Preventive Medicine

Environmental Epidemiology of Sporadic Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease of the elderly. The causes of PD are largely unknown, but probably involve both genetic and environmental factors. Breakthroughs have been made in the past decade to identify genes that are responsible for early-onset familial PD, yet the role of genes in sporadic PD needs to be defined. Twin studies suggest that environmental factors may be crucial in determining the risk of late-onset sporadic PD. To date, strong epidemiological evidence links environmental factors like cigarette smoking and coffee drinking to a lower PD risk, and to a lesser extent, pesticide exposures to a higher PD risk. Several novel findings have emerged from recent prospective studies on PD, such as a positive association with consumption of dairy products, and an inverse relationship with plasma urate concentration. Although gene-environment interactions are thought to be important in PD etiology, they rarely have been investigated. In the search of environmental PD risk factors, future multidisciplinary research is needed that includes input from both genetics and experimental biology. Interaction analysis requires information on both environmental and genetic factors from a large population, and such future studies will benefit from collaborative pooled analysis.

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disease that affects more than 1% of the elderly population in the United States and other Western countries. Clinically, PD is diagnosed by the presence of motor dysfunctions such as rest tremor, bradykinesia, rigidity and postural disability. Pharmaceutical and surgical treatments have been developed over the years to treat effectively motor aspects of Parkinson's symptom (especially in early stages), but no treatment to date has been proven to either cure PD, or attenuate its pathological/clinical progression. Therefore, understanding the causes of PD and searching for preventive and neuroprotective strategies are important.

A small proportion of PD cases have a clear genetic origin. These cases are often characterized by an early-onset and a positive family history. Over the past decade or so, several genes responsible for familial PD have been identified.[1] More recently, large genome-wide association studies showed that *α-synuclein* and *microtubule-associated protein tau* may also contribute to late-onset sporadic PD.[2] These breakthroughs have not only greatly advanced our understanding of the genetic causes of PD, but also shed light on several key pathogenic pathways that may be crucial to both familial and sporadic PD.

PD is age-dependent, and approximately 90% of the cases are sporadic. Monozygotic twin pairs generally are clinically discordant for late-onset PD[3,4] despite a higher clinical concordance for early-onset cases.[3] This suggests that environmental factors may play a prominent role in sporadic cases. Findings on environmental factors and PD have been the subject of several excellent reviews;[5,6] this review therefore aims to provide updates and discusses challenges and needs of future PD epidemiological research.

Epidemiological Evidence for Environmental Factors

Smoking and coffee drinking

To date, the strongest epidemiological evidence of links between environmental factors and sporadic PD has been the inverse association of cigarette smoking and coffee drinking with PD risk.[7,8] A lower PD risk among smokers has been consistently reported by about 60 epidemiological studies. Our recent analysis further suggests that smoking duration is probably more important than intensity in explaining the smoking-PD relationship.[9] Similar to smoking, numerous studies have linked coffee drinking to a lower risk of PD.[7] After stratifying by gender, however, this association became

less evident in women than in men,[10] which triggered investigations into potential interactive effects between caffeine and estrogen therapy on PD.[11] A recent case-control study further examined the potential joint effect of smoking and coffee drinking on PD development. They found that both factors were associated with lower PD risk; however, they were independent of each another as no statistical interaction was observed.[12]

Despite the robustness of epidemiological evidence on smoking or coffee and PD, the nature and implications of these associations remain controversial. Some believe these are causal relationships, others favor the alternative hypothesis that PD patients simply chose not to smoke or drink coffee early in life due to genes, environmental influences, and/or a premorbid "risk-averse" personality. While these debates are expected to continue, accumulating evidence from twin studies,[13,14] and research on passive smoking,[15] trans-generational smoking,[16] and secular trend of smoking[17] favors an etiological explanation of the smoking-PD relationship. Nevertheless, due to the numerous adverse health effects of smoking, the public health and clinical implications of this epidemiological observation are not clear.

