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Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia Aging Study

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Abstract *Background* Increased westernization with Japanese migration to the U. S. in the early 20th century is thought to have altered the risk of cardiovascular disease. Whether similar effects include changes in the risk of Parkinson's disease (PD) is not clear. This report describes the relations between environmental, life-style, and physical attributes and the incidence of PD that have been observed in the Honolulu-Asia Aging Study. *Methods* Beginning in 1965, environmental, life-style, and physical attributes were recorded at selected examinations in a cohort of 8,006 Japanese-American men. Subjects were followed for clinical PD. *Findings* During 30 years of follow-up, PD was observed in 137 men. Overall incidence (7.1/10,000 person-years) was generally higher than in Asia and similar to rates observed in Europe and the U. S. Precursors of PD included constipation, adiposity, years worked on a sugar or pineapple plantation, years of exposure to pesticides, and exposure to sugar cane processing. Factors showing an inverse association with PD included coffee intake and cigarette smoking. Among dietary factors, carbohydrates increased the risk of PD while the intake of polyunsaturated fats appeared protective. Total caloric intake, saturated and monounsaturated fats, protein, niacin, riboflavin, beta-carotene, vitamins A, B, and C, dietary cholesterol, cobalamin, α-tocopherol, and pantothenic acid showed no clear relation with clinical PD. *Interpretation* Findings suggest that several environmental, life-style, and physical attributes appear to be precursors of PD. Whether patterns of precursors can be used to identify individuals at high risk of future PD or can broaden the scope of early interventions or recruitment into neuroprotective trials warrants further study.

Key words Parkinson's disease · risk factor · epidemiology

Introduction

Increased westernization with Japanese migration to the U. S. in the early 20th century is thought to have altered the incidence of cardiovascular disease through changes in diet, behavior, and the environment [12, 20, 36, 38, 44, 46]. Whether similar effects include alterations in the risk of Parkinson's disease (PD) is not known, although worldwide differences in the incidence of PD suggest that geographic variation in unknown risk factor exposures may have a role in its etiology [29, 47]. This report describes the relations between environmental, life-style, and physical attributes and the incidence of PD that have been observed in the Honolulu-Asia Aging Study.

Background and resources

Study sample

From 1965 to 1968, the Honolulu Heart Program began following 8,006 men of Japanese ancestry living on the island of Oahu, Hawaii for the development of cardiovascular disease [15, 19, 45]. At the time of study enrollment, subjects were aged 45 to 68 years. Initial screening included a baseline physical examination and documentation of cardiac and neurologic conditions to identify prevalent cases of cardiovascular disease. Additional follow-up included repeat examinations and the tracking of morbidity and mortality outcomes through a comprehensive system of surveillance based on a review of all hospital discharges, death certificates, and autopsy records. Within the Honolulu Heart Program, the Honolulu-Asia Aging Study was established in 1991 for dedicated research on neurodegenerative diseases and cognitive function in the elderly. Procedures were in accordance with institutional guidelines and approved by an institutional review committee. Informed consent was obtained from the study participants.

PD case finding and diagnosis

In this report, 30 years of follow-up data were available on incident PD since the time of study inception [1965–1968]. Prior to 1991, cases of PD were identified through a review of all hospital records for new and pre-existing diagnoses of PD. Ongoing reviews also included a thorough evaluation of Hawaii death certificates and the medical records of local neurologists for cohort members suspected to have PD.

After 1991, study participants were screened for PD at examinations that occurred from 1991 to 1993. All subjects were questioned about a diagnosis of PD and the use of PD medications by a structured interview. Study participants received further screening by a technician trained to recognize the clinical signs of parkinsonism (including gait disturbance, tremor, and bradykinesia). Those with a history or sign of parkinsonism were referred to a study neurologist who administered standardized questions about symptoms and the onset of parkinsonism, previous diagnoses, and medication use, followed by a comprehensive and standardized neurologic examination. A diagnosis of PD was made by the study neurologists according to published criteria without access to the risk factor data examined in this report [43]. These required that the subject have the following: 1) parkinsonism (e. g., at least two of the four cardinal features: bradykinesia, rest tremor, rigidity, or postural reflex impairment); 2) a progressive disorder; 3) any two of a marked response to levodopa, asymmetry of signs, asymmetry at onset, or initial onset tremor; and 4) absence of any etiology known to cause similar features. Cases of parkinsonism related to progressive supranuclear palsy, multi-system atrophy, cerebrovascular disease, drug induced parkinsonism, post-encephalitic parkinsonism, or post-traumatic parkinsonism were not included among the cases of PD. During repeat exams that were given from 1994 to 1996 and from 1996 to 1998, subjects were again asked about a diagnosis of PD and the use of PD medications. Medical records were further reviewed by the study neurologists who applied the same published criteria used earlier in making a diagnosis of PD [43]. Further description of the diagnosis of PD is described elsewhere [29, 33].

