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Review

The Emerging Evidence of the Parkinson Pandemic

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Abstract. Neurological disorders are now the leading source of disability globally, and the fastest growing neurological disorder in the world is Parkinson disease. From 1990 to 2015, the number of people with Parkinson disease doubled to over 6 million. Driven principally by aging, this number is projected to double again to over 12 million by 2040. Additional factors, including increasing longevity, declining smoking rates, and increasing industrialization, could raise the burden to over 17 million. For most of human history, Parkinson has been a rare disorder. However, demography and the by-products of industrialization have now created a Parkinson pandemic that will require heightened activism, focused planning, and novel approaches.

Keywords: Parkinson disease, epidemiology, demography, aging, survival, smoking, pesticides, solvents

In 1817, a 62-year-old British physician, Dr. James Parkinson, wrote a case series about six individuals who had developed a distressing disease that had "not yet obtained a place in the classification of nosologists" [1]. "Parkinson's disease," as Dr. Jean-Martin Charcot would first term it, did not "appear to have engaged the general notice of the profession" according to Dr. Parkinson [1]. While ancient Indian and Chinese texts reference features of Parkinson disease, Dr. Parkinson was likely describing something novel, something that a senior physician would find noteworthy.

For most of history, Parkinson disease was a rare disorder. In 1855, forty years after Dr. James Parkinson first described the condition, approximately 22 people of 15 million in England and Wales died of the condition [2]. In 2014, roughly 5,000 to 10,000 individuals of 65 million in the United Kingdom suffered the same fate [3]. In less than two centuries, a rare disorder became common.

According to the Global Burden of Disease study, neurological disorders are currently the leading source of disability around the world, and the fastest growing of these disorders (in age-standardized rates of prevalence, disability, and deaths) is Parkinson disease [4]. From 1990 to 2015, the number of individuals with Parkinson disease globally increased 118% to 6.2 million [4]. Studies on the incidence of Parkinson disease over time have yielded inconsistent findings [5–8]. However, the recent Global Burden of Disease study found that age-standardized rates of Parkinson disease increased for every region

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of the world between 1990 and 2016. Overall, age-standardized prevalence rates increased worldwide by nearly 22% [9]. Converging evidence from analyses of global surveys [9], medical records of large institutions [10], national census bureaus [11], and death certificates [12] suggests that the incidence of Parkinson disease may be rising. To better understand these trends, prospective cohort studies and detailed registries are needed [9].

In this paper, we focus on what is generally termed Parkinson disease, realizing that the total burden caused by additional parkinsonian disorders—such as vascular parkinsonism or neurodegenerative atypical parkinsonism—is even greater.

The Parkinson pandemic

Though non-infectious, the Parkinson pandemic exhibits many of the characteristics of a pandemic [13]. Pandemics extend over large geographic areas, and Parkinson disease is increasing in every major region of the world [9]. Pandemics also tend to migrate, and the burden of Parkinson disease, while increasing everywhere, appears to be shifting in response to changes in aging and industrialization. Indeed, one study concluded that the burden, driven by demographic changes, would shift from the West to the East, especially China [14]. Like other pandemics, the Parkinson pandemic is experiencing exponential growth, and no one is immune to the condition.

More generally, the Parkinson pandemic is similar to the pandemic of non-communicable diseases as articulated by Allen [15]. He argues that many chronic conditions (e.g., diabetes) that are now leading sources of death and disability in the world "are actually communicable conditions, and although the vectors of disease are nontraditional, the pandemic label is apt" [15]. Social, political, and economic trends are fueling the rise of many non-communicable conditions, and the "various 'vectors of disease' include ultraprocessed food and drink, alcohol, tobacco products, and wider social and environmental changes that limit physical activity" [15].