Pesticides

Other than smoking and coffee drinking, pesticide use is probably the most frequently examined environmental factor in PD epidemiology. Results from earlier case-control studies on pesticide use and PD are also not very consistent.[18] Nevertheless, a meta-analysis indicated an about two-fold higher risk among persons exposed to pesticides.[19] Furthermore, recent prospective cohorts seem to be supportive for a role of pesticide in PD etiology.[20-22] Fewer attempts have been made to evaluate pesticides by functional groups, with preliminary data supporting positive associations of PD with exposures to herbicides, insecticides, and organochlorines, but not fungicides.[18] Information on specific chemicals that are candidates from experimental and pathological studies (e.g., paraquat, dieldrin, or rotenone) is largely lacking.[23-26] In this regard, two ongoing case-control studies will be valuable given their detailed or novel exposure assessment on pesticide uses in agricultural populations.[27,28]

Plasma urate and dairy consumption

Over the past years, several large prospective studies have been made available for PD research, and these have provided some novel leads. Most of these cohorts were initially designed for cancer or cardiovascular research making their focus on diet and other lifestyle factors. Of the most noteworthy findings is an inverse association between pre-diagnostic plasma urate and PD risk, reported consistently in four prospective studies.[29-32] A mini meta-analysis showed a 20% lower risk of PD for each standard deviation increment of plasma urate.[31] Further, in a secondary analysis of a clinical trial, higher urate in plasma or cerebrospinal fluid predicted a slower PD progression.[33] The results are fairly consistent in men, although some uncertainties exist among women. A potential protective role of urate in PD is biologically plausible given its antioxidant activities,[34-36] particular against peroxynitrite. This epidemiology observation should therefore be carefully examined in future experimental studies.[37] Three prospective analyses also reported a positive relationship between dairy or milk consumption and PD.[38-40] The result again is more consistent in men than in women. Interestingly, as higher dairy consumption lowers plasma concentration of urate,[41] the two seemingly independent observations on PD (with dairy products and urate) may actually be related.

Epidemiological Findings on Other Environmental Factors

Dietary fats, antioxidants and plasma cholesterol

Earlier case-control findings on dietary factors (energy and dietary fat with a higher PD risk and antioxidants with a lower PD risk) have received little support from recent prospective studies.[42-45] Conversely, recent findings suggest that higher plasma cholesterol[46-49] and also intake of certain fatty acids [42,43] may be associated with a lower PD risk.

Exercise and obesity

Physical therapy (including exercise) is an integral part of PD treatment regimens; further recent evidence from prospective studies suggests that moderate to vigorous exercise may protect against PD.[50,51] Although it is difficult to exclude the possibility of reverse causality, detailed epidemiological analyses and animal experimental data is consistent with the notion that exercise may protect dopaminergic neurons. Data on obesity in relation to PD[52-55] have however been inconsistent.

Medication use

The suggestion that PD may involve neuroinflammation[56] led to the hypothesis that non-steroidal antiinflammatory drugs (NSAIDs) might be useful in PD prevention. Earlier epidemiological studies showed that use of non-aspirin NSAIDs, ibuprofen in particular, was related to a 30-40% lower risk of PD.[57,58] These results were confirmed in some, but not all of the later studies.[59-62] More recently, statins have been examined in relation to PD; the results are also not entirely consistent either.[46,63-65]

Occupational factors and head injury

The hypothesis that welding, as a surrogate for manganese exposure, may increase PD risk was little supported by the overall epidemiological literature.[66-68] Associations between other occupational factors and PD have not been studied as frequently, with a few reports of a higher PD risk among teachers and physicians.[67,69] Finally, a positive association between head injury and PD was reported in some,[70,71] but not all,[72,73] of previous epidemiological studies. This relationship received new support from a recent analysis among 93 elderly twin pairs that were discordant for PD.[74]

Methodological Considerations in PD Epidemiology

Case-control studies have made important contributions to research into the role of smoking, coffee-drinking, pesticide use, and other factors. Such studies, preferably with incident cases, will continue to play an important role in PD research especially when exposure that can be reliably measured in a retrospective manner. For investigation of dietary and lifestyle factors, however, the case-control design has inherent limitations because of the potential for recall and selection biases, as well as the difficulty of controlling for reverse causality.

