Association of Coffee and Caffeine Intake With the Risk of Parkinson Disease

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Context The projected expansion in the next several decades of the elderly population at highest risk for Parkinson disease (PD) makes identification of factors that promote or prevent the disease an important goal.

Objective To explore the association of coffee and dietary caffeine intake with risk of PD.

Design, Setting, and Participants Data were analyzed from 30 years of follow-up of 8004 Japanese-American men (aged 45-68 years) enrolled in the prospective longitudinal Honolulu Heart Program between 1965 and 1968.

Main Outcome Measure Incident PD, by amount of coffee intake (measured at study enrollment and 6-year follow-up) and by total dietary caffeine intake (measured at enrollment).

Results During follow-up, 102 men were identified as having PD. Age-adjusted incidence of PD declined consistently with increased amounts of coffee intake, from 10.4 per 10000 person-years in men who drank no coffee to 1.9 per 10000 person-years in men who drank at least 28 oz/d ($P<.001$ for trend). Similar relationships were observed with total caffeine intake ($P<.001$ for trend) and caffeine from noncoffee sources ($P=.03$ for trend). Consumption of increasing amounts of coffee was also associated with lower risk of PD in men who were never, past, and current smokers at baseline ($P=.049$, $P=.22$, and $P=.02$, respectively, for trend). Other nutrients in coffee, including niacin, were unrelated to PD incidence. The relationship between caffeine and PD was unaltered by intake of milk and sugar.

Conclusions Our findings indicate that higher coffee and caffeine intake is associated with a significantly lower incidence of PD. This effect appears to be independent of smoking. The data suggest that the mechanism is related to caffeine intake and not to other nutrients contained in coffee.

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PARKINSON DISEASE (PD) afflicts 3% of the population older than 65 years[1] and is a significant source of morbidity and health services use. Based on the projected growth of the US population, this percentage could double in the next 30 to 40 years.[2] While rare genetic forms exist, determinants of typical late-onset disease appear to be largely environmental.[3,4] No treatment has definitively been shown to prevent disease or slow progression. Identification of risk factors may lead to an understanding of pathogenic mechanisms and to effective strategies for prevention.

Coffee intake has been inversely associated with PD occurrence in some studies, but evidence has been equivocal.[5-8] In an earlier longitudinal study from the Honolulu Heart Program, coffee intake measured prospectively appeared to be protective against PD, but not after adjustment for cigarette smoking.[5]

This article presents an expanded analysis of the relationship between consumption of coffee and dietary caffeine and risk of PD within the Honolulu Heart Program cohort, based on longer follow-up and nearly twice the number of incident PD cases than were previously available.[5] The role of other nutrients contained in coffee are also examined.

METHODS

The Honolulu Heart Program was established in 1965 with the examination of 8006 men of Japanese ancestry 45 to 68 years old and living on the island of Oahu, Hawaii. The initial examination consisted of face-to-face

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interviews and physical evaluation. Demographic, dietary, and health status data were obtained.[9,10] The study is now in its 34th year of follow-up with continued surveillance of hospitalization and death records. Follow-up examinations were performed from 1968 to 1971, 1971 to 1974, 1991 to 1993, and 1994 to 1996. Research on neurodegenerative diseases of aging began in 1991 with establishment of the Honolulu-Asia Aging Study. Procedures were approved by an institutional review committee and informed consent was obtained from all participants. Details regarding study design have been previously published.[5,11,12]

PD Case Finding and Diagnosis

For this report, 30 years of follow-up data were available. Incident cases of PD were identified through 4 sources.[13] Prior to 1991, the sources were: (1) review of all cohort members' hospitalization records for all diagnoses of PD, (2) ongoing review of all Hawaii death certificates, and (3) review of medical records of all patients with PD from the offices of local neurologists cross-checked with the cohort member list.[5,13]