The pandemic's causes

The Parkinson pandemic is fueled by aging populations, increasing longevity, declining smoking rates, and the by-products of industrialization. The incidence of Parkinson disease increases with age and rises sharply at around age 65 [16]. The world's population is aging, as the number and proportion of individuals over 65 is rapidly increasing (Fig. 1). The combined result of these two factors is an unprecedented rise in the number of people with Parkinson disease. By 2040, the number of people with Parkinson disease is projected worldwide to exceed 12 million [17]. Importantly, Parkinson disease does not only affect older individuals, and many under 50 develop the disease.

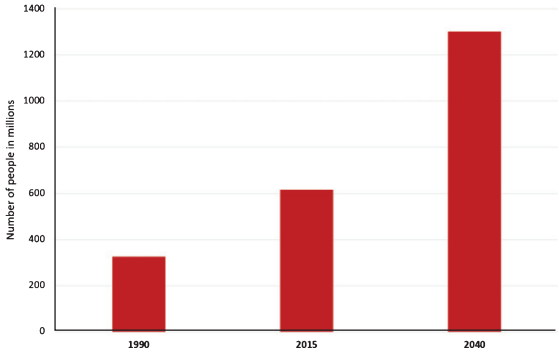

Fig. 1. World population 65 and older, 1990–2040 [33, 34].

In addition to aging, other factors will likely raise the global burden of Parkinson disease past current forecasts. The number of people with a disease is a function of the incidence of the disease and the survival of those with the condition. Increasing longevity for those with and without Parkinson disease will contribute to a higher burden of the disease. Independent of Parkinson disease, global life expectancy has increased by six years in the last two decades [18]. According to a recent study by Wannevich and colleagues, secular trends in life expectancy will increase the survival of 65-year-old individuals in France with Parkinson disease by about 3 years between 2010 and 2030. This increase in longevity will lead to a 12% increase in the age-standardized prevalence rate over 20 years [19]. In addition, increasing longevity will likely increase the number of individuals with advanced Parkinson disease who are more difficult to treat and who usually have much less access to care.

Although a global health boon, declining smoking rates in some countries may lead to a higher incidence of Parkinson disease. Numerous studies have found that the risk of Parkinson disease is decreased among smokers by approximately 40% [20]. If the association is causal, which remains to be determined, decreasing smoking rates could lead to higher rates

of Parkinson disease. Indeed, a 2018 study by Rossi and colleagues estimated that declining smoking rates in the U.S. might increase the number of individuals with Parkinson disease by 10% above projections that only estimate the effect of aging [11]. Another study identified a rising incidence in Parkinson disease between 1976 and 2005, particularly in men over age 70, which could be due in part to decreasing smoking in previous decades [5].

Finally, the by-products of industrialization may be contributing to the rising rates of Parkinson disease. Numerous by-products of the Industrial Revolution, including specific pesticides, solvents, and heavy metals, have been linked to Parkinson disease [21]. Countries that have undergone the most rapid industrialization have seen the greatest increase in the rates of Parkinson disease. For example, from 1990 to 2016, the adjusted prevalence rates of Parkinson disease in China increased more than in any other country and more than doubled [9]. In addition, the global use of pesticides is at or near its highest levels [22]. The use of specific pesticides linked to Parkinson disease also persists. For instance, although 32 countries have banned the use of paraquat, which is strongly linked to Parkinson disease, the United States continues to use paraquat in ever greater quantities [23]. Some countries that have banned the pesticide, such as England (home to the seminal description of the disease), continue to export the pesticide to other countries, including Brazil, Columbia, South Africa, Taiwan, and the United States [24].

Other neurotoxic chemicals linked to Parkinson disease, such as trichloroethylene, also see continued use. Over half of Superfund sites in the U.S., including one under the headquarters of Google in Mountain View, CA, where the chemical was used in the semiconductor industry by titans like Fairchild Semiconductor and Intel, are contaminated [25]. In addition, global use of the solvent is projected to increase by 2% per year and by 4% per year in China, even though there are multiple reports on the "the toxicity of trichloroethylene" that date back to at least 1932 and include a letter published in the *Journal of the American Medical Association* [26].

