Diet and Parkinson's Disease: A Potential Role of Dairy Products in Men

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Diet may play a causative role in Parkinson's disease (PD), but potential associations between diet and PD risk rarely have been assessed in prospective studies. We investigated associations between food intakes and PD risk in two large prospective cohorts in which 210 incident PD cases in men and 184 in women were documented. A positive association was found between dairy intake and PD risk in men (relative risk [RR] comparing extreme categories, 1.8; *p* trend = 0.004), but not in women (RR, 1.1; *p* trend = 0.9). No other food groups were associated with PD risk in either men or women. Further analyses among men showed significant positive associations with PD risk for intakes of several dairy foods as well as dairy calcium (RR, 1.5; *p* trend = 0.02), dairy vitamin D (RR, 1.6; *p* trend = 0.004), dairy protein (RR, 1.6; *p* trend = 0.01), and lactose (RR, 1.8; *p* trend = 0.002), but not dairy fat (RR, 1.1; *p* trend = 0.4). Intakes of calcium, vitamin D, and protein from other dietary or supplemental sources were not related to PD risk in men. Our results suggest that higher intake of dairy products may increase the risk of PD in men; however, this finding needs further evaluation, and the underlying active components need to be identified.

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Although genetic components may be important in determining susceptibility to early onset Parkinson's disease (PD),[1] most PD cases are nonfamilial and probably involve environmental risk factors. Oxidative stress is thought to contribute to PD pathogenesis,[2,3] but epidemiological evidence supporting a protective role of dietary antioxidants is weak.[4–11] Potential roles of other foods and nutrients in determining PD risk have been little investigated, and the results are inconsistent. Elevated risks have been reported for higher intakes of total energy,[6,7] dietary fats,[6,10–12] carbohydrate,[7,13] monosaccharide and disaccharide,[7] chocolates and desserts,[14] iron,[11] and lutein,[11] and reduced risk for higher intakes of potatoes,[14] niacin, and foods containing niacin.[7,15] Most of these studies used a retrospective case–control design that is not well suited for such investigations because of the potential for recall and selection biases[16] and because of the difficulty of controlling for the effects that the disease status may have on diet. Using prospective data from the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS), we evaluated the overall associations between major food groups and PD risk. To further explore the strong positive association between dairy products and PD risk found in men, we also presented related analyses on dairy foods and associated nutrients.

Patients and Methods

Study Population

The HPFS cohort was established in 1986, when 51,529 male health professionals, aged 40 to 75 years, responded to a mailed questionnaire that included a 131-item food frequency questionnaire (FFQ),[17] in addition to questions on disease history and lifestyle. Dietary information was updated in 1990 and 1994 with similar FFQs. The NHS cohort was established in 1976 when 121,700 registered nurses, aged 30 to 55 years, provided detailed information about their medical history and lifestyle practices.[18] A 61-item FFQ was first administered to the NHS participants in 1980, and expanded FFQs were used in 1984, 1986, 1990, and 1994. In both cohorts, follow-up surveys are performed biennially to update information on potential risk factors for chronic diseases and to ascertain whether major diseases have occurred. A question on lifetime occurrence of PD was first included in the 1988 (HPFS) and 1994 (NHS) questionnaires, and a question on PD diagnosis within the previous 2 years was asked in the subsequent questionnaires. Participants who had received a diagnosis of PD, stroke, or cancer (other than nonmelanoma skin cancer) at baseline were excluded from the analyses. In addition, we also excluded participants with

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Table 1. Relative Risks[a] and 95% Confidence Intervals of Parkinson's Disease According to Baseline Intakes of Food Groups among Men (1986–1998) and Women (1980–1998)