After 1991, the diagnosis of PD was based on complete reexaminations of the entire cohort from 1991 to 1993 and 1994 to 1996. During the 1991 to 1993 examination,[13] all subjects were questioned about history of PD, symptoms of parkinsonism (tremor, bradykinesia, rigidity, or postural instability), and PD medications by structured interview. Research technicians were trained to recognize clinical signs of parkinsonism including gait disturbance, tremor, or bradykinesia. Subjects with a history of PD or parkinsonism symptoms or signs were referred to a study neurologist who administered standardized questions about symptoms and onset of parkinsonism, previous diagnoses, and medication usage, followed by a comprehensive and standardized neurological examination that included the Unified Parkinson's Disease Rating Scale.[14] Diagnosis of PD was based on consensus from 2 neurologists according to published criteria.[15] These require that the subject have the following: (1) parkinsonism; (2) a progressive disorder; (3) any 2 of 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 other neurodegenerative disorders, cerebrovascular disease, medications, trauma, or postencephalitic parkinsonism were not included among cases of PD. Additional cases of PD were identified during the 1994 to 1996 examination through structured interviews inquiring about history of PD or PD medications. These cases were confirmed by a study neurologist through record review and application of the criteria above.

Age at diagnosis was used instead of age at onset to avoid inaccuracies associated with recall of symptom onset for a chronic disease with gradual onset. At study enrollment, there were 2 prevalent cases of PD excluded from this analysis, leaving 8004 available for prospective follow-up.

Measurement of Coffee Intake and Other Covariates

At study enrollment (1965-1968), nutrient intake was determined by a dietitian based on 24-hour dietary recall methods.[16] The 24-hour dietary recall was validated against a full week dietary record for 329 of the 8006 men in the original cohort. Comparison between the 2 assessments showed no significant differences in mean intake of 9 nutrients.[16] Coffee was assessed as caffeinated only (decaffeinated coffee was not assessed) and intake was measured as the number of 4-oz cups in the 24 hours encompassed by the intake record. (To convert ounces to milliliters, multiply by 30.) Intake categories were then defined as none, 4 to 8 oz/d, 12 to 16 oz/d, 20 to 24 oz/d, and 28 oz/d or more. Dietary recall also assessed intake of milk and sugar (separately and as additives to coffee), as well as green tea, black tea, other caffeinated beverages, and caffeine from other sources. Six years later (1971-1974), as part of a food frequency questionnaire, subjects were asked about coffee intake in the prior week and if the average serving size was small (4 oz), medium (6 oz), or large (8 oz). For this examination, total coffee intake was assessed without regard to caffeinated vs decaffeinated. Intake was converted to average daily consumption defined as none, more than 0 to 8 or less oz/d, more than 8 to 16 or less oz/d, more than 16 to 24 or less oz/d, and more than 24 oz/d.

Total dietary caffeine and dietary caffeine from noncoffee sources were calculated from the baseline 24-hour dietary intake record. Most caffeine from noncoffee sources came from tea or cola beverages, with a small proportion from chocolate. Subjects were classified by quintiles of caffeine intake per day for both measurements. Other nutrients were determined from the same 24-hour dietary recall based on consumption of individual food items using computer software (Nutritionist IV, N-Square Computing, Salem, Ore). Multiple nutrients were examined, including niacin. Data on dietary caffeine and other nutrients were available only from the baseline 1965 to 1968 examination. Pack-years of smoking were assessed at study enrollment (1965-1968) and 6 years later (1971 to 1974). Other dietary measures from the baseline examination included total energy intake and saturated fat level. Alcohol consumption, total serum cholesterol level, and physical activity were also assessed at enrollment.