Statistical methods

After the measurement of an environmental, life-style, or physical attribute, age-adjusted incidence rates of PD in person-years were estimated according to various attribute levels [17, 23]. All subjects were free of PD when follow-up began at the examination when an attribute was first observed. Independent effects of an attribute on the risk of PD were examined through the use of proportional hazards regression models [7]. Relative risks of PD were also estimated comparing the risk of PD between attribute levels. For analyses based on a small number of PD cases, p-values were estimated from permutation tests for exact logistic regression [27]. All reported p-values were based on two-sided tests of significance.

Findings

Among the men enrolled in the Honolulu-Asia Aging Study, the average age at the time of study inception (1965–1968) was 54 years (range: 45–68). In 30-years of follow-up, 137 developed PD (7.1/10,000 person-years).

The average age at the time of diagnosis was 73 years (range: 54–89), and the average time to a diagnosis was 19 years (range: 2–30). Although we describe new observations from the Honolulu-Asia Aging Study, sample sizes and event counts may vary due to when follow-up began or through updated evidence for a definitive diagnosis of PD. In addition to the presentation of new data, we also expand on findings in earlier manuscripts from the Honolulu-Asia Aging Study based on sample sizes and event counts that were used in those original reports.

Cigarette smoking and coffee intake

Data from a variety of sources suggest that smoking is protective against PD [13, 33], although the biological basis that underlies the relation between smoking and PD is poorly understood. Identification of a protective effect of smoking is important since it could shed light on the unknown pathogenic mechanisms of PD along with similar relations that have been observed in Alzheimer's disease [14, 41].

Prospective follow-up in the Honolulu-Asia Aging Study confirms that cigarette smoking is inversely related to the risk of clinical PD [13, 33]. In the most recent report from Hawaii [33], 51 % of all PD cases (52/102) occurred in 28 % of the men who reported that they never smoked cigarettes. Among the 52 cases, only 19 would have been expected to occur had the risk of PD been similar to those who were former or current smokers. The association between smoking and PD is also unexplained by early mortality in men who smoked cigarettes and is independent of other factors that have been linked to PD, including the intake of coffee.

In addition to cigarette smoking, coffee has also been shown to have a protective effect on the risk of PD [33]. An effect further appears to be reproducible for different follow-up periods and with different methods of quantifying coffee intake (24-hour recall methods versus food frequency questionnaires). Based on 30 years of follow-up, nondrinkers of coffee experienced a 5-fold excess in the risk of PD as compared to men who consumed 28 oz/day or more (10.4 versus 1.9/10,000 person-years, respectively). The risk of PD also declined consistently with each increase in amount of coffee consumed ($p < 0.001$). Among all PD cases, 31 % (32/102) occurred in the 16 % of men who reported that they were nondrinkers of coffee. Among the 32 cases, only 13 would have been expected to occur had the risk of PD been similar to those who consumed any amount of coffee.

For both cigarette smoking and coffee intake, effects are independent and strong. In the Honolulu-Asia Aging Study [33], the highest rate of PD occurred in men who neither smoked cigarettes nor drank coffee (15.1/10,000 person-years) as compared to an absence of PD in current smokers and those who consumed the most amount of coffee on a daily basis (≥ 28 oz/day). Although cigarette smoking reduced the risk of PD, there was a near constant dose-response relation between coffee intake and PD incidence for men who never smoked cigarettes, for those who were past smokers, and for those who were current smokers.

Plantation work

In 1983, a description of parkinsonism in heroin addicts exposed to the neurotoxin MPTP intensified the search for environmental risk factors for PD [24]. MPTP is a contaminant contained in a synthesized recreational narcotic that has similarities in structure to the herbicide paraquat [37]. MPTP also has a toxic mode of action comparable to the insecticide rotenone [5]. Since these reports first appeared, special efforts have focused on identifying a role of agricultural chemicals in the etiology of PD. Subsequently, numerous case-control studies have found that well water, farming, rural living, and exposure to pesticides are associated with an increased risk of PD [32].

Political and social pressures that led to the migration of Japanese to the U. S. in the early 20th century help make the Honolulu-Asia Aging Study a valuable resource for the study of the relation between a constellation of factors associated with agriculture and the risk of PD. Cohort members were either immigrants or the progeny of immigrants from the same regions of Japan who migrated to Hawaii as contract laborers to serve in the sugar and pineapple industries. It provides a useful opportunity to examine the effects of a dominant and relatively homogeneous industry (plantation work) on the risk of PD.