Food Group	Quartiles (servings/day)				*p*
	1	2	3	4	
Dairy					
Total dairy					
Men	<1	1–1.7	1.7–2.9	>2.9	
No. of cases	43	51	46	70	
RR (95% CI)	1.0 (ref.)	1.3 (0.8–1.9)	1.3 (0.8–2.0)	1.8 (1.2–2.8)	0.004
Women	≤1.2	1.2–1.9	1.9–3.1	≥3.2	
No. of cases	44	50	51	39	
RR (95% CI)	1.0 (ref.)	1.3 (0.9–2.0)	1.3 (0.9–2.0)	1.1 (0.7–1.7)	0.9
Low-fat dairy					
Men	<0.2	0.2–0.6	0.7–1.2	>1.2	
No. of cases	45	42	54	69	
RR (95% CI)	1.0 (ref.)	1.0 (0.7–1.6)	1.2 (0.8–1.8)	1.3 (0.9–1.9)	0.1
Women	<0.1	0.1–0.5	0.6–1.1	≥1.2	
No. of cases	38	40	43	63	
RR (95% CI)	1.0 (ref.)	0.8 (0.5–1.3)	0.9 (0.6–1.3)	1.2 (0.8–1.8)	0.1
High-fat dairy					
Men	≤0.4	0.4–0.9	0.9–1.5	≥1.5	
No. of cases	54	48	56	52	
RR (95% CI)	1.0 (ref.)	1.0 (0.7–1.5)	1.2 (0.8–1.8)	1.2 (0.8–1.7)	0.5
Women	≤0.5	0.6–1.0	1.1–1.8	≥1.9	
No. of cases	46	50	43	45	
RR (95% CI)	1.0 (ref.)	1.2 (0.8–1.7)	1.1 (0.8–1.8)	1.1 (0.7–1.7)	0.7
Meat					
Total meat					
Men	≤0.8	0.8–1.2	1.2–1.8	≥1.8	
No. of cases	64	46	51	49	
RR (95% CI)	1.0 (ref.)	0.9 (0.6–1.3)	1.1 (0.8–1.7)	1.2 (0.7–1.8)	0.4
Women	≤1.0	1.0–1.5	1.5–2.0	≥2.0	
No. of cases	57	31	56	40	
RR (95% CI)	1.0 (ref.)	0.6 (0.4–0.9)	1.1 (0.7–1.7)	0.8 (0.5–1.3)	0.8
Red meat					
Men	≤0.4	0.4–0.8	0.9–1.3	>1.3	
No. of cases	65	42	52	51	
RR (95% CI)	1.0 (ref.)	0.9 (0.6–1.3)	1.2 (0.8–1.8)	1.2 (0.8–1.9)	0.2
Women	≤0.8	0.8–1.3	1.3–1.8	≥1.9	
No. of cases	58	39	51	36	
RR (95% CI)	1.0 (ref.)	0.8 (0.5–1.2)	1.0 (0.7–1.5)	0.7 (0.4–1.2)	0.3
Chicken					
Men	<0.2	0.2–0.3	0.4	≥0.5	
No. of cases	79	33	64	34	
RR (95% CI)	1.0 (ref.)	1.1 (0.8–1.7)	1.1 (0.8–1.5)	0.8 (0.5–1.2)	0.5
Women	≤0.1	0.1	0.2–0.3	≥0.4	
No. of cases	28	73	28	55	
RR (95% CI)	1.0 (ref.)	0.9 (0.6–1.4)	1.0 (0.6–1.8)	0.9 (0.6–1.4)	0.9
Fish					
Men	<0.2	0.2	0.3–0.4	≥0.5	
No. of cases	71	35	46	58	
RR (95% CI)	1.0 (ref.)	1.0 (0.7–1.5)	0.8 (0.6–1.2)	0.9 (0.6–1.3)	0.7
Women	0	0.1	0.1	≥0.4	
No. of cases	14	66	62	42	
RR (95% CI)	1.0 (ref.)	1.3 (0.7–2.3)	0.9 (0.5–1.6)	1.2 (0.6–2.2)	0.9
Fruits					
Men	≤1.3	1.3–2.1	2.1–3.1	≥3.1	
No. of cases	41	46	70	53	
RR (95% CI)	1.0 (ref.)	0.8 (0.5–1.2)	1.0 (0.7–1.6)	0.7 (0.4–1.1)	0.1
Women	≤1.1	1.1–1.9	1.9–2.7	≥2.8	
No. of cases	30	45	60	49	
RR (95% CI)	1.0 (ref.)	1.1 (0.7–1.8)	1.4 (0.9–2.1)	1.0 (0.6–1.6)	0.9