Together, all of these factors—aging populations, increasing longevity, decreasing smoking rates, and the by-products of industrialization, alone or in combination—may underlie the large number of individuals affected with Parkinson disease. Assuming a 12% increase due to increasing longevity, a 10% increase due to decreasing smoking, and that about half (10%) of the observed increase in age-adjusted prevalence rates persists due to environmental factors, the burden of Parkinson disease could exceed 17 million by 2040 (Fig. 2) [9, 11, 19].

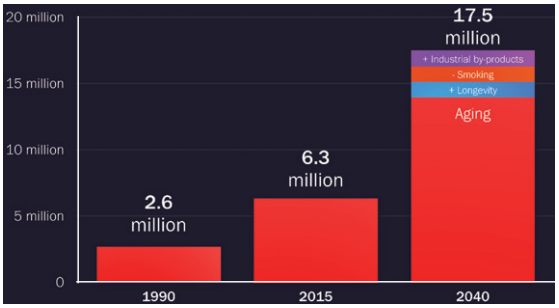

Fig. 2. Projected global burden of Parkinson disease accounting for changes in aging, longevity, smoking rates, and industrialization, 1990–2040.

While these projections are clearly speculative, they highlight the potential growth of the Parkinson pandemic. In addition, as Strickland and Bertoni noted in 2004, "It is interesting that as methods improve, estimates of the prevalence (of Parkinson disease) increase, suggesting that undercounting is the major problem in counting Parkinson's patients" [27].

Why worry?

Parkinson disease is increasing and may be a creation of our times. As opposed to most diseases whose burden decreases with improving socioeconomic level, the burden of Parkinson disease does the opposite. Disability due to Parkinson disease increases with the Socio-demographic Index, a compound measure of income per capita, education, and fertility, and is the only neurological disorder to do so [9]. As GDP per capita rises, so too does the rate of Parkinson disease (Fig. 3). While the association is modest, the direction of the relationship is concerning and again highlights the role that human activities, especially industrialization, may be playing in the increasing burden of Parkinson disease. The lifetime risk of Parkinson disease, including for the readers of this paper, is now 1 in 15 [19, 28].

The tide of Parkinson disease is rising and spreading. Parkinson disease exacts an enormous human toll on those with the disease and those around them. The strain of caregiving has adverse health consequences of its own [29]. The economic costs of Parkinson disease are also substantial, poised to grow, and at least

