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Review

The Changing Landscape of Parkinson Epidemiologic Research

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Abstract. Despite recent successes in understanding the genetics of Parkinson's disease (PD), the causes of late-onset sporadic PD remain elusive. Many of the epidemiologic findings on PD etiology have been challenged by alternative explanations such as reverse causation. This is mainly because PD often takes decades to develop before it can be diagnosed late in life. Convincing evidence shows that this prodromal stage of PD is characterized by various prodromal symptoms such as olfactory impairment and rapid-eye-movement sleep behavior disorder (RBD). As they likely reflect PD pathogenesis years, if not decades, before nigrostriatal involvement, research on these symptoms may represent an unprecedented opportunity to dissect the etiology of PD. Using PD prodromal symptoms as intermediate phenotypes, we may be able to identify factors that contribute to the development of these symptoms and factors that modify their progression to clinical PD. Further, this line of research will also enable examinations of novel etiological hypotheses of PD development such as the microbiome and prion hypotheses. In this article, the author used olfactory impairment and RBD as examples to illustrate the promises and challenges of epidemiologic research on prodromal symptoms to understand PD etiology.

Keywords: Epidemiology, Parkinson's disease, olfaction disorders, REM sleep behavior disorder, risk factors, smoking

INTRODUCTION

The past two decades have seen evolutionary advances in understanding the genetics of complex diseases, including Parkinson's disease (PD). With the most recent report [1], approximately 40 PD susceptibility loci have been identified from seminal genome-wide association studies with tens of thousands of PD cases and controls. Although these genetic findings have significantly improved our understanding of PD etiology with novel mechanistic insights [2], their overall contribution to late-onset sporadic PD remains uncertain. Environmental factors and gene-environment interactions may also play important role in PD etiology [3]; however, this line of research has been hampered by the many challenges of studying PD etiology in epidemiologic studies.

CONTROVERSIES ABOUT PD EPIDEMIOLOGIC FINDINGS: CIGARETTE SMOKING AS AN EXAMPLE

PD is a relatively rare disease that predominantly affects adults 65 years or older. However, the disease may take decades to develop before a clinical diagnosis is even possible late in life. Particularly with the emergence of large cohorts for PD research in the past two decades, epidemiologic studies have identified or confirmed a range of factors in association with PD risk [3]. Although a detailed discussion of these findings is beyond the scope of this paper, I summarized major PD "etiological" findings from

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epidemiologic studies in Table 1. Most of these findings are reasonably consistent across studies. Further, these factors are modifiable, and if proven causal, they will have profound implications in PD prevention. There are, however, debates about the causality for most of these associations. I will use cigarette smoking as an example to illustrate the main controversies.

A strong inverse association with cigarette smoking is the most robust epidemiologic finding for PD [4, 5]. This observation started with case-control studies about fifty years ago [6] and was later confirmed in numerous epidemiologic studies, including recent large prospective cohorts [4, 7]. The risk reduction was substantial with about 50% lower risk among active smokers as compared to never smokers [8]. Most studies also demonstrated strong dose-response relationships with quantitative matrixes of smoking, including duration, intensity, pack-years, and years since last smoking. Recent analyses further suggest that the duration of smoking, not intensity, is underlying the association of smoking with PD [4, 5, 7]. In addition to cigarette smoking, several studies also evaluated passive smoking [9–12] or smokeless tobacco use (e.g., chewing and snus use) [13–15] in relation to PD. Although such data are still preliminary, evidence supports inverse associations. Interestingly, one study [16] reported higher intake of nicotine from foods (e.g. eggplants and potatoes) was also modestly associated with a lower risk of PD. As dietary contribution to nicotine is almost negligible as compared to that from cigarettes, this observation, together with data on smoking duration, suggests that if nicotine is indeed neuroprotective against PD, its biological effect may be saturated at a very low dose but require a long-term exposure.

While the epidemiologic evidence is overwhelming, debates on the causality between smoking and PD has never abated [17]. There are two major alternative explanations: 1) the personality hypothesis that individuals predisposed to PD tend to have a risk-averse personality and thus are less like to start smoking in early life; and 2) the reverse causation hypothesis that smokers are more likely to quit smoking during prodromal PD for various reasons (e.g., nonmotor symptoms). Although there is important evidence against alternative explanations [18–21], it is sparse and modest. Given the presumed decades-long and complex prodromal development of PD, one cannot exclude alternative explanations.