Based on 30-years of follow-up, recent data have demonstrated that differences in the risk of PD are modest for men who spent 10 years or less as a plantation worker, while beyond 10 years, risk of PD nearly doubles [32]. For men who worked 10 years or less on a plantation, incidence of PD ranged from 5 to 6/10,000 person-years as compared to 10.3/10,000 person-years in those who worked more than 20 years ($p = 0.011$). Although findings were based on accurate plantation work histories that were collected at the beginning of study inception [1965–1968], specific data on sugarcane and pineapple plantation exposures were not available.

Nevertheless, at repeat examinations that occurred 6 years into follow-up [1971–1974], participants received an additional exam where inquiries were made about nonspecific exposures to sugarcane processing that lasted for at least a year. Based on 24-years of follow-up after this exam, data suggest that sugarcane processing is associated with the risk of PD. As seen in Fig. 1, however, the association appears most apparent in men who did not smoke cigarettes. For nonsmokers, the incidence

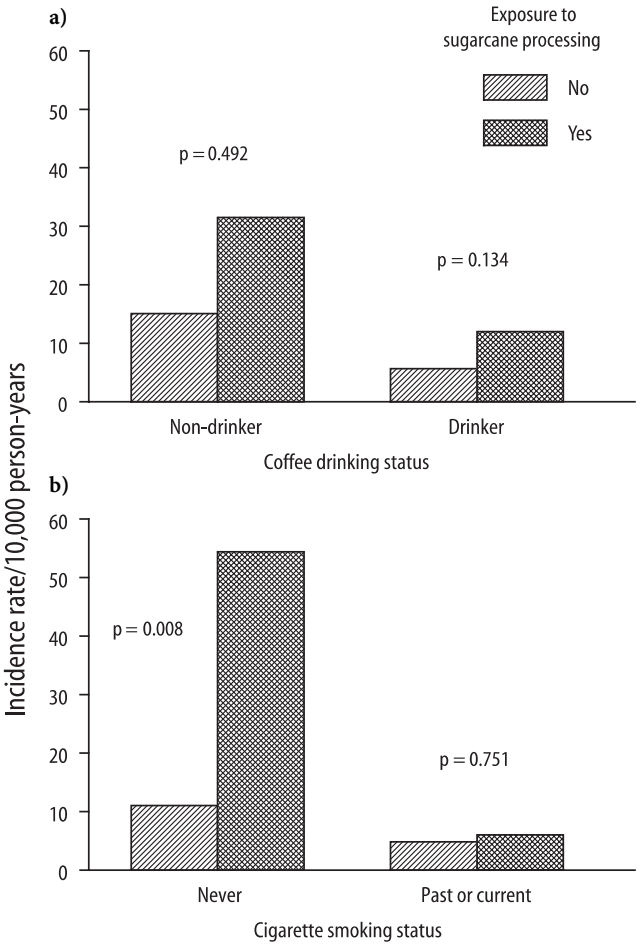


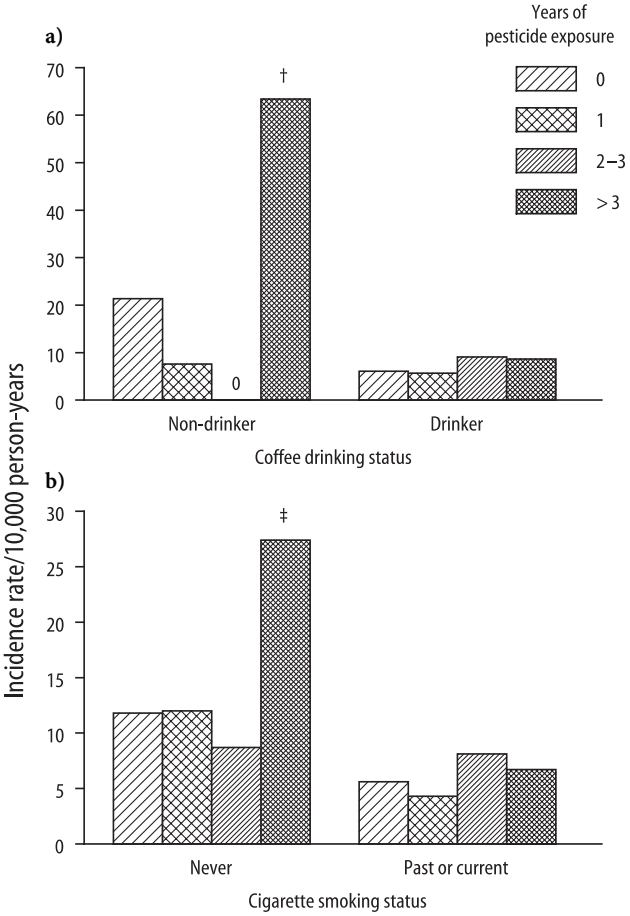
Fig. 1 Age-adjusted incidence of PD according to exposure to sugar cane processing for at least 1 year as reported at physical examinations received from 1971 to 1974 within coffee drinking (**a**) and cigarette smoking (**b**) strata