Statistical Methods

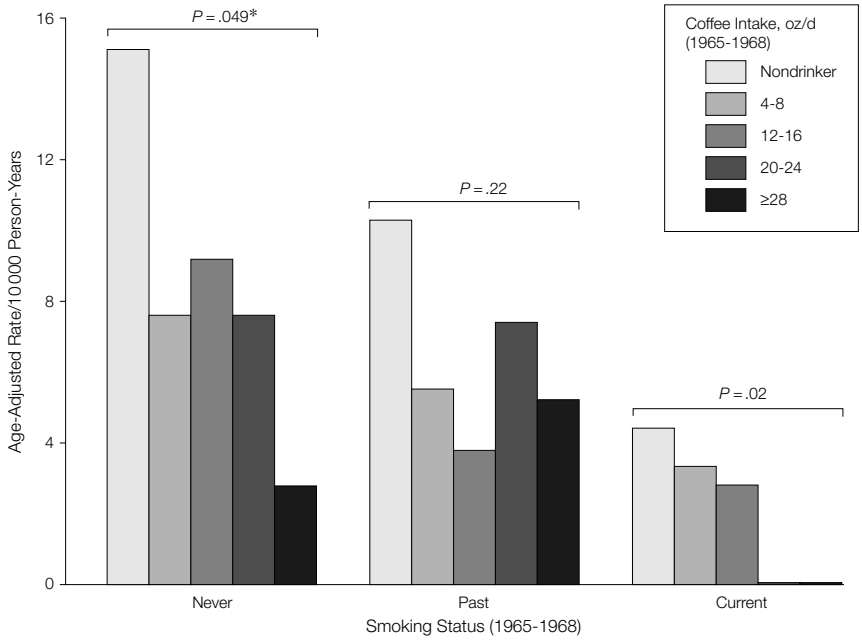
Incidence rates in person-years were estimated within categories of coffee consumption based on 30 years of follow-up for the 8004 men whose intake was determined at the 1965 to 1968 baseline examination. Similar rates were derived according to quintiles of total caffeine intake and for caffeine intake from noncoffee sources. Incidence rates were similarly estimated according to categories of coffee intake based on 24 years of follow-up for the 5933 men whose intake was also determined 6 years later (1971-1974). Unadjusted and age-adjusted incidence rates are provided.[17]

Table 1. Unadjusted and Age-Adjusted Incidence of Parkinson Disease (PD) According to Amounts of Coffee Consumed per Day

Coffee Intake, oz/d	No. of Cases of PD/No. of Subjects at Risk	Incidence Rate/10 000 Person-Years		Adjusted Relative Hazard (95% CI) Compared With the Top Category of Coffee Intake*
		Unadjusted	Adjusted for Age	
Based on 30 Years of Follow-up After the 1965 to 1968 Examinations				
Nondrinker	32/1286	10.5	10.4	5.1 (1.8-14.4)†
4 to 8	33/2576	5.5‡	5.3§	2.7 (1.0-7.8)
12 to 16	24/2149	4.7‡	4.7‡	2.5 (0.9-7.3)
20 to 24	9/1034	3.6‡	3.7‡	2.0 (0.6-6.4)
≥28	4/959	1.7‖	1.9‖	Reference
Test for trend	. . .	*P*<.001	*P*<.001	*P*<.001
Nondrinkers vs drinkers	. . .	. . .	. . .	2.2 (1.4-3.3)¶
Based on 24 Years of Follow-up After the 1971 to 1974 Examinations				
Nondrinker	17/539	17.4	17.3	3.0 (1.1-8.4)#
>0 to ≤8	25/2383	5.6‖	5.4‖	1.1 (0.4-2.9)
>8 to ≤16	16/1445	5.9‡	5.9‡	1.1 (0.4-3.0)
>16 to ≤24	8/989	4.2‖	4.3‖	0.8 (0.3-2.6)
>24	5/577	4.6‡	5.0‡	Reference
Test for trend	. . .	*P* = .008	*P* = .005	*P* = .03
Nondrinkers vs drinkers	. . .	. . .	. . .	2.9 (1.7-5.1)¶

*Adjusted for age and pack-years of cigarette smoking. CI indicates confidence interval.
†Significant excess risk of PD, *P*<.01.
‡Significantly different from nondrinkers, *P*<.01.
§Significantly different from nondrinkers, *P*<.05.
‖Significantly different from nondrinkers, *P*<.001.
¶Significant excess risk of PD, *P*<.001.
#Significant excess risk of PD, *P*<.05.

Figure 1. Age-Adjusted Incidence of Parkinson Disease



Age-adjusted incidence based on 30 years of follow-up according to coffee intake at the time of study enrollment (1965-1968) for those who were never, past, and current cigarette smokers. Asterisk indicates test for trend.

To test the possibility that the effect of coffee on PD changed over time and to estimate the independent effect of coffee and caffeine intake on risk of PD after adjusting for age and pack-years of cigarette smoking, proportional hazards regression models were used.[18] In addition, coffee and caffeine intake were modeled as continuous variables. The significance of the regression coefficients that were associated with coffee and caffeine when modeled as continuous variables comprised a test for trend or a test for a dose-response relationship between coffee intake and risk of PD. Relative hazards of PD (and associated confidence intervals) were estimated comparing risk of disease between amounts of coffee consumed. All reported *P* values were based on 2-sided tests of significance. Alcohol was modeled as a continuous measure in the number of grams per day consumed. Other covariates were also modeled as continuous variables (saturated fat level, physical activity, total energy intake, and total serum cholesterol level). Hypertension and diabetes were modeled through the use of indicator variables.