In addition to smoking, recent large epidemiologic analyses have also identified or confirmed inverse associations of PD with several other lifestyle factors [3], including coffee consumption, tea drinking, physical activities, plasma urate, plasma cholesterols, use of ibuprofen, statins, and L-type calcium channel blockers, as well as positive associations with head injury, pesticide use, and high intake of dairy or milk (Table 1). For each, there is evidence from multiple studies [3]. However, compared with smoking and PD, these associations are weaker in strength and less consistent across studies. For most of these findings, the same arguments for alternative explanations apply. For example, several cohort studies have showed an inverse association of physical activity with PD, especially vigorous exercise [22, 23]. While this association is biologically plausible, one may reasonably argue that people in prodromal PD may have lower physical capacity and thus are less physically active years prior to PD diagnosis (i.e., reverse causation). Further, compared to habitual smoking, other lifestyle and environmental exposures are often much more difficult to measure, adding complexity to causal inference.

CHALLENGES TO STUDY PD RISK FACTORS IN EPIDEMIOLOGY

Many of these controversies stem from the fact that PD prodromal development takes decades and involves multiple organs. The Braak hypothesis, although somewhat controversial, posits PD pathogenesis starts in the olfactory bulb, lower brain stem, or even periphery nerves before spreading to midbrain [24, 25]. This prodromal stage may take two decades or longer [25]. In support of this, clinical and epidemiologic studies have documented various nonmotor symptoms, such as olfactory impairment, sleep disturbances, and constipation years, if not decades, prior to PD clinical diagnosis. It is conceivable that, during this prolonged process, many etiological factors may come into play to initiate PD pathogenesis, modify its progression, or both. To date, few efforts have been made to document roles of these factors [26, 27]. Further, some of these factors may change over time as a result of PD prodromal development. For example, anosmia or sleep disturbances in prodromal PD may lead to reduced coffee drinking, and fatigue, pain, and subtle motor symptoms may lead to less physical activity. Unfortunately, available epidemiologic studies have largely ignored this complex and dynamic prodromal stage of PD, and have taken a black-box approach by examining a snapshot of risk factors at a single time

Table 1
Summary of selected epidemiologic findings on potential modifiable "protective" or "risk" factors for PD

	Study design	Main findings	Major alternative explanations	Epidemiologic evidence against alternative explanations
Potential modifiable "protective" factors				
Smoking	Cohort [4, 7] & case-control [5]	Strong inverse association, very consistent	Reverse causation / personality	Moderate with evidence on passive smoking [9–12], twin studies [18, 19], transgenerational exposure [20], secular trend [21]
Coffee drinking	Cohort [80, 81] & case-control [82]	Moderate inverse association, consistent	Reverse causation / personality	Weak, specificity to caffeinated coffee and caffeine from other sources (e.g., tea drinking) [81, 83, 84]
Exercise	Mostly cohorts [22, 23]	Moderate inverse association, consistent	Reverse causation	Weak or none
Plasma urate	Mostly cohort [85] & nested case-control [86]	Moderate inverse association, consistent	Reverse causation	Weak, Mendelian randomization analysis on PD progression [87]
Total/LDL cholesterols	Cohort [88] & case-control [89]	Moderate inverse association, mostly consistent	Reverse causation, confounding	Weak or none
NASIDs / Ibuprofen	Cohort [90] & case-control [91]	Moderate inverse association, mostly consistent	Confounding	Specificity to ibuprofen [90, 92]
Statins	Cohort [88, 93] & case-control [94, 95]	Moderate inverse association, inconsistent	Confounding, especially by indication (i.e., high cholesterol)	Little, inconsistent evidence for lipophilic statins [95, 96]
Calcium channel blocker	Cohort [97] & case-control [98]	Mixed and inconsistent	Confounding	Weak or none
Potential modifiable "risk" factors				
Pesticides	Mostly case-control [99, 100]	Moderate to strong positive association, consistent	Recall bias	One cohort study [101], and evidence on specific pesticides [99, 100]
Head injury	Mostly case-control [75, 102]	Moderate positive association, mostly consistent	Reverse causation / recall bias	Modest suggestive evidence on head injury in early life [75, 76]; use of negative controls [103]
Dairy products	Mostly cohort [104, 105]	Moderate positive association, mostly consistent	Confounding	Modest suggestive evidence on specific types of dairy [104–106]

Only listed representative publications; I did not automatically consider supportive data from prospective studies as evidence against reverse causation given the long prodromal period of PD.

point in relation to PD diagnosed years or decades later (Fig. 1).