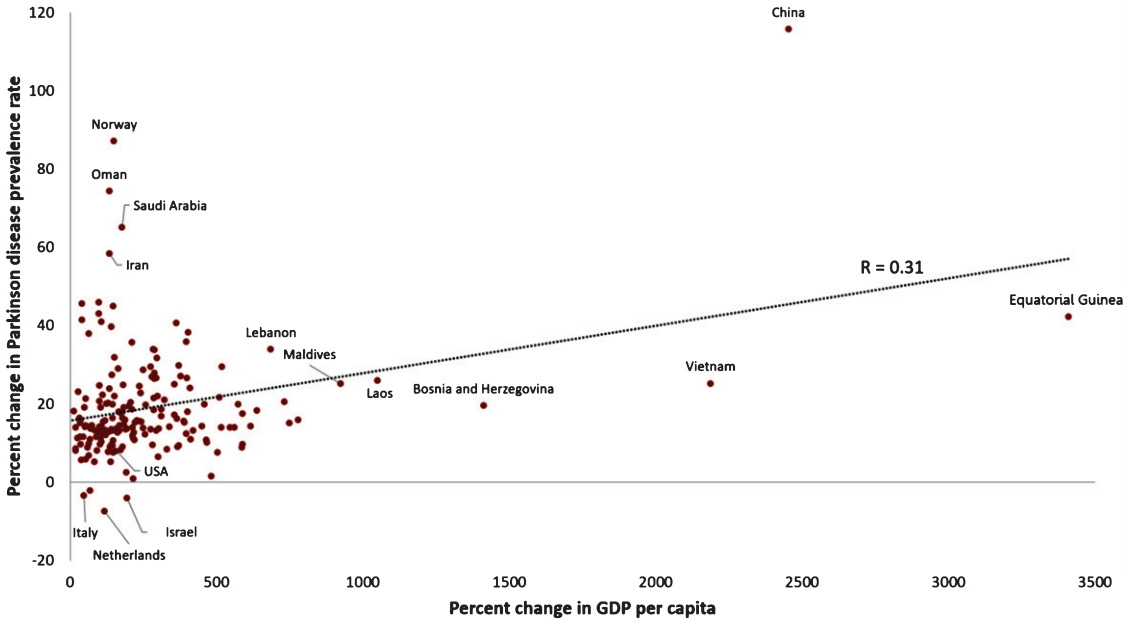

Fig. 3. Correlation between increasing gross domestic product (GDP) per capita and increasing Parkinson disease prevalence rate, 1990–2016 [4, 35].

in the U.S., overwhelmingly directed at institutional care, which few desire [30, 31]. Fortunately, the clues to the causes of the pandemic are all around us. What is missing is a willingness to act.

The way forward

In the past century, society has successfully confronted pandemics of polio, breast cancer, and HIV. Central to the success of these efforts was unbridled activism. From a March of Dimes to the White House for polio to the courageous disclosure of breast cancer by First Lady Betty Ford to a Quilt covering the National Mall for AIDS, those with and affected by the disease made their voices heard and their diseases recognized. This activism helped to prevent polio and HIV, advocate for additional private and public resources, care for all those affected, and treat the conditions with novel therapies.

Following these examples, those with and at risk for Parkinson disease can form a "PACT" to ***p***revent, ***a***dvocate for, ***c***are, and ***t***reat the disease. Where feasible, we should prevent Parkinson disease by reducing and in some cases eliminating the use of chemicals known to increase the risk of Parkinson disease. We have the means to prevent potentially millions from ever experiencing the debilitating effects of Parkinson disease. However, we also need to secure additional monies to better understand the root causes—environmental, genetic, and biological—of the disease and to expand new care models that seek to bring expert care to all [32]. Finally, Parkinson disease needs new highly effective therapies; the most effective therapy (levodopa) is now fifty years old.

The Parkinson pandemic is preventable, not inevitable.

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CONFLICTS OF INTEREST

Dr. Dorsey has served as a consultant to 23andMe, Abbott, Abbvie, American Well, Biogen, Clintrex, DeciBio, Denali Therapeutics, GlaxoSmithKline, Grand Rounds, Lundbeck, MC10, MedAvante, medical-legal services, Mednick Associates, NINDS, Olson Research Group, Optio, Prilenia, Putnam Associates, Roche, Sanofi, Shire, Sunovion, Teva, UCB, and Voyager. He has received honoraria from the AAN, ANA, and the University of Michigan.

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Dr. Sherer has no financial disclosures.

Dr. Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. Dr. Okun's DBS research is supported by: R01 NR014852 and R01NS096008. Dr. Okun has previously received honoraria. Dr. Okun has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge (movement disorders books). Dr. Okun is an associate editor for *New England Journal of Medicine Journal Watch Neurology* and *JAMA Neurology*. Dr. Okun has participated in CME and educational activities on movement disorders (in the last 36 months) sponsored by PeerView, Prime, QuantiaMD, WebMD, Medicus, MedNet, Henry Stewart, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic, Abbvie, Allergan, and ANS/St. Jude, and the PI has no financial interest in these grants. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria.

Prof. Bloem currently serves as Associate Editor for the Journal of Parkinson's disease, serves on the editorial of Practical Neurology, has received honoraria from serving on the scientific advisory board for Zambon, Abbvie, Biogen and UCB, has received fees for speaking at conferences from AbbVie, Zambon and Bial, and has received research support from the Netherlands Organization for Scientific Research, the Michael J Fox Foundation, UCB, Abbvie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, and the Parkinson Vereniging.

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