorder Society. SES=socioeconomic status.