PRODROMAL SYMPTOMS: A MAJOR OPPORTUNITY TO DISSECT PD ETIOLOGY

Although challenging, prodromal PD presents a major opportunity to improve our understanding of disease etiology [28] (Fig. 2). Using prodromal symptoms as intermediate phenotypes, scientists will have the first serious opportunity to unveil how PD starts and develops in its early stages. Further, investigation on progression from prodromal symptoms to PD may eventually lead to prevention of the disease. Second, research on prodromal PD will enable scientists to examine novel etiological hypotheses. Examples include the two-hits hypothesis [29], the microbiome hypothesis [30], and the prion-like

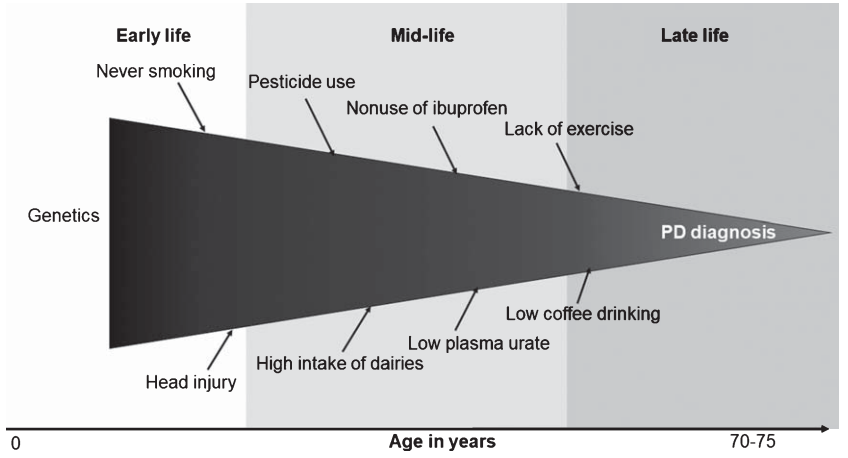

Fig. 1. The black-box approach to Parkinson's disease (PD) etiological research.

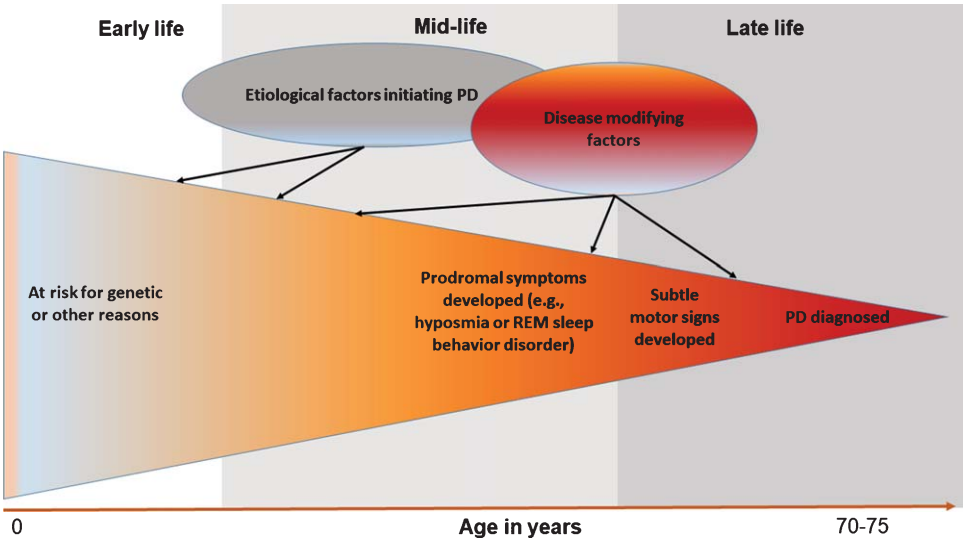

Fig. 2. Research on prodromal symptoms of Parkinson's disease (PD) helps dissect disease etiology.

hypothesis about PD development [31]. As there are excellent reviews on these novel etiological hypotheses [29–31], this review focuses on how research on prodromal symptoms may lead to a better understanding of factors that contribute to various stages of PD development. I will illustrate these ideas using olfactory impairment and rapid-eye-movement sleep behavior disorder (RBD) as examples, and will discuss the complexities in their implementation. I choose to focus on these two symptoms because olfactory impairment is the most sensitive and RBD the most specific prodromal symptom of PD, and because both symptoms are important parts of the international Movement Disorder Society newly proposed research criteria for prodromal PD [32].

