Consumption of milk and calcium in midlife and the future risk of Parkinson disease

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Abstract—*Objective:* To examine the relation between milk and calcium intake in midlife and the risk of Parkinson disease (PD). *Methods:* Findings are based on dietary intake observed from 1965 to 1968 in 7,504 men ages 45 to 68 in the Honolulu Heart Program. Men were followed for 30 years for incident PD. *Results:* In the course of follow-up, 128 developed PD (7.1/10,000 person-years). Age-adjusted incidence of PD increased with milk intake from 6.9/10,000 person-years in men who consumed no milk to 14.9/10,000 person-years in men who consumed >16 oz/day ($p = 0.017$). After further adjustment for dietary and other factors, there was a 2.3-fold excess of PD (95% CI 1.3 to 4.1) in the highest intake group (>16 oz/day) vs those who consumed no milk. The effect of milk consumption on PD was also independent of the intake of calcium. Calcium from dairy and nondairy sources had no apparent relation with the risk of PD. *Conclusions:* Findings suggest that milk intake is associated with an increased risk of Parkinson disease. Whether observed effects are mediated through nutrients other than calcium or through neurotoxic contaminants warrants further study.

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Evidence suggests that diet and nutrient intake may have an important association with the risk of Parkinson disease (PD), although findings are largely from retrospective case-control studies where selection bias and uncertainty in dietary recall are common.[1] Recently, investigators from the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS) provided prospective evidence for an association between the high intake of dairy products and an increased risk of PD.[1] It remains uncertain, however, whether associations include commonly consumed dairy products and related nutrients such as milk and dietary calcium.

We examined the relation between milk and calcium intake in midlife and the future risk of PD. Findings are based on 30 years of follow-up of the sample of men who were enrolled in the Honolulu Heart Program from 1965 to 1968. All men were free of PD when follow-up began.

Methods. *Background and study sample.* From 1965 to 1968, the Honolulu Heart Program began following 8,006 men of Japanese ancestry living on the island of Oahu, HI, for the development of cardiovascular disease.[2,3] At the time of study enrollment, subjects were ages 45 to 68. Initial screening consisted of a baseline physical examination and documentation of cardiac and neurologic conditions to identify prevalent cases of cardiovascular disease. Since the time of study entry, subjects have undergone a comprehensive system of follow-up for morbidity and mortality outcomes through repeat examinations, surveillance for all hospital discharges, and a thorough review of medical records, death certificates, and autopsy reports by a panel of physician experts. Procedures have been in accordance with institutional guidelines and approved by an institutional review committee. Written informed consent has been obtained from the study participants.

For this report, follow-up began at the time of the baseline examination (1965 to 1968). These were the only examinations in the Honolulu Heart Program where data on the intake of milk and dietary calcium were collected. There were two men with prevalent PD at the baseline examination who were excluded from follow-up. Only men whose dietary intake was reported as being "fairly typical" of their usual dietary habits are considered in this report. Here, "fairly typical" is loosely defined as anything other than a major difference in under- or overeating (or drinking). Small variations were not recorded. Based on this latter criterion, an additional 500 men were excluded. The final sample that was available for follow-up included 7,504 men.

Dietary measurements and confounding information. Information on the intake of milk and dietary calcium was obtained by a dietitian based on 24-hour recall methods.[4] Dietitians used standardized methods to obtain individual recall of food intake through the use of food models and serving utensils to illustrate portion sizes.[4,5] Collected data were validated against a 7-day diet record in 329 of the 8,006 men in the original cohort.[6] There were

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Table 1 *Incidence of PD over 30-year period of follow-up within ranges of midlife milk intake*

Milk intake, oz/d	Sample size	Incident PD cases	Incidence of PD, rate/10,000 person-years	
			Unadjusted	Age adjusted
0	2,674	43	6.8	6.9
>0–8	3,228	47	6.1	5.9
>8–16	1,089	20	7.4	7.4
>16	513	18	14.5*	14.9*
Test for trend†			$p = 0.022$	$p = 0.017$

* Excess risk of PD vs men in the lowest intake range ($p < 0.01$).
† Test for trend is based on modeling milk as a continuous variable.