of PD was increased by nearly 5-fold in those exposed to sugarcane processing as compared to those who were not (Fig. 1b, p = 0.008). Regardless of coffee drinking status, the corresponding risk was 2-fold (Fig. 1a), although not statistically significant. For non-cigarette smokers, the effect of sugarcane processing on the risk of PD also appeared to be independent of years worked on a plantation. Additional interpretations suggest that cigarette smoking is associated with a reduced susceptibility to PD that might otherwise be attributed to sugarcane processing.

Exposure to pesticides

Findings of an association between plantation work and the risk of PD in the Honolulu sample [32] has further suggested that increasing years of exposure to pesticides also elevates the risk of PD, although results were not statistically significant (p = 0.101). As with sugarcane processing, however, additional analyses indicate that cigarette smoking reduces the susceptibility to PD associated with pesticide exposure. Reduced susceptibility also seems to occur for coffee drinkers.

The risk of PD in men who drank coffee (Fig. 2a right panel) or smoked cigarettes (Fig. 2b right panel) appeared unrelated to years of exposure to pesticides. In the absence of these factors, however, susceptibility to pesticides seems to increase. Among nondrinkers of coffee, risk of PD was 3-times higher in men who were exposed to pesticides for more than 3 years (63.4/10,000 person-years) as compared to men with no exposure to pesticides (21.4/10,000 person-years, p = 0.044). Risk of PD in nonsmokers also seemed to increase susceptibility to pesticides for exposures beyond 3 years versus men who were not exposed (27.4 versus 11.8/10,000 person-years, p = 0.053). While interactions were not statistically significant, such findings suggest that the risk of PD may have multi-factorial origins and variations in susceptibilities.



Significant excess versus unexposed men: †p = 0.044, ‡p = 0.053

Fig. 2 Age-adjusted incidence of PD according to self-reported years of pesticide exposure reported at physical examinations received from 1971 to 1974 within coffee drinking (**a**) and cigarette smoking (**b**) strata

Unfortunately, the data in Fig. 2 are based on self-reported exposures to pesticides at either work or at home. While reported responses can be quite variable, documentation of home exposure is difficult since it depends on individual recall and knowledge about product contents and cumulative exposure experiences. Regular exposure to pesticides at work may also have been more common than perceived, and many who reported not being exposed could have had high levels of exposure.

In response to these issues, exposure to pesticides was independently estimated using occupation and industry codes created by the U. S. Bureau of the Census [40] that were collected among the study participants at the time of study inception [1965–1968]. Through resources available at the U. S. National Institute for Occupational Safety and Health, a measure of exposure was assigned to each occupational and industrial code combination with the following definitions: 0 = none, 1 = low, 2 = moderate, and 3 = high. In addition to data on usual occupation and industry, years spent in these occupations and industries were also collected. Based on these additional data, an overall measure of intensity to pesticide exposure was created by multiplying the exposure associated with an occupational and industrial code combination (0, 1, 2, or 3) by the number of years spent in that job related combination. The average value of the overall intensity measure was 4.6 (range: 0 to 153).

Based on the occupation and industry work histories, an association between pesticide exposure and the risk of PD appears to be confirmed (Fig. 3). As with the self-reported measure, susceptibility to PD seemed reduced in men who smoked cigarettes or drank coffee. For nondrinkers of coffee, however, there is a near linear increase in the incidence of PD with increasing intensity of pesticide exposure ($p = 0.009$). A similar trend also seems to occur in nonsmokers, although it is not statistically significant ($p = 0.084$).