Olfactory impairment is the most prevalent nonmotor symptom among PD patients. Our recent meta-analyses showed that 76% of PD patients had olfactory impairment as compared to 19% of controls [33]. Further, case-control analyses showed that, at the population level, olfactory impairment is the most predictive nonmotor symptom that could efficiently differentiate PD cases from controls [34]. The Braak hypothesis further suggests olfactory impairment is one of the earliest symptoms of PD. However empirical data from population-based prospective studies are limited [33] and the temporal relationship has been poorly understood. For example, in the Honolulu Asia Aging Study (HAAS) [35], a poor sense of smell predicted PD risk within four years but not

beyond. The Prospective Evaluation of Risk factors for Idiopathic Parkinson's Syndrome (PRIPS) study only reported data up to 5 years of follow-up [36]. We recently analyzed data from the Health ABC study with a median of 10 years of follow-up [37]. Compared to participants with good olfaction, those with poor olfaction were about 5-times more likely to develop PD, and the risk persisted beyond five years of follow-up. Given the one-time only assessment of olfaction in these studies, age at evaluation (∼79 in HAAS and ∼76 in Health ABC), and length of follow-up, current data likely have underestimated the number of years of olfactory impairment leading to PD.

The Parkinson's At-Risk Study (PARS) further investigated factors that contributed to the conversion from olfactory impairment to PD [38]. The study followed 152 hyposmia patients for four years and 19 converted to PD as compared to none of the 26 individuals with normal olfaction. Of those with hyposmia, dopamine transporter neuroimaging deficit greatly predicted conversion rate to PD (relative risk (RR) = 17.5, 95% confidence interval (CI): 7.0–43.4). In addition, age >65 years (RR = 2.5, 95% CI: 1.0–6.0) and constipation (RR = 2.7, 95% CI: 1.2–6.2) were also associated with higher conversion rate. Comparable RRs were also reported for RBD (RR = 2.8) and depression (RR = 2.4), but likely due to the small numbers, the differences were not statistically significant. Further, convertors were more likely to be men (74% vs. 53%), but no statistical testing was reported. The study did not examine lifestyle or environmental factors such as smoking, coffee drinking, head injury, or pesticide use.

Causes for olfactory impairment are also poorly understood. Knowledge comes mainly from clinical studies of acquired causes such as sinonasal diseases and head trauma. Except for age and male sex [39], impacts from other demographics, lifestyle, and environmental exposures on olfaction are largely unknown. Table 2 summarizes current literature on olfactory impairment for factors that have shown a robust association with PD. With few exceptions [40, 41], the data are exclusively from cross-sectional analyses, and only smoking has been evaluated in more than a few studies. The results on smoking are not consistent, mostly positive [39, 42–45] or null [46–49], but inverse associations were also reported [50, 51]. A recent meta-analysis [52] showed that while past smoking was not related to olfactory impairment (odds ratio (OR) = 1.05, 95% CI: 0.91–1.21), current smoking was associated with a higher prevalence (OR = 1.59, 95% CI: 1.37–1.85). This meta-analysis, however, did not include the most recent and the largest analysis to date (n = 8,557) where a modest non-statistically significant inverse association with current smoking was suggested (OR = 0.79, 95% CI: 0.58–1.06) [49].

Three studies have further examined smoking and olfaction among PD cases [53–55], aiming to explore whether smoking protects phenotypical conversion from olfactory impairment to PD. However, analyses of smoking and olfaction conditioned on PD will create a collider issue in epidemiologic causal inference and thus might have generated spurious findings [56]. Taken together, the overall epidemiological data do not support a major role of cigarette smoking in olfactory impairment and data of phenotypical conversion is lacking.

RBD is another research focus of prodromal PD. Approximately 40% of PD patients have RBD and about a half may have developed prior to PD diagnosis [33]. Unlike olfactory impairment and other prodromal symptoms, clinically diagnosed RBD with polysomnography (PSG) confirmation is very specific to PD or related synucleinopathy [57, 58]. Clinical studies suggest up to 80% of PSG-confirmed RBD patients eventually develop PD, dementia with Lewy bodies, or multiple system atrophy [57, 58]. The exact temporal relationship of RBD to PD is yet to be defined, but the leading time is likely beyond a decade. In an extreme example, evidence of RBD was found up to five decades before neurodegenerative diagnoses [59]. Although this clinical link has been solidly established, the contribution of RBD to PD in the general population is yet to be defined. Clinical diagnosis of RBD requires PSG evidence, which is often infeasible in large population-based studies. Several RBD screening questionnaires have been developed with high sensitivity and specificity in clinic-based validation studies [60–63]. However, when applied in the general population, they often gave a prevalence of 3–7% for the so-called "probable" RBD (pRBD) [64–67], much higher than the expected ∼1% for RBD [68, 69]. This may be largely attributed to false positives from obstructive sleep apnea or RBD mimics; on the other hand, it is also possible that RBD is underdiagnosed in the general population as patients with violent behaviors and physical injuries may be much more likely to end up in sleep clinics than those with mild symptoms [69].