RESULTS

The median age of the 8004 men at study enrollment (1965-1968) was 53 years (range, 45-68 years). The median length of follow-up was 27 years, minimum follow-up was 0.8 years to the first death, and maximum follow-up was 30 years from the baseline examination. Among the men, 102 developed PD over the 30 years of follow-up. The median age of PD diagnosis was 73.6 years (range, 54-89 years), and the median interval between baseline examination and PD onset was 16.6 years (range, 2-30 years).

Coffee drinkers had significantly lower incidence of PD than nondrinkers (*P*<.001). This effect was apparent when examining incidence of PD based on 30 and 24 years of follow-up according to amounts of coffee consumed at the time of study enrollment and at the 1971 examination (TABLE 1). At each examination, increasing

amounts of coffee consumed were associated with decline in PD incidence ($P<.01$). For nondrinkers of coffee, after adjustment for age and pack-years of cigarette smoking, risk of PD was 2 to 3 times greater than for reported coffee drinkers ($P<.001$). Based on data collected at the time of study enrollment, nondrinkers of coffee had a risk of PD more than 5 times that of men who consumed 28 oz of coffee or more per day ($P<.01$).

The progressively lower risk of PD with increasing amounts of coffee consumed was also observed in men who were never, past, and current smokers (FIGURE 1). For consumption determined at the baseline examination, the dose trend was statistically significant for men who never smoked cigarettes ($P=.049$) and for current smokers ($P=.02$).

The incidence of PD by quintile of caffeine intake at study enrollment (1965-1968) was examined for both total caffeine and caffeine from sources other than coffee (TABLE 2). For both sources of caffeine, dose relationships with PD development were similar to those shown for coffee consumption.

Although the protective effect of dietary caffeine showed a similar dose-response pattern for both drinkers and nondrinkers of coffee, it was significant only in coffee drinkers. The lack of a significant association in noncoffee drinkers may have been due to a small sample size.

Cumulative incidence curves for PD over time by amounts of coffee consumed and by caffeine intake from noncoffee sources reveal the magnitude of dose effect between exposure categories (FIGURE 2). For men who were nondrinkers of coffee and those who consumed 28 oz or more per day, differences in the cumulative incidence of PD became apparent as early as 10 years into follow-up (Figure 2, top). A similar divergence is apparent between men who consumed the least and the most amounts of caffeine from noncoffee sources (Figure 2, bottom).

As noted earlier, methods for case finding changed after 1991. This had no effect on the observed relationships between PD and coffee or caffeine intake. The association between coffee intake at study enrollment and risk of PD remained statistically significant for men whose diagnosis of PD occurred before ($P=.005$) and after 1991 ($P=.01$).

Coffee intake determined at study enrollment was also significantly associated with PD that occurred in the first ($P=.048$) and second ($P=.002$) 15 years of follow-up. In both instances, risk of PD declined with increasing amounts of coffee consumed.

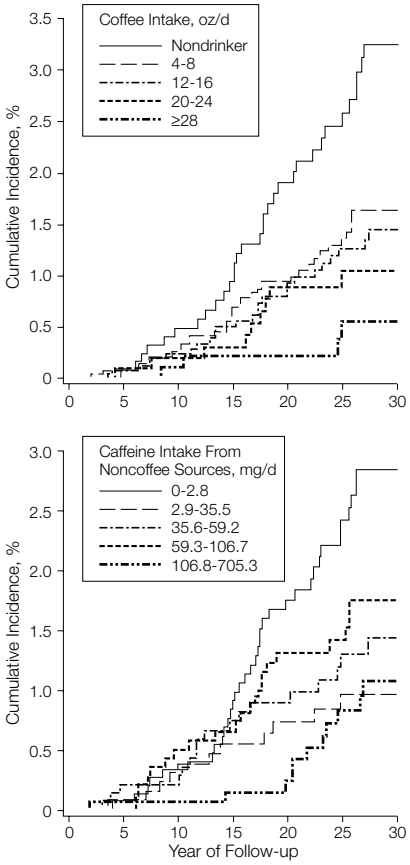
Among the other nutrients contained in coffee that were analyzed, including niacin, no associations were observed with risk of PD nor did they alter the association between coffee and caffeine intake with risk of PD. Adjustment for alcohol consumption, hyper-