PD = Parkinson disease.

no significant differences between the methods of assessing dietary intake for 15 nutrient categories, and day-to-day variation was less than typical among Western cultures.[6] Nutrient intake levels were estimated by grouping foods into standard portions in 54 categories. Levels of nutrient intake for each category were then obtained from the US Department of Agriculture Handbook no. 8 and from a food table specifically designed for the Honolulu Heart Program.[7] Dietary calcium was further stratified as being derived from dairy and nondairy sources. Dairy sources included whole and skim milk, cheese, butter, and ice cream. Calcium intake from nondairy sources was largely from meats, fish, grains, soy products, and fruits and vegetables. Other dietary data considered in this report include the intake of coffee, total kilocalories, and fat. Data on the supplemental intake of calcium through nondietary sources were not available.

To help isolate the independent effect of milk and dietary calcium intake on the risk of PD, several risk factors measured at the time of dietary assessment were also considered as possible confounding variables. They included age, pack-years of cigarette smoking, and years worked on a plantation. Adjustments were also made for triceps skinfold thickness because of the observation that midlife adiposity has been shown to be related to the future risk of PD.[8] As body composition is often associated with levels of physical activity, additional adjustment controlled for the "physical activity index," a common measure used to quantify overall metabolic output in a typical 24-hour period and known to be inversely related to the risk of coronary heart disease and stroke.[9,10] Further description of the data collection methods for the other risk factors has been published elsewhere.[2,3]

PD case finding and diagnosis. For this report, 30 years of follow-up data were available on incident PD after collection of the dietary information (1965 to 1968). Prior to 1991, cases of PD were identified through a review of all hospital records of study participants for new and pre-existing diagnoses of PD, an ongoing review of all Hawaii death certificates, and a review of medical records at the offices of local neurologists for all cohort members suspected to have PD.

From 1991 to 1993, the Honolulu–Asia Aging Study was established for the study of neurodegenerative diseases in the surviving members of the Honolulu Heart Program.[11] During this time, all participants were screened for PD through structured interviews concerning the diagnosis of PD and the use of PD medications. 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.[12] These required that the subject have the following: 1) parkinsonism (e.g., bradykinesia or resting tremor combined with 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, multisystem atrophy, cerebrovascular disease, drug-induced parkinsonism, postencephalitic parkinsonism, or posttraumatic parkinsonism were not included among the cases of PD. During repeat exams that were given from 1994 to 1996 and from 1997 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.[12] Further description of the diagnosis of PD is provided elsewhere.[13,14]

Statistical methods. Crude and age-adjusted incidence rates of PD in person-years were estimated according to ranges of milk and calcium intake based on the 30 years of follow-up in the 7,504 men who were examined from 1965 to 1968.[15] Age-adjusted risk factors were also derived across the ranges of dietary intake.[15] To test for an effect of milk and calcium intake on the risk of PD, proportional hazards regression models were examined.[16] Adjustments were also made for age, coffee intake, pack-years of smoking, the physical activity index, triceps skinfold thickness, intake of total kilocalories and fat, and years worked on a plantation. In addition to a test for trend in the changing risk of PD with changes in milk and calcium intake, relative risks (and 95% CIs) were estimated comparing the risk of PD in the higher milk intake ranges vs the lowest. All reported p values were based on two-sided tests of significance.

Results. The average age at study enrollment (1965 to 1968) of the 7,504 men was 54.5 ± 5.6 years (range 45 to 68 years). During the 30 years of follow-up, 128 developed PD (7.1/10,000 person-years). The average age at the time of diagnosis was 73.4 ± 7.5 years (range 54 to 89 years), and the average time to a diagnosis was 18.4 ± 7.2 years (range 2 to 30 years).

Incidence of PD is further described in table 1 according to ranges of milk consumed at the time when follow-up began. For men who consumed no milk, the age-adjusted incidence was 6.9/10,000 person-years. For those who consumed >16 oz/day, incidence more than doubled (14.9/10,000 person-years; $p < 0.01$).