Table 1. Continued

Food Group	Quartiles (servings/day) 1	2	3	4	*p*
Vegetables					
Men	≤1.9	1.9–2.8	2.8–3.9	≥3.9	
No. of cases	50	51	60	49	
RR (95% CI)	1.0 (ref.)	1.0 (0.7–1.5)	1.1 (0.7–1.6)	0.8 (0.5–1.2)	0.2
Women	≤1.1	1.2–1.7	1.7–2.5	≥2.5	
No. of cases	37	42	54	51	
RR (95% CI)	1.0 (ref.)	1.1 (0.7–1.7)	1.3 (0.9–2.0)	1.1 (0.7–1.8)	0.5
Chocolate candies or brownie					
Men	0	0.1	0.1–0.2	≥0.3	
No. of cases	75	36	40	59	
RR (95% CI)	1.0 (ref.)	0.9 (0.6–1.3)	0.8 (0.5–1.1)	1.2 (0.8–1.7)	0.1
Women	0	0.1	0.1	≥0.4	
No. of cases	65	52	30	37	
RR (95% CI)	1.0 (ref.)	1.1 (0.8–1.6)	1.0 (0.7–1.6)	1.2 (0.8–1.8)	0.5
Other sweets or desserts					
Men	≤0.3	0.4–0.8	0.8–1.5	≥1.5	
No. of cases	49	46	50	65	
RR (95% CI)	1.0 (ref.)	1.1 (0.7–1.7)	1.1 (0.7–1.7)	1.3 (0.9–2.0)	0.2
Women	≤0.1	0.2–0.4	0.4–0.9	≥0.9	
No. of cases	46	44	50	44	
RR (95% CI)	1.0 (ref.)	1.1 (0.7–1.7)	1.2 (0.8–1.8)	1.1 (0.7–1.7)	0.8
Cereals					
Men	<0.1	0.1–0.4	0.4–0.9	≥0.9	
No. of cases	51	35	50	74	
RR (95% CI)	1.0 (ref.)	0.7 (0.4–1.0)	0.9 (0.6–1.3)	1.0 (0.7–1.5)	0.6
Women	0	0.1	0.1–0.4	≥0.8	
No. of cases	47	26	71	40	
RR (95% CI)	1.0 (ref.)	1.4 (0.9–2.2)	1.5 (1.0–2.2)	1.4 (0.9–2.2)	0.2
Other starch foods					
Men	≤1.6	1.6–2.4	2.4–3.7	≥3.7	
No. of cases	59	41	61	49	
RR (95% CI)	1.0 (ref.)	0.8 (0.5–1.3)	1.2 (0.8–1.9)	0.9 (0.6–1.5)	1.0
Women	≤1.2	1.2–1.9	1.9–3.1	≥3.1	
No. of cases	56	47	44	37	
RR (95% CI)	1.0 (ref.)	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.7 (0.5–1.2)	0.2

[a]Adjusted for baseline age (5-year increment), lengths of follow-up (time periods), smoking (never smokers, past smokers, and current smokers [cigarettes per day: 1–14, ≥15]), energy intake (quintiles), caffeine intake (quintiles), body mass index (kg/m^2, men: quintiles; women: <21, 21–22.9, 23–24.9, 25–28.9, ≥29), alcohol consumption (gm/day, men: 0, 1–9.9, 10–19.9, 20–29.9, >30; women: 0, 1–4.9, 5–9.9, 10–14.9, ≥15), and physical activity (men: quintiles; women: hours of moderate or vigorous activity per week, <1, 1–1.9, 2–3.9, 4–6.9, ≥7).

RR = relative risk; CI = confidence interval.

extreme daily energy intakes (<800 or >4,200Kcal for men and <500 or >3,500 for women) or incomplete FFQ at baseline (>70 blanks for men and >10 for women). We followed 47,331 eligible men and 88,563 women from baseline (1986 and 1980, respectively) to 1998 or dates of PD diagnoses or deaths, whichever occurred first. These studies were approved by the Human Subjects Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

Parkinson's Disease Case Ascertainment

We contacted the neurologists identified by cohort participants who reported a new diagnosis of PD and asked them to confirm the diagnosis by providing their judgments on the clinical certainty of the diagnosis (definite, probable, or possible), and to provide information on cardinal signs and response to L-dopa, or to send us a copy of the medical record.[19] In the case that a neurologist did not respond, we wrote to the patient's internist or general physician. Deaths in the cohorts were reported by family members, coworkers, or postal authorities or were identified by searching the National Death Index. If PD was listed as a cause of death in the death certificate, we requested permission from the family to contact the treating neurologist or physician and followed the same procedure as for the nonfatal cases. Most PD cases were confirmed by their treating neurologists (76% in men and 85% in women); the remaining cases were confirmed by their internists or by reviewing the medical records.