Table 2. Unadjusted and Age-Adjusted Incidence of Parkinson Disease (PD) According to Total and Noncoffee Amounts of Caffeine Consumed per Day Based on 30 Years of Follow-up Beginning From 1965 to 1968

Quintile of Caffeine Intake, mg/d	No. of Cases of PD/No. of Subjects at Risk	Incidence Rate/10 000 Person-Years		Adjusted Relative Hazard (95% CI) Compared With the Top Category of Caffeine Intake*
		Unadjusted	Adjusted for Age	
Total Caffeine				
0-123	35/1522	9.8	9.7	5.1 (2.1-12.3)†
124-208	17/1396	5.2‡	5.0‡	2.6 (1.0-6.6)
209-287	26/1607	6.8	6.7	3.8 (1.6-9.3)§
288-420	12/1485	3.4‖	3.4‖	2.0 (0.7-5.3)
421-2716	6/1481	1.7¶	1.8¶	Reference
Test for trend	. . .	$P<.001$	$P<.001$	$P<.001$
Caffeine From Noncoffee Sources				
0-2.8	35/1642	9.2	9.2	2.7 (1.4-5.4)§
2.9-35.5	11/1389	3.4‖	3.4‖	1.2 (0.5-2.7)
35.6-59.2	18/1486	5.1‡	5.1‡	1.6 (0.7-3.3)
59.3-106.7	21/1487	5.9	5.9	1.9 (0.9-4.0)
106.8-705.3	11/1487	3.1‖	3.1‖	Reference
Test for trend	. . .	$P = .03$	$P = .03$	$P = .03$

*Adjusted for age and pack-years of cigarette smoking. CI indicates confidence interval.
†Significant excess risk of PD, $P<.001$.
‡Significantly different from nondrinkers, $P<.05$.
§Significant excess risk of PD, $P<.01$.
‖Significantly different from nondrinkers, $P<.01$.
¶Significantly different from nondrinkers, $P<.001$.

Figure 2. Cumulative Incidence of Parkinson Disease



Cumulative incidence according to coffee intake (top panel) and caffeine intake from noncoffee sources (bottom panel) at the time of study enrollment (1965-1968).

tension, cholesterol level, total energy intake, and saturated fat level had no effect on results of the model. Consumption of milk and sugar also failed to alter the reported findings.

COMMENT

To our knowledge, this is the first prospective study demonstrating a significant inverse association between coffee consumption measured during midlife and incident PD with a dose-response relationship. The finding was consistent whether coffee intake was determined by 24-hour recall or by food frequency questionnaire. The association was also observed for coffee intake measured at different examinations 6 years apart. Based on estimates of total or noncoffee caffeine and other nutrients contained in coffee derived from information collected at study inception, it appears caffeine may be the responsible constituent.

Previous studies have also suggested coffee consumption may be inversely related to risk of PD. In an earlier article from the Honolulu Heart Program, based on 58 cases also included in the case panel presented here, Grandinetti and colleagues[5] reported that coffee drinking was inversely related to PD, although the association was not statistically significant after controlling for cigarette smoking and alcohol consumption. The current report, based on longer follow-up and additional PD cases, found coffee drinking to be inversely related to PD risk independent of smoking and alcohol. Although 2 retrospective studies found that persons with PD were less likely to be coffee drinkers than persons without PD, the results were not statistically significant.[7,8] In 2 other case-control studies, individuals with PD consumed significantly less coffee prior to the diagnosis of PD than controls.[6,19] In both studies, a significant inverse dose-response relationship between coffee intake and PD was observed. However, the authors noted that retrospective assessment of coffee intake could be biased by current dietary habits.[6]

The lower frequency of coffee consumption during midlife among men who eventually developed PD could reflect a psychological or physiological intolerance to caffeine among persons with a constitutional propensity to develop PD. Alternatively, regular exposure to caffeine over many years might counteract the aging-related neurodegenerative processes that cause loss of dopaminergic neurons.