Table 2 describes the incidence of PD within quartiles of dietary calcium intake from dairy and nondairy sources. Whereas risk of PD rose with increasing amounts of calcium consumed from dairy sources, effects of calcium were weak and largely explained by concomitant milk intake. After additional adjustment for milk consumption, calcium had no effect on the risk of PD. Calcium consumed from nondairy sources also had no association with PD incidence ($p = 0.704$), further suggesting that calcium is unrelated to the risk of PD.

Among the possible confounders considered in this report, age, pack-years of smoking, and triceps skinfold

Table 2 *Incidence of PD over 30-year period of follow-up within quartiles of midlife intake of calcium from dairy and nondairy sources*

Quartile of calcium intake, mg/d	Sample size	Incident PD cases	Incidence of PD, rate/10,000 person-years	
			Unadjusted	Age adjusted
Dairy sources				
0–1	1,821	32	7.4	7.6
2–126	1,840	27	6.1	5.9
127–315	1,962	28	6.0	5.9
316–2,455	1,881	41	8.9	9.0
Test for trend*			$p = 0.063$	$p = 0.046$
Nondairy sources				
0–200	1,883	32	7.3	7.1
201–262	1,860	37	8.2	8.2
263–340	1,887	34	7.4	7.4
341–1,251	1,874	25	5.5	5.6
Test for trend			$p = 0.537$	$p = 0.704$

* Test for trend is based on modeling calcium as a continuous variable.

PD = Parkinson disease.

thickness declined with increasing amounts of milk consumed ($p < 0.001$). In contrast, the intake of total calcium, coffee, and total kilocalories and fat increased ($p < 0.001$). Although differences were modest, physical activity increased with increasing amounts of milk consumed ($p < 0.05$). Milk intake was unrelated to years worked on a plantation.

To help determine whether the excess risk of PD in those who consumed milk could be attributed to confounding from other factors, the effect of milk intake on PD was further adjusted for age, coffee intake, pack-years of smoking, physical activity, triceps skinfold thickness, total kilocalories and fat intake, and years worked on a plantation. Findings are shown in table 3 with and without the additional adjustment for the intake of calcium.

Table 3 *Adjusted relative risk of PD for men who consumed milk vs those who consumed no milk*

Milk intake, oz/d	Adjusted relative risk* (95% CI)	
	Without adjustment for calcium intake	With adjustment for calcium intake
0	Ref.	Ref.
>0–8	0.9 (0.6,1.4)	1.0 (0.6,1.5)
>8–16	1.2 (0.7,2.0)	1.3 (0.7,2.4)
>16	2.3† (1.3,4.1)	2.6‡ (1.1,6.4)
Test for trend§	$p = 0.007$	$p = 0.085$

* Adjusted for age, coffee intake, pack-years of smoking, physical activity, tricep skinfold thickness, total kilocalories and fat intake, and years worked on a plantation.
† Excess risk of PD vs men who consumed no milk ($p < 0.01$).
‡ Excess risk of PD vs men who consumed no milk ($p < 0.05$).
§ Test for trend is based on modeling milk as a continuous variable.

PD = Parkinson disease.

When unadjusted for total calcium intake, there was a rise in the risk of PD with increased amounts of milk consumed ($p = 0.007$). Although the dose–response relation between milk intake and the risk of PD declined in significance after accounting for calcium intake ($p = 0.085$), a more than twofold excess in the risk of PD persisted in those who consumed the most milk (>16 oz/day) vs those who consumed no milk ($p < 0.05$). The effect of milk intake on PD was also unaltered in the presence of other risk factors including plantation work and elevated triceps skinfold thickness.

Whether milk intake has a different effect on PD that occurs before age 65 vs PD that occurs later is shown in the figure (top). Although sample sizes and statistical power are reduced, men who consumed the most milk (>16 oz/day) continued to have an excess risk of PD vs men who consumed no milk regardless of the age at diagnosis ($p < 0.05$).