Given the connection of PSG-confirmed RBD to clinical synucleinopathy, several studies have investigated factors that may modify RBD pheno-

Table 2
Current literature on olfactory impairment or RBD for selected well-established associations for PD

	Olfactory impairment		RBD	
	Risk or prevalence	Conversion to PD	Risk or prevalence	Conversion to PD or another synucleinopathy
Demographics				
Age	Age dependency similar to PD [39, 41, 49, 51]	Older age [38]	Modest [27] or no age effect [64, 67]	Older age [26, 107]
Male sex	Modest male to female ratio similar to PD [39, 41, 49]	Proportionally more men converted [38], but statistics not reported.	High male dominance of RBD in clinical samples [58, 108–111]; moderate sex ratio for pRBD in population-based studies [64, 67].	Null [26, 107]
Potential modifiable "protective" factors				
Smoking	Mostly positive [39, 42, 45, 112–114] or null [40, 44, 47, 49, 52, 115–117]; inverse also reported [50, 51]	No data	Positive [27] and null [64, 67]	Null [26, 107]
Coffee drinking	Rarely examined, inverse [116]	No data	Null [27, 64, 67]	Null [26]
Exercise	Inverse [41, 51] or null [114, 116]	No data	Null [64]; inverse [67]	No data
Potential modifiable "risk" factors				
Pesticides	Rarely examined, case report [118], suggestive positive [119] or null [116]	No data	Positive [27]; Non-significantly positive [64]	Inverse [26]
Head injury	Evidence largely on post-traumatic olfaction impairment [120]; limited and inconsistent data on age-related olfactory impairment, positive [114] or null [49, 51]	No data	Positive [27, 64, 67]	Null [26]

typical conversion and have found influences from olfactory impairment and other nonmotor symptoms [57, 70]. One study further examined potential roles of lifestyle and environmental exposures [26] on RBD phenotypical conversion. In this 4-year follow-up of 305 RBD patients, age is associated with conversion, but neither sex, smoking, caffeine intake, head injury, obesity, nor alcohol drinking was associated with the conversion rate. Ironically, insecticide use, either occupational or non-occupational, was associated with a substantially lower probability of phenotypical conversion [26]. This study also reported that higher plasma cholesterol level was associated with a lower likelihood of conversion, which is consistently with epidemiologic findings on PD [26].

To our best knowledge, only three epidemiologic studies have examined factors that affect the risk or prevalence of RBD, including a multicenter case-control study with PSG-confirmed RBD [27] and two cross-sectional analyses in China with pRBD from screening [64, 67]. Unlike olfactory impairment, age does not appear to be a strong risk factor for RBD [27, 64, 67]. Smoking was positively associated with RBD in the case-control study [27], but not in the two cross-sectional analyses [64, 67]. Coffee drinking or caffeine intake was not related to RBD in all three studies [27, 64, 67]. Interestingly, these data consistently support positive associations of RBD with head injury and pesticide use [27, 64, 67], consistent with findings on PD. In addition to these well-known risk factors for PD, these studies also consistently identified an association of RBD with lower education [27, 64, 67], a proxy of lower socio-economic status and possibly more hazardous environmental exposures.

These findings on olfactory impairment or RBD are very preliminary. Nevertheless, they suggest that cigarette smoking is not inversely associated with the presence of either symptom. These preliminary data, however, do not necessarily rule out the possibility that smoking reduces PD risk. First, smoking may have differential roles in the development as compared to progression of these symptoms, and the latter has not been thoroughly examined. It is possible that smoking may selectively protect nigrostriatal dopaminergic neurons at later stage of prodromal PD, rather than earlier Lewy pathology accumulation at relevant extranigral structures [26]. Second, 15–25% of older adults suffer from olfactory impairment [39, 49], which might be caused by a range of reasons. It is likely that only a minority of olfactory impairment have a root in neurodegeneration, and of these only a fraction will eventually progress to PD. Consistent with this possibility, a poor sense of smell is associated with incidental Lewy body disease among individuals who died without any clinical symptoms [71, 72]. In the case for RBD, as only about 20% of PD patients develop RBD prior to PD clinical diagnosis [33], we could not exclude differential relationships between smoking and PD subtypes. In support of this argument, a recent study found that PD patients with RBD were more likely to be smokers as compared with patients without RBD [73]. Future well-planned prospective research on prodromal symptoms will be needed to clarify the role of smoking in prodromal PD.