Exposure Assessment

Participants were asked how often, on average, they had consumed a specified amount of food during the previous 12

months, with nine categories ranging from "never" to "six or more times per day." The nutrient composition of foods was estimated from the Harvard University Food Composition Database that was derived from the US Department of Agriculture[20,21] and supplemented with information from manufacturers[17] and data from peer-reviewed literature. Food and nutrient intakes assessed by this questionnaire have been validated previously against dietary records in both men and women.[17,22–24]

Statistical Analyses

Participants were categorized into quartiles separately in men and in women according to their food group intakes from low to high (25% participants in each category). Four-level categorical variables were used for intakes of individual dairy items because their distributions usually were skewed. Nutrient intakes were classified into quintiles (20% participants in each category) according to their sources: dairy products, other foods, or supplements. Intakes of calcium, vitamin D, and lactose were adjusted for energy intake, using the residual method.[25] Protein and fat intakes were expressed as percentage of energy. The median of each category was used as a continuous variable to test for trend and to simultaneously adjust for nutrients from different sources. In each analysis, the lowest intake category was used as the reference group.

Relative risks (RRs) were calculated by dividing the incidence rate of PD in each exposure category by the corresponding rate in the reference category, adjusting for baseline age in 5-year increment and smoking status with the Mantel–Haenszel method.[26] Multivariate analyses used pooled logistic regression with 2-year intervals, which is equivalent to a Cox proportional hazards analysis when the probability of an event within each interval is low.[27] Covariates included baseline age, lengths of follow-up, smoking status, energy intake, caffeine intake, body mass index, physical activity, and alcohol consumption. Because the age and smoking adjusted RRs were similar to the multivariate RRs, the latter was presented for simplicity. In the main analyses, men were classified according to their baseline intakes. However, we also incorporated the repeated dietary information by relating the PD risk to the cumulative updated average intakes from all available questionnaires before the beginning of each 2-year follow-up period. The results for all PD cases are presented in this article because the exclusion of possible cases did not change the results.

The latency period for PD may be longer than a few years.[28] To address the possibility that undiagnosed PD might have affected the results, we did a lag analysis by excluding the first 6 years of follow-up. In addition, we also examined the associations between dairy nutrients and PD risk among men within strata of baseline age (<65 and ≥ 65), smoking (never and ever smokers), and caffeine intakes (quintile 1, quintiles 2 and 3, and quintiles 4 and 5).

Results

We documented 210 incident PD cases in men and 184 in women. Most diagnoses were considered clinically definite (61% of men and 71% of women) or probable (30% of men and 21% of women). Intake of dairy products was positively associated with PD risk in men (Table 1). Compared with men who consumed less than 1 serving per day, those with 2.9 or more servings per day had 80% increased risk (multivariate RR, 1.8; 95% confidence interval [CI], 1.2–2.8; p trend = 0.004). In the 6-year lag analysis, the association was even stronger (RR, 2.7; 95% CI, 1.5–5.1; p trend = 0.003). However, dairy intake was not associated with PD risk in women; the RR between women who had 3.2 or more servings per day and women with up to 1.2 serving per day was 1.1 (95% CI, 0.7–1.7). No significant associations with PD risk were seen for other food groups in either men or women.

Among men, PD risk increased significantly with greater intakes of cream cheese, other cheese, and sour cream, and marginally with skim or low fat milk intake (Table 2). No individual dairy item was associated with PD risk in women (data not shown).