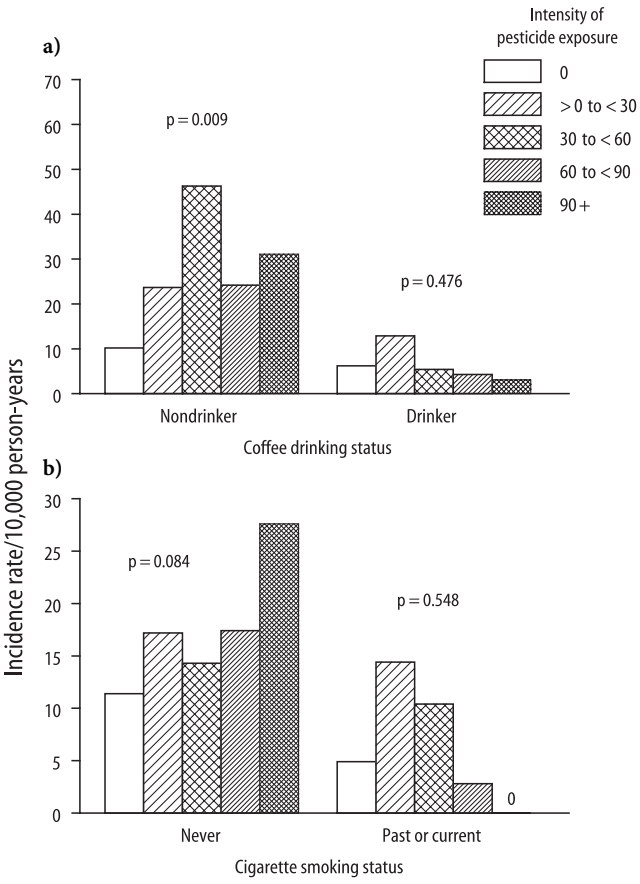


Fig. 3 Age-adjusted incidence of PD according to intensity of pesticide exposures associated with industrial and occupational codes recorded at physical examinations received at the time of study enrollment (1965–1968) within coffee drinking (**a**) and cigarette smoking (**b**) strata

Constipation

Since the time of James Parkinson, constipation has been known to be common in patients with PD [31]. Recent data suggest that up to 80 % of PD patients are afflicted with constipation [18], and some believe that defecatory dysfunction could be associated with PD severity and duration [9]. Although subject to uncertain recall of constipation histories, two case reviews further suggest that constipation may predate PD. In one series, 178 PD patients were asked to recall their bowel habits prior to the diagnosis of PD. Among this group, 46 % reported having constipation, while in spouse controls (largely women), 28 % had complaints of constipation [22]. In another report, constipation was reported to have occurred prior to a diagnosis of PD in 10 of 12 patients by an average of 16 years [4].

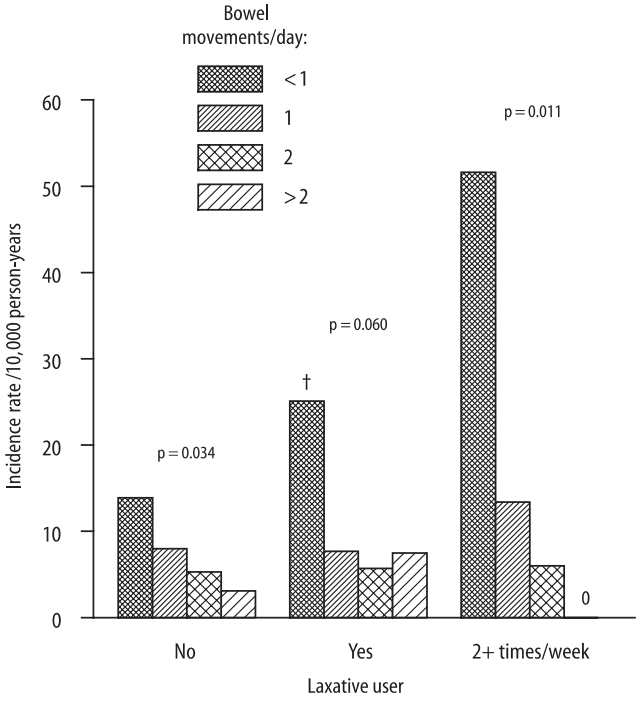
Recently, the Honolulu-Asia Aging Study has more clearly demonstrated that constipation predates PD based on 24 years of follow-up after data were first collected on bowel movement frequency at examinations that occurred from 1971 to 1974 [1]. A major strength of this finding is that it is based on the collection of bowel movement patterns following a standardized research protocol well before the development of PD. Here, age-adjusted incidence declined consistently from 18.9/10,000 person-years in men with < 1 bowel movement/day to 3.8/10,000 person-years in those with > 2/day ($p = 0.005$). Use of cigarettes and coffee intake failed to alter the association between bowel movement frequency and the risk of PD.

Data further suggest that the greatest risk of PD is likely to occur when constipation is resistant to treatment. In the Honolulu sample, the age-adjusted risk of PD was highest (51.6/10,000 person-years) in the cohort of men who reported using laxatives at least 2 times per

week and continued to have < 1 bowel movement/day (see Fig. 4). Among heavy users of laxatives, rates of PD declined as bowel movement frequency increased ($p = 0.009$), suggesting that the type of constipation associated with PD (unresponsive to therapy) is unique. This seems reasonable since most constipation is unrelated to PD.