Although data are not entirely consistent, a recent meta-analysis showed that a history of head trauma was associated with ∼60% higher risk of PD [74]. Two studies further showed that head injury in early life was especially associated with a higher risk of PD [75, 76]. The recent data on poor olfaction and RBD [27, 64, 67] further add to the evidence that head injury plays a role in early stages of PD development.

The apparently contradictory data on pesticides and RBD prevalence versus phenotypical conversion are also interesting. Two studies showed that occupational pesticide exposure was associated with having RBD [27, 64], whereas the 4-year follow-up study found that pesticide exposure was associated with lower phenotypical conversion [26]. While these data are preliminary and chance could not be excluded, it is possible that pesticides may be associated with a higher risk of RBD but a slower progression to clinical outcomes [26]. This differential relationship awaits confirmation and clarification.

CHALLENGES AND FUTURE RESEARCH

Although a prolonged prodromal PD development offers new and exciting opportunities to dissect the etiology and natural history of PD, such research is still in its infancy. Many challenges exist. From an epidemiologic perspective, the biggest obstacle is the lack of specificity of these symptoms to clinical PD and possibly to its underlying pathology. With the exception of PSG-confirmed RBD, other prodromal symptoms are fairly common in the general population and can be caused by many reasons unrelated to neurodegeneration. For example, the most common causes for olfactory impairment are chronic rhinosinusitis, upper respiratory tract infections, and head injury. Current epidemiologic studies on PD often failed to differentiate various causes among older adults. Further, as discussed earlier, it is likely that, even among older adults with neurodegeneration-related olfactory impairment, only a small proportion will progress to a full blown clinical PD in their lifetime. Simultaneous consideration of multiple prodromal symptoms may increase the specificity, but this approach will inadvertently decrease sensitivity and data generalizability. Second, prodromal PD development may take two decades or longer, and we know little about the temporal relationships of nonmotor symptoms in prodromal PD. Most available epidemiologic studies assessed nonmotor symptoms only once late in life. They are therefore not very informative about key research questions such as when these symptoms start and how they progress or fluctuate in prodromal PD. The prodromal PD development is likely a highly dynamic process that requires repeated symptomatic assessments and monitoring.

An ideal epidemiologic study on PD etiology should encompass the full spectrum of PD prodromal development with the following characteristics: a sufficiently large population-based study sample free of major prodromal symptoms of neurodegeneration at enrollment, detailed assessments of risk factors, and decades of follow-up with updated exposure assessments and monitoring of nonmotor and motor symptoms as well as disease outcomes. Such a study is however infeasible and cost prohibitive. Alternative approaches have been taken, mostly focusing on at-risk populations to study phenotypical conversion. For example, the PARS Study targets individuals with a positive family history of PD, who were first screened with a sense of smell test, and then followed individuals who had olfactory impairment

with repeated dopamine transporter imaging and clinical assessments [38]. On the other hand, the TREND (Tübinger evaluation of Risk factors for the Early detection of NeuroDegeneration) study follows a risk-enriched population with symptoms of hyposmia, RBD, and depression [77]. There is also the aforementioned exemplary international collaboration to investigate phenotypical conversion from clinically diagnosed RBD to neurodegenerative diseases [26]. While these studies are instrumental to understanding symptom progression and phenotypical conversion, they had limited data on risk factors and do not address how these symptoms occur in the first place. There are ongoing efforts to adapt large prospective epidemiologic studies initially designed to study cancer and cardiovascular diseases for research on prodromal PD. Examples include the Health Professionals Follow-up Study and the Nurses' Health Study [78], the Rotterdam Study [79], the Atherosclerosis Risk In Communities Study [49], and the Health ABC Study [49]. These cohorts are typically large and population-based, recruited participants in their mid-adulthood, have collected enormous risk factor data (e.g., diet, lifestyle, environment, and genetics), and have followed participants for decades. Further, these cohorts all have parallel research on clinical PD and thus allow for investigations on these symptoms in the context of PD development. We expect these large cohort studies, together with clinical and epidemiologic efforts on phenotypical conversion, will bring answers to fundamental questions about PD etiology and beyond.

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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