With the exception of dairy fat, nutrient intakes from dairies showed positive associations with PD risk in men (Fig). The strongest association was found with lactose (multivariate RRs between extreme intake quintiles, 1.8; 95% CI, 1.1–2.8; p trend = 0.002). The corresponding RR for dairy fat was 1.1 (95% CI, 0.7–1.7; p trend = 0.4). A slightly elevated risk was found for higher animal fat intake in men (highest vs lowest quintiles RR, 1.4; 95% CI, 0.9–2.2), but the trend was not statistically significant (p trend = 0.1). Moreover, PD risk was not associated with intake of calcium, vitamin D, or protein from nondairy sources in men (Tables 3 and 4).

As with the food group analyses, we also observed stronger associations between dairy nutrient intakes and PD risk in men in the 6-year lag analyses. Using the lowest quintile as the reference, we found that the multivariate RRs for quintiles 2 to 5 were 1.1, 1.6, 1.9, and 2.4 (p trend = 0.001) for dairy vitamin D and 1.6, 2.0, 2.4, and 2.8 (p trend = 0.003) for lactose, respectively. Subgroup analyses by age, smoking, and caffeine intake showed no significant differences across strata. Results of analyses excluding possible PD cases were similar to those presented above. Similar positive associations in men also were observed in analyses using the cumulative average intakes, but the results were generally less strong. Compared with the lowest quintile, the cumulative multivariate RRs associated with quintiles 2 to 5 were 1.1, 1.6, 1.7, and 1.5 (p trend = 0.07) for dairy vitamin D and 1.0, 1.6, 1.3, and 1.7 (p trend = 0.02) for lactose, respectively.

Discussion

Among men, PD risk was positively associated with intake of certain dairy products. Men in the highest quintile of intakes of lactose, dairy calcium, dairy vitamin D, or dairy protein had a 50 to 80% increase in PD risk compared with men in the lowest quintile. However, dairy intake was not associated with PD risk

Table 2. Relative Risks[a] and 95% Confidence Intervals of Parkinson's Disease according to Baseline Intakes of Individual Dairy Foods among Men (1986–1998)

Dairy Food Type	Categories (servings/week or day)				*p*
Whole milk	Never	≤1/week	<1/day	≥1/day	
Person-years[b]	343,100	63,957	38,708	28,171	
No. of cases[b]	134	15	22	13	
RR (95% CI)	1.0 (ref.)	0.7 (0.4–1.1)	1.4 (0.9–2.1)	1.1 (0.6–1.9)	0.5
Skim or low-fat milk	Never	≤1/week	<1/day	≥1/day	
Person-years	128,837	70,584	137,433	166,585	
No. of cases	44	22	43	89	
RR (95% CI)	1.0 (ref.)	1.0 (0.6–1.7)	0.8 (0.5–1.3)	1.4 (0.9–2.0)	0.05
Cream cheese	Never	1–3/month	1/week	>1/week	
Person-years	289,410	132,518	32,348	22,576	
No. of cases	106	48	13	19	
RR (95% CI)	1.0 (ref.)	1.0 (0.7–1.5)	1.1 (0.6–2.0)	1.9 (1.1–3.1)	0.01
Other cheese	Never	≤1/week	2–4/week	≥5/week	
Person-years	35,342	188,101	192,154	92,468	
No. of cases	17	75	65	47	
RR (95% CI)	1.0 (ref.)	1.1 (0.7–2.0)	1.1 (0.6–1.9)	1.7 (0.9–3.0)	0.03
Sour cream	Never	1–3/month	1/week	>1/week	
Person-years	248,114	161,619	45,521	25,105	
No. of cases	105	46	20	17	
RR (95% CI)	1.0 (ref.)	0.9 (0.6–1.3)	1.5 (0.9–2.4)	1.7 (1.0–2.9)	0.02
Cottage cheese	Never	1–3/month	1/week	>1/week	
Person-years	180,249	168,341	71,250	70,238	
No. of cases	65	67	22	34	
RR (95% CI)	1.0 (ref.)	1.0 (0.7–1.5)	0.7 (0.5–1.2)	0.9 (0.6–1.4)	0.5
Ice cream	Never	1–3/month	1/week	>1/week	
Person-years	101,907	187,411	94,543	117,434	
No. of cases	53	64	28	52	
RR (95% CI)	1.0 (ref.)	0.7 (0.5–1.1)	0.6 (0.4–1.0)	0.8 (0.6–1.2)	0.9
Yogurt	Never	1–3/month	1/week	>1/week	
Person-years	301,345	90,245	36,420	49,501	
No. of cases	122	23	10	26	
RR (95% CI)	1.0 (ref.)	0.7 (0.5–1.1)	0.8 (0.4–1.5)	1.3 (0.8–2.0)	0.3
Sherbet	Never	1–3/month	1/week	>1/week	
Person-years	296,111	114,173	32,333	27,561	
No. of cases	115	36	9	18	
RR (95% CI)	1.0 (ref.)	0.8 (0.6–1.2)	0.7 (0.4–1.4)	1.3 (0.8–2.2)	0.4
Cream	Never	1–3/month	<1/day	≥1/day	
Person-years	361,891	48,790	34,755	25,880	
No. of cases	141	12	19	7	
RR (95% CI)	1.0 (ref.)	0.7 (0.4–1.3)	1.5 (0.9–2.4)	0.8 (0.4–1.7)	0.8
Butter	Never	1–3/month	1–4/week	≥5/week	
Person-years	243,372	80,593	103,188	70,275	
No. of cases	116	27	37	19	
RR (95% CI)	1.0 (ref.)	0.9 (0.6–1.3)	1.0 (0.7–1.5)	0.7 (0.4–1.1)	0.2