Whether milk intake has both long- and short-term effects on PD is also described in the figure (bottom). Although a test for a change in the relation between milk consumption and the risk of PD with time is not significant, it appears that the effect of milk on the risk of PD is strongest in the first 15 years of follow-up ($p < 0.01$) vs PD that was diagnosed in the second 15 years of follow-up. Although there appears to be a nonlinear relation between milk intake and the risk of PD in the first 15 years of follow-up, curvature in this relation could not be carefully assessed owing to the small number of cases that were observed to occur in this time period.

Discussion. Findings suggest that milk intake is associated with the future risk of PD that is independent of total kilocalories, dietary calcium, and other confounding variables. An apparent association between dietary calcium and PD is also explained by concomitant milk intake. In addition, calcium intake from nondairy sources was not related to PD, further

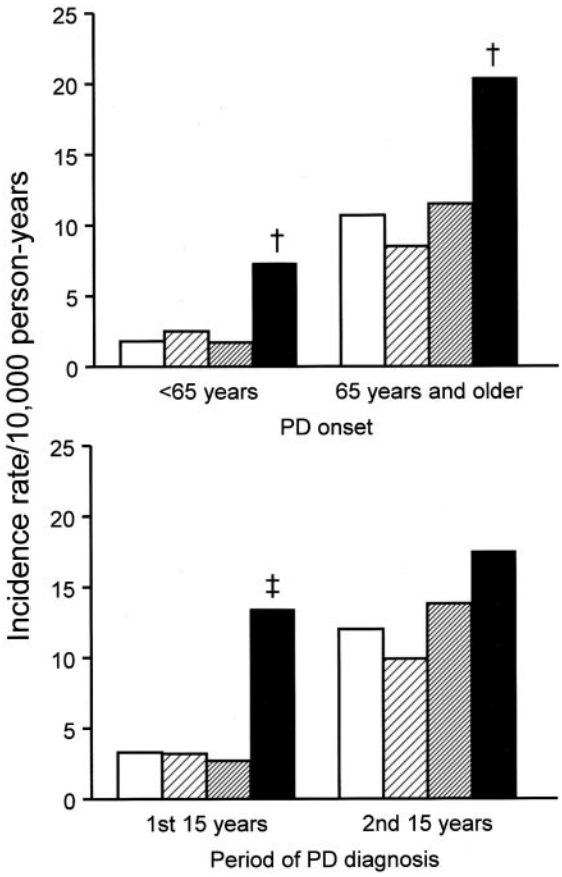

Figure. Age-adjusted incidence of early and late Parkinson disease (PD) onset (<65 and ≥65 years, respectively) and the incidence of PD in the first and second 15 years of follow-up according to milk intake during midlife. Milk intake increases from 0 (open columns), >0 to 8 (wide-hatched columns), >8 to 16 (thin-hatched columns), to >16 (filled columns) oz/day from left to right within each of the four-bar groupings. †Excess risk of PD vs men who consumed no milk ($p < 0.05$*). ‡Excess risk of PD vs men who consumed no milk (*$p < 0.01$*).*

suggesting that a role for calcium in altering PD risk is absent. A recent study from the HPFS and NHS provides similar findings with regard to nondairy calcium.[1] Although the HPFS and NHS investigators found a significant relation between calcium from dairy products and the risk of PD, it is not clear if associations could be attributed to milk intake as it was in the current report. Regardless, general findings of an effect of dairy products on the risk of PD in separate cohorts of men suggest that the observed relation between dairy products and PD could be real. The lack of a similar finding for women in the HPFS and NHS,[1] however, is difficult to resolve, although it could be important.

Although a more specific link between milk and PD was less apparent in the HPFS and NHS than in the Honolulu Heart Program,[1] differences in findings could be attributed (in part) to differences in study methods. For example, the current report assessed data from 24-hour dietary recall methods, whereas the HPFS and NHS collected data from a food frequency questionnaire.[1] In the latter study, dairy intake is measured as the number of servings consumed during a period of time, whereas in the current report, findings are presented according to amounts of milk or calcium consumed per day. Data from the Honolulu Heart Program, however, suggest that the amount of milk consumed may be more important than its frequency of intake. Although the age-adjusted incidence of PD in the current report increased consistently with increasing frequency of intake (from 5.5/10,000 person-years in men who rarely drank milk to 8.7/10,000 person-years in men who consumed milk regularly; $p = 0.047$), the association was not significant after adjustment for other factors. Nevertheless, there was a tendency for men who consumed the largest amounts of milk on a regular daily basis to also have the highest incidence of PD.