Body fat distribution

While loss in body fat is common in patients with clinical PD [6, 8], reported findings based on cross-sectional and case-control studies (with uncertain recall and timing of anthropometric histories) are far from clear. In a recent mouse study with genetically induced obesity, there was an increased vulnerability to the neurotoxicants methamphetamine and kainic acid through reductions in levels of striatal dopamine and tyrosine hydroxylase and to elevated levels of glial fibrillary acidic protein, a sensitive indicator of neuronal damage [35]. Evidence for an effect of complex nervous system interactions involving autonomic dysfunction on appetite regulation and energy metabolism [21], and recent observations that obesity in humans is related to the depletion of striatal dopamine receptor availability suggests that nigrostriatal system disorders have associations with both PD and adiposity [42].



†Significant excess of PD vs. men with more frequent bowel movements ($p = 0.009$).

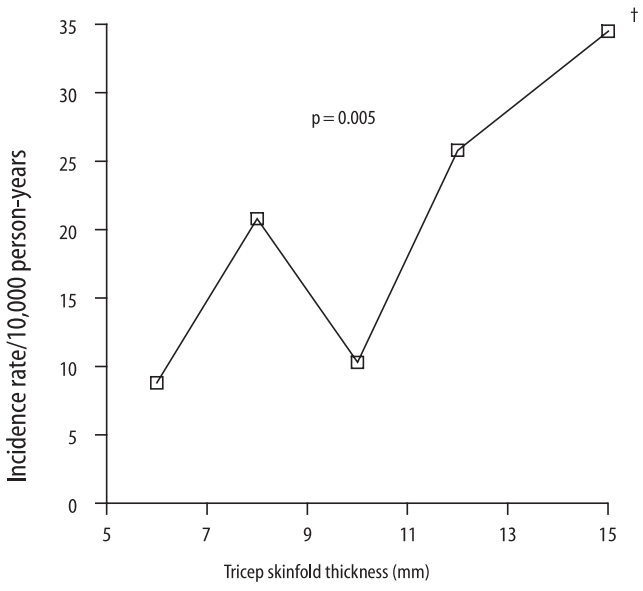
Fig. 4 Age-adjusted incidence of PD according to bowel movement frequency and the use of laxatives reported at physical examinations received from 1971 to 1974. The p-values represent a test for trend based on modeling bowel movement frequency as a continuous variable

To help address this issue more clearly, the Honolulu-Asia Aging Study was able to access archived data on body composition that was collected at more than one physical examination following standardized procedures of measurement [2]. Based on measurements of body mass index (BMI), subscapular skinfold thickness (SSF), and tricep skinfold thickness (TSF) at the time of study enrollment [1965–1968], the leanest group of men were found to experience the lowest incidence of PD over 30-years of follow-up. Among the measures of adiposity, age-adjusted incidence of PD increased consistently by three-fold from 3.7/10,000 person-years in the bottom quartile of TSF (1–5 mm) to 11.1/10,000 person-years in the top quartile (11–32 mm, $p < 0.001$). Associations of TSF with PD were also independent of cigarette smoking, coffee consumption, physical activity, daily caloric and fat intake, and the other measures of adiposity ($p < 0.001$). While rates of PD were lowest in the bottom quartile of BMI and SSF versus higher quartiles, associations with PD were weaker than they were for TSF. The association of TSF with clinical onset before age 65 years was similar to that observed in later life. Neither cigarette smoking nor coffee intake reduced the susceptibility to PD that was associated with an elevated TSF.

In addition to levels of adiposity observed in middle adulthood [2], those that were measured in later life also appeared to be related to the risk of clinical PD (see Fig. 5).

During a repeat physical examination that was given from 1991 to 1993, measurements of BMI, SSF, and TSF were available in 3,512 surviving members of the original cohort aged 71 to 93 years. In the remaining 5 to 7 years of follow-up, 27 men developed PD (20.3/10,000 person-years). Age-adjusted incidence of PD for men in the bottom quintile of TSF (2–6.5 mm) was 8.8/10,000 person-years versus 34.5/10,000 person-years in those in the top quintile (13–30 mm).

Although it might be expected that the small number of PD cases would limit statistical power, the incidence of PD continued to rise significantly with increasing TSF ($p = 0.005$). Effects also remained significant after adjustment for age, BMI, and SSF ($p = 0.013$). As with adiposity measures observed in mid-life, associations between BMI and SSF were not statistically significant. These findings further suggest that the association between adiposity and PD observed in middle adulthood also extends to the elderly.



† Plotted according to median tricep skinfold thickness within a quintile.