[a]Adjusted for baseline age (5-year increment), lengths of follow-up (time periods), smoking (never smokers, past smokers, and current smokers [cigarettes/day: 1–14, ≥15]), energy intake (quintiles), caffeine intake (quintiles), body mass index (quintiles), alcohol consumption (gm/day: 0, 1–9, 10–19, 20–29, ≥30), and physical activity (quintiles).
[b]Numbers may not add up to total because of missing values.

in women, and no other food groups were associated with PD risk in either men or women.

In contrast with previous epidemiological investigations on diet and PD, our study was prospectively designed with repeated dietary assessments and long follow-up periods. Intakes of foods and nutrients derived from our FFQs reasonably reflected the long-term intakes of the study populations.[17,22–24] The positive associations between dairy and PD risk in men cannot be explained by dietary changes due to early PD symptoms because they became stronger after excluding the first 6 years of follow-up. Because of the prospective design, any misclassification of baseline exposures would most likely be nondifferential and would have attenuated the true associations.

Unlike previous case–control studies,[14,15] we did not find an increased PD risk for greater intake of chocolates or desserts, or any association between PD risk and other starch foods or meats. Instead, we identified a strong positive association between dairy intake and

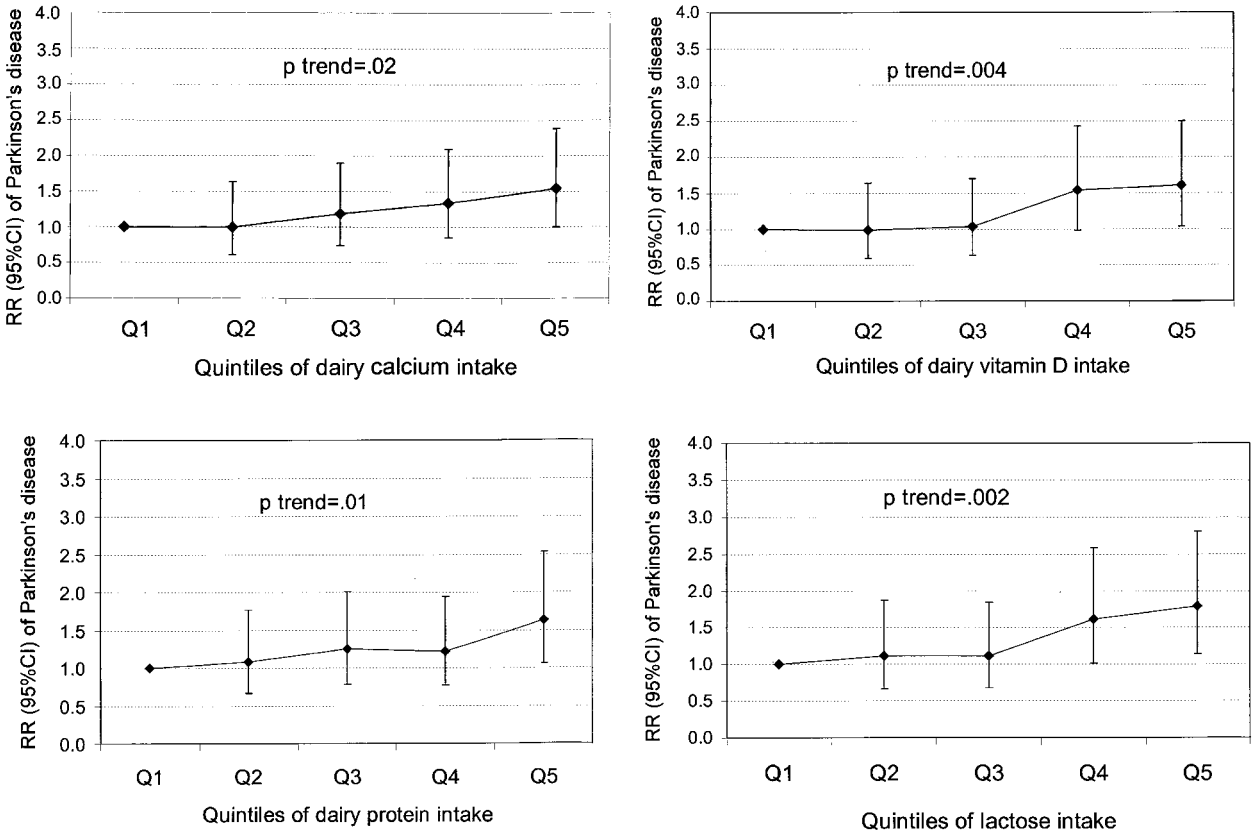

Fig. Multivariate relative risks of Parkinson's disease according to quintiles of intake of dairy calcium, dairy vitamin D, dairy protein, and lactose, adjusting for baseline age (5-year increment), smoking (never smokers, past smokers, and current smokers [cigarettes per day, 1–14, ≥15]), energy intake (quintiles), caffeine intake (quintiles), body mass index (quintiles), alcohol consumption (gm/day: 0, 1–9, 10–19, 20–29, ≥30), and physical activity (quintiles) in men. RR = relative risk; CI = confidence interval.