Although this may be the first published report to describe an association between milk intake and PD, presumably other investigators have also considered the possibility for such a relation, although with limited success. Studies of diet and PD, however, are often based on retrospective case-control designs where recall of food intake prior to the onset of PD (possibly by many years) can be subject to considerable variation and error. A strength of the current report and the HPFS and NHS is that both were based on prospective follow-up for incident PD.[1] As PD is a relatively uncommon disease, careful studies of the incidence of PD require long and costly periods of prospective follow-up.

Although the accurate collection of dietary intake data is known to be difficult, data in both the HPFS and NHS and the Honolulu Heart Program reflect intake at the time of questioning. Observations from the current report may also be less prone to the deficiencies of a 24-hour recall as only subjects who reported that consumption was "fairly typical" were considered for follow-up. Although in need of confirmation, this suggests that the effect of milk intake on the risk of PD could be through habitual rather than sporadic consumption of milk. Whether significant changes in milk intake occurred over long periods of time or whether the one-time measurement of milk intake in the current report reflects life-long consumption is not known.

Unfortunately, there are no clear explanations for the relation between milk intake and the risk of PD. As milk is a complex mixture of nutrients, any of its nutritional constituents could act as candidate mediators in the association between milk and PD. Calcium, however, is unlikely to be among these mediators because its intake from nondairy food items had no relation with PD. In the Honolulu Heart Program, total fat and protein also had no relation with the risk of PD. In addition, intakes of cheese, butter, and ice cream were unrelated to PD, although these food items are more likely to be consumed sporadically as compared with milk. Milk was also related to PD regardless of whether it was whole

or skim. Given the strong correlation between milk consumption and the intake of lactose and vitamin D in the Honolulu Heart Program, it was not possible to identify a distinct role for these nutrients in the development of PD. Although intakes of vitamins and supplements were not recorded, their routine use may have been minimal at the time when follow-up began (1965 to 1968). Nevertheless, an effect of dietary supplements on the risk of PD warrants consideration, particularly because supplements may be a less complex source of nutrients as compared with milk.

Effects of milk and dairy products could also have a role in altering the absorption of neuroprotective compounds associated with antioxidant capacity.[17-19] Rather than milk intake having an effect on PD, metabolic characteristics such as lactose intolerance could be protective. This is unlikely, however, as after removing men in the Honolulu Heart Program who consumed no milk (and presumably those most likely to be lactose intolerant), the association between milk intake and PD persisted.

Contamination of milk with neurotoxins may be of critical importance. High levels of organochlorine residues have been detected in milk,[20-24] and substantia nigra organochlorine levels have been found to be higher in cases of PD than in cases of Alzheimer disease and controls.[25,26] Other contaminants that have been found in milk include tetrahydroisoquinoline (used in the synthesis of pesticides),[27,28] which is known to induce parkinsonism in primates.[29,30]

A role for neurotoxins in Hawaii may be especially important, where, from 1981 to 1982, the milk supply on the island of Oahu was found to be contaminated with heptachlor (a chlorinated cyclodiene pesticide) from chopped pineapple leaves used as cattle feed.[22-24] At the time when follow-up began in the current report, much of the milk consumed in Hawaii came from local producers and local dairy farms. It is not clear, however, if this is true for other dairy products. Pesticides have also been shown to be a potent risk factor for PD in the Honolulu cohort.[31,32] Whether heptachlor contamination occurred prior to 1981 is uncertain.[23,24]

Whereas the findings from the Honolulu Heart Program are consistent with recent observations of an association between dairy products and PD,[1] additional confirmation is needed, particularly in terms of identifying the specific constituents of milk that contribute to the association between milk and PD. Whether observed effects are mediated through nutrients other than calcium or through neurotoxic contaminants warrants further study.

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