Fig. 5 Age-adjusted incidence of PD by median levels of tricep skinfold thickness within quintile ranges in men aged 71 to 93 years at physical examinations received from 1991 to 1993. The p-value represents a test for trend based on modeling tricep skinfold thickness as a continuous variable

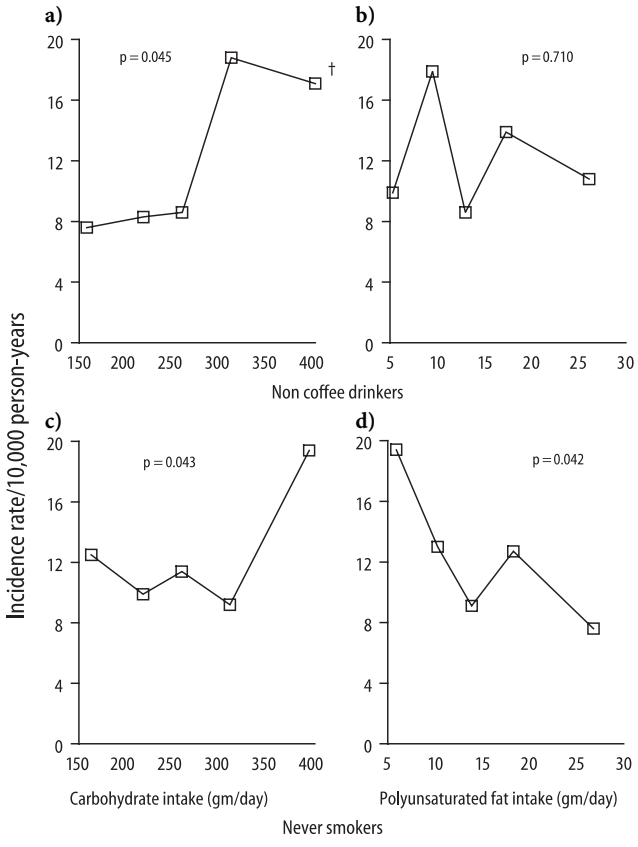
Dietary intake

Studies of the relation between diet and PD often report conflicting results. Most are based on case-control designs with the usual limitations involving uncertain recall of past dietary behaviors. In one case-control study, comparisons were made between dietary histories using food-frequency questionnaires [16]. Patients with PD were found to have consumed higher levels of carbohydrates and lower amounts of beta-carotene and niacin prior to disease onset than controls. There were no apparent associations observed between protein and fat intake and PD. In contrast, others report that higher caloric and fat intake consumed during the year prior to study enrollment are associated with PD, while there was no association with carbohydrates [25]. Based on measures of dietary habits followed during most of adult life, an increase in the intake of animal fat and vitamin D was described in patients with PD versus matched controls [3].

Similar dietary data were collected in the Honolulu-Asia Aging Study at the time of study enrollment [1965–1968] with 30 years of follow-up for the first appearance of clinical PD. Here, nutrient intake was determined by a dietitian based on 24-hour recall methods and validated against a full week of dietary records in a subset of the original cohort. Comparisons between the two assessment methods showed no significant differences between the instruments for measuring dietary intake, and day-to-day variation was less than typical in western cultures [26]. While errors in recall are less of an issue here, it is likely that other errors in measurement (also shared with case-control studies) are not entirely removed. For example, 24-hour recall may not reflect typical dietary patterns, and some groups, particularly obese individuals, often under-report true dietary intake [34, 39]. Nevertheless, these types of studies are often considered to be the best available. In the presence of the errors in data collection in dietary surveys, it is likely that the observed effects of food intake on disease provide an underestimate of true associations. Unfortunately, because of the high level of correlation that exists among dietary intake variables, identifying specific relations is extremely difficult in any cohort or case-control study.

Based on the calculation of micronutrient intake from the 24-hour recall data in the Honolulu-Asia Aging Study, there is some consistency with associations that have been reported elsewhere, while most appear to be absent. Among the latter, total caloric intake, protein, niacin, riboflavin, beta-carotene, vitamins A, B, and C, dietary cholesterol, cobalamin, α-tocopherol, and pantothenic acid had no clear relation with clinical PD. Although the intake of vitamin E in the Honolulu-Asia Aging Study was modestly related to a reduced odds of PD, legumes (a food rich in vitamin E) were associated with a marked protective effect [30]. Associations appeared for other dietary variables, but most consistently in subjects who were nonsmokers and nondrinkers of coffee. Further work in this area is ongoing in the Honolulu-Asia Aging Study.

Among the associations identified thus far, intake of carbohydrates and polyunsaturated fats appear to have the most consistent relation with the risk of PD. Associations observed in the Honolulu-Asia Aging Study are described in Fig. 6 for those who were nondrinkers of coffee (Fig. 6a, b) and in those who reported never smoking cigarettes (Fig. 6c, d). Here, the age-adjusted incidence of PD is plotted by median intake values within quintile ranges of the daily intake of carbohydrates (Fig. 6a, c) and polyunsaturated fat (Fig. 6b, d) based on dietary intake that was observed at the time of study enrollment (1965–1968). For carbohydrates (Fig. 6a, c), PD incidence rose significantly with increasing intake for both non coffee drinkers and never smokers ($p < 0.05$). Differences in the risk of PD, however, were modest up to the 4^{th} and 5^{th} quintiles of carbohydrate intake. In contrast, the intake of polyunsaturated fats appeared protective against PD, particularly in men who never smoked cigarettes ($p = 0.042$). For those who were never smokers of cigarettes, the effects of carbohydrates and polyunsaturated fats were also independent of each other. Saturated and monounsaturated fates were unrelated to the risk of PD in this sample of men.