PD risk. Dairies are major dietary sources of animal fat and vitamin D. Greater animal fat intake was related to higher PD risk in previous investigations.[6,10,12] One study further reported elevated risks for higher intakes of vitamin D and vitamin D–containing foods, but which were attributed to the correlation between vitamin D and animal fat intake.[10] Our results suggested that PD risk is not significantly associated with intake of dairy fat or animal fat, but rather with intakes of nonfat constituents of dairy foods in men. The lack of association between PD risk and calcium, vitamin D, and protein from nondairy foods or supplements suggests that intake of these nutrients is not causally related to PD risk. Although lactose intake tended to have the strongest association with PD, its role cannot be assessed independently from other components that are specific for dairies. Therefore, these nutrients should be considered only as different summarizations of dairy intake and may be confounded by other unmeasured constituents or contaminants.

The exact cause of dopaminergic neuron death in PD is not clear; however, the process may include oxidative stress and mitochondrial dysfunction.[29–32] There is no clear evidence linking intake of milk or its components to these potential neurotoxic events. Repeated oral infusions of milk decreased extracellular dopamine concentrations in newborn rats[33] and decreased dopamine D2 receptor occupancies in the striatum, septum, and hypothalamus of fetal rats,[34] but these experiments provide little information on the effects of milk consumption in adult animals. Increased intracellular calcium concentration has been implicated in death of dopaminergic neurons,[35] and regions of substantia nigra pars compacta that are poor in calbindin D_{28K} are most likely to be damaged in PD.[36,37] In vitro experiments suggest that pretreatment with vitamin D_3 may protect dopaminergic neurons from toxins by reducing oxidative stresses[38–40] but at higher concentration it might enhance the neurotoxic effect.[38] Whether these mechanisms are relevant to PD cause is uncertain.