Several large population-based cohorts have been recently made available for PD research.[39,43,57,75,76] Other than the Rotterdam study, all cohorts were initially designed for cancer or cardiovascular research. Table 1 summarizes the population characteristics and main findings from major cohorts with multiple publications. In addition, several other cohorts, including the Physician Health Study[77,78] and the Singapore Chinese Health study,[79] and the NIH-AARP Diet and Health Study, just began to publish results on PD recently. In most of the cohorts, pre-diagnostic biospecimens are available for at least a portion of the study participants,

Table 1. Summary of major prospective studies on Parkinson's disease.*

Study	HAAS	NHS/HPFS	CPS II-N	Rotterdam	FINRISK†
Population	US-Japanese Americans	US-Whites	US-Whites	Dutch-Whites	Finnish-Whites
Sample size (women/men)	0 / ~8k	~120k / ~50k	~81k / ~65k	~4.8k / ~3.2k	~32k / 30k
Baseline age	45-68	30 to 75	50-74	55-106	25-74
Baseline year	1965-	1980s-	1992-	1990-	various
Case identification	Clinical examination & medical records	Self-reports followed by physician confirmation	Self-reports followed by physician confirmation	Clinical examination	National Insurance database
No. of incident case	128[40]	508[99]	~413[57]	88[100]	633[75]
Exposure assessment	Face to face interview	Self-administered questionnaire	Self-administered questionnaire	Face to face interview	Self-administered questionnaire
Blood	yes	yes, a portion	yes, a portion	yes	Yes, a portion
Major findings‡					
Smoking/coffee	↓[76]	↓[10 101]	↓[102]	n/a	↓[82]
Plasma urate	↓[29]	↓ (HPFS)[31]	n/a	↓[30]	n/a
Dairy /milk	↑[40]	↑[39]	↑[38]	n/a	n/a
Pesticide / surrogates	↑[20]	n/a	↑[22]	n/a	n/a
NSAIDs	n/a	↓[58]	↓[57]	--[100]	n/a
Moderate to vigorous exercise	n/a	↓[50]	↓[51]	n/a	n/a
Obesity measures	↑[55]	↑[53]	n/a	n/a	↑[54]

* HAAS: Honolulu Asia Aging Study; NHS:' Nurse's Health Study; HPFS: Health Professionals Follow-up Study, CPS II-N: Cancer Prevention Study II Nutrition Cohort; FINRISK: also called FINMONICA - the Finnish part of MONItoring trends and determinants of CArdiovascular disease. The numbers of participants and PD cases were estimated based on published data; only incident cases were considered.

†The FINRISK study consists of seven independent cross-sectional population surveys in six geographic areas of Finland in 1972, 1977, 1982, 1987, 1992, 1997 and 2002.

‡ ↑ exposure was associated with higher risk; ↓ exposure was associated with lower risk; -- no association; n/a: not reported.

and therefore they will help tremendously in identifying novel PD biomarkers. These cohorts included various populations and had different methods of exposure assessment, outcome identification, and varying lengths of follow-up, and yet, they have generated several consistent and novel epidemiological findings. Good examples are the association of PD with plasma urate and dairy consumption. These cohorts are expected to make further contributions to understanding the causes of PD. This is particularly true for biomarker research as prospective design is the only way to obtain samples prior to PD onset.[29-31,47,80]

These cohort studies also have several limitations. First, all but one of these cohorts were initially designed for other research priorities. Thus, some relevant exposures for PD, such as occupational history and pesticide use, were often not assessed. Second, due to the low incidence of PD, these studies at most have a few hundred cases, often insufficient to examine weak to moderate relationships or gene-environment interaction. Accordingly, pooled analyses from multiple cohorts with similar exposure assessments will eventually be necessary, much as was pioneered in cancer research and in a recent project on smoking and PD.[8] Finally, as some cohorts included hundreds of thousands of

participants, direct clinical examinations by study related neurologists were impractical. Potential PD cases were often identified either via self-report,[52,81] or via searches of insurance and/or pharmaceutical databases.[82] In some cohorts, self-reports were further followed by confirmation from the participant's treating neurologist.[10,57] Although these case identification methods will introduce reporting and diagnostic errors, it has been a feasible approach to identify PD cases in large prospective cohorts.