The pharmacological effects of caffeine could also modulate neurotransmitter and receptor systems of brainstem pigmented nuclei or striatum. Caffeine is a known central nervous system stimulant thought to act through adenosine receptor antagonism. Adenosine receptor agonists produce decreased locomotor activity in rodents, possibly through inhibition of dopamine neurotransmission.[20,21] Recent reports indicate that adenosine A2 receptor antagonists improve motor deficits in primates treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[22,23] Caffeine given to mice with pharmacologically induced dopamine depletion prevents akinesia.[20] This dopaminelike effect may be related to removal of tonic inhibition by adenosine on dopaminergic neurotransmission rather than direct stimulation of dopamine receptors by caffeine.[20,24] Thus, rather than having a direct biological effect on the pathogenesis of PD, coffee and other caffeine sources may be a form of self-medication that decreases clinical expression of parkinsonism by increasing central dopaminergic tone. Clinical studies do not consistently support this, however. Two small clinical trials of caffeine given concomitantly with either a dopamine agonist or levodopa to patients with PD have demonstrated no increased efficacy with caffeine.[25,26] One open-label trial of theophylline, another adenosine receptor antagonist, in 15 parkinsonian patients appeared to show improvement in disability scores.[27]

Two case-control studies[6,19] indicated that niacin contained in coffee might be neuroprotective. However, micronutrient analysis in this study included niacin, and this hypothesis was not supported.

Other explanations for our findings must be considered. If coffee consumption were associated with increased mortality, then selective survival of noncoffee drinkers may explain the inverse relationship between coffee and PD. A previous article from the Honolulu Heart Program found that coffee drinking is associated with higher cholesterol levels.[28] If this effect were enough to increase cardiovascular mortality, then heavy coffee drinkers may have been more likely to die before developing PD. This is not likely in our analysis. Adjustment for cholesterol level had no effect on the results and no association was found between coffee drinking and mortality ($P=.90$). Finally, an earlier article from the Honolulu Heart Program shows no relationship between coffee drinking and coronary artery disease risk.[29]

Incomplete PD case ascertainment among heavy coffee drinkers could also lead to an apparent protective effect of coffee drinking if heavy coffee intake were associated with not participating in follow-up examinations. To evaluate the possibility of missed cases in the heavy coffee-consuming group, additional analyses were performed to examine participation in the 1971 and 1991 examinations based on coffee consumption at the 1965 examination. There was no trend for nonparticipation in subsequent examinations with increased coffee consumption at the baseline examination. Similarly, there was no trend for nonparticipation in the 1991 examination based on coffee consumption at the 1971 examination. Since coffee drinking is not associated with mortality or with nonparticipation at subsequent examinations, it is unlikely that missed cases due to nonparticipation were preferentially heavy coffee drinkers. Associations between coffee and PD were also similar and statistically significant between the first and second 15 years of follow-up.

One other possibility is that individuals destined to develop PD used caffeine-containing analgesics and other medications more commonly than others and reduced their coffee intake to

avoid excess caffeine. Because consumption of nondietary caffeine-containing products was not assessed in the Honolulu Heart Program, this issue cannot be addressed.

There are potential limitations to this study. The population is Japanese-American men with older age at diagnosis. A recent report of concordance of PD among twins[3] suggests that older-onset PD may be more likely related to environmental factors compared with younger-onset cases with a stronger genetic component. This implies that when assessing environmental risk factors for PD, the use of an older population may improve chances of a successful yield.

Generalizations to younger-onset cases, women, and other ethnic groups cannot be made with certainty. A recent review of the worldwide frequency of PD suggests that incidence is somewhat lower in Japan, with crude incidence rates ranging from 5.4 to 10.2 compared with rates in northern Europe (range, 6-16), and Rochester, Minn (crude incidence, 19.7-23).[30] Those studies with the highest rates included all forms of parkinsonism (including drug induced and vascular) as cases. These data have been interpreted to suggest that PD may be more common in whites; however, it is entirely possible that differences are related to case finding and case definition methods.[31] Although the cause of PD is not known, the clinical syndrome and neuropathological characteristics are identical and risk factor profiles are similar in ethnic groups worldwide.[31]

Most important, the observational nature of the study design prevents concluding that coffee or caffeine directly protect against development of PD. However, prospective assessment of exposures and unbiased case-finding methods are unique strengths that enhance the importance of the findings. The possibility that caffeine has a protective effect against PD should be investigated further with future epidemiological, clinical, and basic science research.

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