† Plotted according to median intake within a quintile.

Fig. 6 Age-adjusted incidence of PD by median intake values within quintile ranges of daily intake of carbohydrates and polyunsaturated fats at the time of study enrollment [1965–1968] for nondrinkers of coffee and in nonsmoking men. The p-values represent a test for trend based on modeling each intake value as a continuous variable

Discussion

While geographic variation in the incidence PD is consistent with an environmental role in the development of PD, more convincing evidence is based on differences in the risk of PD that have been observed to occur with migration. For example, migration from Asia and western Africa to the U. S. has resulted in an increase in the incidence of PD within these ethnic communities as compared to reported rates from countries of origin [29, 47]. The incidence of PD in the Japanese-American men enrolled in the Honolulu-Asia Aging Study is also higher than in Japan and are typical of rates that have been observed in Europe and the U. S. Although difficulties in how PD is defined can contribute to these differences, findings from the current report suggest that a role of environmental, life-style, and physical attributes on the risk of PD is real. Specifically, observations suggest that precursors associated with PD can include coffee intake, cigarette smoking, plantation work, exposure to pesticides, constipation, body fat distribution, and possibly diet.

Although associations between these precursors and PD are important, it is also noteworthy to draw attention to the long delay from the time of precursor measurement to the time of diagnosis of clinical PD. In many instances, delays in diagnosis exceeded 15 years after risk factor measurement [2]. Such long latency periods are in contrast to the estimated 3 to 6 year preclinical periods based on findings from neuroimaging and neuropathology studies [10, 28]. While further explanation is needed, the long interval between precursor measurement and the diagnosis of PD may provide some insights into the pathogenesis of PD and to Lewy body formation that can begin as early as 25 years of age [11]. The possibility that PD neuropathology has origins in early life suggests that PD progression is slower and more subtle than previously thought. Based on an increased risk of PD due to long-term exposures to pesticides and plantation work in the Honolulu-Asia Aging Study, this may also mean that the development of PD is not inevitable if exposures can be limited or removed. It further suggests that prevention of PD could begin in early adulthood.

Explanations for the observed relations between a precursor and PD are unclear. It must first be noted that the term precursor does not imply that factors associated with PD are casual or are the result of processes leading to PD. At the very best, findings merely suggest that these factors can predate a diagnosis of clinical PD. In some instances, cumulative exposure to a precursor during early life may contribute to increased PD risk indirectly by increasing susceptibility to other factors that cause PD in later life.

In other cases, the effects of these precursors on PD progression could be more direct. Dietary intake of antioxidants could reduce oxidative stress and free-radical damage to neurons in the substantia nigra. Others have suggested that toxic levels of iron and manganese promote oxidative stress [3]. Effects of coffee and cigarette smoking could be important by modulating neurotransmitter and neuroreceptor systems in the brainstem and corpus striatum or by directly interfering with the uptake of neurotoxins [13, 33]. Findings of an association between pesticides and PD by two methods of quantification are consistent with the growing evidence for a neurotoxic role of pesticides on selective nigral injury, Lewy body formation, and responses to levodopa [32].

Based on the observation that coffee intake and cigarette smoking seem to reduce the susceptibility to PD due to other precursors, findings further support the possibility that a high risk of PD requires exposure to a combination of factors. Genetic susceptibility may also have an important role. The complex interaction among a constellation of these factors and their role in PD development may offer a partial explanation for why iden-

tification of risk factors for PD has been illusive. Although discouraging, this also suggests that reduced exposure to any single precursor could sufficiently delay or eliminate neuropathologic processes that lead to PD through the requirement that precursors need to coexist for PD progression to continue.

Whether combinations of precursors, particularly cigarette smoking, coffee intake, and possibly constipation histories can be used as enrollment criteria for the study of PD deserves consideration. Such design strategies could increase the potential for maximizing therapeutic effects in a clinical trial. It might also seem reasonable that, in prospective cohort studies of precursors of PD, focus should be on those groups where risk is highest, where accrual of events is quicker, and lengths of follow-up can be reduced. Identifying collections of precursors for PD (in combination with a family history and emerging movement abnormalities) could also lead to more effective strategies for identifying early or suspected disease, as well as provide for different approaches to prevention and intervention.

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