Recent experimental studies have implicated early-life or even prenatal factors in PD etiology.[83-85] As PD often occurs later in life, neither the traditional case-control nor the prospective cohort design is well-equipped to address early-life exposures. A life course approach, coupled with wise utilization of unique historical birth cohorts, events, or linkable records, may represent a sensible way to address this challenge.[86]

Future Research Needs in PD Epidemiology

Research in women

The age-specific incidence of PD is up to 50% lower in women than in men, and it is not clear what contribute to this gender difference.[87-89] Estrogen has been proposed as a factor, but epidemiological evidence related to the role of estrogen or reproductive factors in PD is inconsistent.[90] Conducting epidemiological study of PD among women is difficult, partially because of the lower incidence.[87,89] As a result, few female-specific PD risk factors have been identified; and for some risk factors consistently identified in men (e.g., coffee, urate, and dairy products), the results were less clear in women.[10,38,91] Some risk factors may be truly gender-specific, but for others, inconsistent results in women may be due to inadequate statistical power. Regardless of the causes of gender disparity in PD research, future large and well-designed PD investigations in women are clearly warranted for both mechanistic and public health implications.

Research on early markers prior to PD diagnosis

Recent pathological evidence suggests that the nigral pathology associated with PD motor symptoms is a relatively late event in PD pathogenesis.[92] Some of the non-motor symptoms and signs, such as olfaction dysfunction,[93] rapid eye movement sleep behavioral disorder (RBD),[94] constipation[95] and depression,[96] may predate the onset of motor symptoms. Both olfactory dysfunction and RBD have been linked to early PD or α-synucleinopathy in neuroimaging studies.[97,98] Therefore, one emerging direction of epidemiologic research in PD is the investigations into these preclinical symptoms of PD. Research on early markers of PD may further our understanding of PD etiology, help identify "at risk" population, and eventually lead to new strategies for disease prevention and treatment.

Gene-environment interactions

Gene-environment interactions have been little investigated in PD research. Several obstacles have impeded our efforts towards understanding gene-environment interactions in PD. First, most of the currently available studies have small sample sizes that may be insufficient for interaction analysis, and that can easily give rise to false positives and publication bias. Pooled analysis from multiple studies (published and unpublished) should also be encouraged. Second, detailed environmental data collection in most study a setting is difficult, and is often deemed less important by PD geneticists. As a result, many large genetic studies on PD have collected little or no environmental information. Finally, interaction research is restricted by our poor knowledge on the biological mechanisms of suspected genetic and environmental factors in the etiology of sporadic PD.

Interdisciplinary collaborative research

Epidemiological research on disease etiology is driven by evidence accumulation from multiple well-designed studies. In sporadic PD, fairly consistent evidence has been obtained for a few non-genetic factors. Epidemiological studies themselves, however, cannot prove causality or ascertain the underlying biological mechanisms. This is particularly true for neurodegenerative disorders, in part due to their insidious onset, long latency, and our limited knowledge on pathogeneses. Therefore, PD epidemiology must lead to high quality experimental efforts to clarify causality and unveil mechanisms. Unfortunately, such coordinative research has been too infrequent.

In summary, recent genetic research has identified several important genes responsible for early-onset familial PD, but environmental factors are still considered important in the development of late-onset sporadic PD. Cigarette smoking and coffee drinking have been consistently associated with a lower risk of PD in numerous epidemiological studies. Further, recently available prospective studies have also provided new support for a role of pesticides in PD, and revealed consistent evidence on several novel PD related factors. Compared with men, PD is less investigated in women. Future epidemiological research on PD etiology should include more women, "at risk" or "preclinical" populations, and be integrated with genetic and basic scientific experimental efforts.

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