An alternative explanation to our findings is that

Table 3. Relative Risks[a] and 95% Confidence Intervals of Parkinson's Disease according to Baseline and Updated Supplemental Calcium or Vitamin D Intakes among Men (1986–1998)

Supplement Type				*p*
Calcium supplements intake				
Baseline (mg)	0	1–200	>200	
Person-years	401,423	61,586	58,651	
No. of cases	157	26	27	
RR (95%, CI)	1.0 (ref.)	0.9 (0.6–1.4)	0.9 (0.6–1.4)	0.7
Simple updated				
Person-years	371,754	74,237	52,464	
No. of cases	126	41	28	
RR (95%, CI)	1.0 (ref.)	1.3 (0.9–1.9)	1.3 (0.8–1.9)	0.2
Vitamin D supplement intake				
Baseline (IU)	0	1–399	≥400	
Person-years	325,538	80,618	115,504	
No. of cases	114	36	60	
RR (95%, CI)	1.0 (ref.)	1.2 (0.8–1.7)	1.2 (0.9–1.7)	0.3
Simple updated				
Person-years	305,606	75,454	117,396	
No. of cases	99	39	57	
RR (95%, CI)	1.0 (ref.)	1.5 (1.1–2.2)	1.2 (0.9–1.7)	0.2

[a]Adjusted for age (5-year increment), lengths of follow-up (time periods), smoking (never smokers, past smokers, and current smokers), energy intake (quintiles), caffeine intake (quintiles), body mass index (quintiles), alcohol consumption (gm/day: 0, 1–9, 9–19, 20–29, ≥30), physical activity (quintiles), and dietary calcium or vitamin D intake (quintiles); confounders also were updated in simple updated analyses.

RR = relative risk; CI = confidence interval; IU = International unit.

Table 4. Relative Risks[a] and 95% Confidence Intervals of Parkinson's Disease among Men When Baseline Intakes of Selected Nutrient from Dairy and Nondairy Sources Were Mutually Adjusted (1986–1998)

		Dairy Products		Nondairy Foods		Supplements	
Nutrient	Unit	RR (95% CI)	*p*	RR (95% CI)	*p*	RR (95% CI)	*p*
Calcium	400mg	1.3 (1.0–1.6)	0.03	0.8 (0.3–1.8)	0.6	0.9 (0.7–1.3)	0.7
Vitamin D	160 IU	1.4 (1.1–1.9)	0.005	1.0 (0.7–1.5)	1.0	1.1 (0.9–1.2)	0.3
Fat	5% energy	1.1 (0.9–1.5)	0.4	1.0 (0.9–1.1)	0.9	—	—
Protein	5% energy	1.6 (1.0–2.6)	0.03	0.9 (0.7–1.2)	0.6	—	—
Lactose	25mg	1.7 (1.2–2.4)	0.002	—	—	—	—

[a]Adjusted for baseline age (5-year increment), lengths of follow-up (time periods), smoking (never smokers, past smokers, and current smokers [cigarettes per day: 1–14, ≥15]), energy intake (quintiles), caffeine intake (quintiles), body mass index (quintiles), alcohol consumption (gm/day: 0, 1–9, 10–19, 20–29, ≥30), and physical activity (quintiles).

RR = relative risk; CI = confidence interval.

some unmeasured components in dairy products may increase PD risk. Tetrahydroisoquinolines[41] have been found in a variety of foods such as milk and cheeses.[42,43] Tetrahydroisoquinolines can cross the blood–brain barrier[42,44] and have been shown to induce parkinsonism in mouse and monkey.[45–48] β-Carbolines and derivatives are dopaminergic neurotoxins with structural similarity to 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine.[49] Although these compounds are primarily endogenously synthesized, their precursors, biogenic amines, are found in fermented foods such as cheeses.[50–52] Finally, we cannot exclude the possibility that contamination of dairy with pesticides or polychlorinated biphenyls contributes to our results. Several of these compounds have been shown to have selective toxicity for nigrastriatal neurons in animal models.[53,54]

In summary, we found a positive association between dairy consumption and risk of PD in men. The fact that a similar association was not present in women requires caution in interpreting the results. Conversely, gender differences in risk factors for PD have been previously reported, most notably for caffeine that was strongly associated with PD risk in men but not in women.[19,55] Although we cannot exclude the possibility of a chance finding, the association we found in men was strong and consistent between foods and nutrients and suggests that further research is

needed to address the possibility that certain compounds in dairy products may influence the risk of PD among men.

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