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Original Contribution

Consumption of Dairy Products and Risk of Parkinson's Disease

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The authors prospectively investigated the association between intake of dairy products and risk of Parkinson's disease among 57,689 men and 73,175 women from the American Cancer Society's Cancer Prevention Study II Nutrition Cohort. A total of 250 men and 138 women with Parkinson's disease were identified during follow-up (1992–2001). Dairy product consumption was positively associated with risk of Parkinson's disease: Compared with the lowest intake quintile, the corresponding relative risks for quintiles 2–5 were 1.4, 1.4, 1.4, and 1.6 (95 percent confidence interval (CI): 1.1, 2.2; p for trend = 0.05). A higher risk among dairy product consumers was found in both men and women, although the association in women appeared nonlinear. Meta-analysis of all prospective studies confirmed a moderately elevated risk of Parkinson's disease among persons with high dairy product consumption: For extreme intake categories, relative risks were 1.6 (95 percent CI: 1.3, 2.0) for both sexes, 1.8 for men (95 percent CI: 1.4, 2.4), and 1.3 for women (95 percent CI: 0.8, 2.1). These data suggest that dairy consumption may increase the risk of Parkinson's disease, particularly in men. More studies are needed to further examine these findings and to explore underlying mechanisms.

dairy products; diet; milk; Parkinson disease

Abbreviation: CI, confidence interval.

Diet may play an important role in the etiology of Parkinson's disease, either by altering the oxidative balance in the brain or by serving as a vehicle for environmental neurotoxins. Few epidemiologic studies have been able to examine potential associations between diet and Parkinson's disease because of the relatively low incidence of the disease and its insidious onset. Most of the published articles have described case-control studies (1–4), which may not be well-suited for investigating associations between diet and neurodegenerative diseases because of the potential for recall and selection bias (5, 6). After analyzing prospective data from the Health Professionals Follow-up Study and the Nurses' Health Study, we initially reported an unexpected positive association between consumption of dairy products and risk of Parkinson's disease in men but not in women (5). In a recent analysis of data from the prospective Honolulu-Asia Aging Study, a cohort comprising only men, Park et al. (7) found that higher midlife consumption of milk, but not of other dairy items, was related to a greater risk of Parkinson's disease in later life. Here, by taking advantage of data on the American Cancer Society's well-established Cancer Prevention Study II Nutrition Cohort, we were able to prospectively investigate further the associations between dairy products, individual dairy food items, and nutrients derived

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TABLE 1. Characteristics of the study population according to baseline consumption of dairy products, Cancer Prevention Study II Nutrition Cohort, 1992–2001*

	Quintile of dairy product intake				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Mean intake (g/day)	78.1	178.6	285.5	415.3	815.0
Range of intakes (g/day)	0–133.6	133.7–228.5	228.6–345.9	346.0–502.0	502.1–3,488.6
Age (years)	62.1	62.6	62.5	62.8	62.9
% men	41.0	43.6	44.8	45.8	45.0
Cigarette smoking (%)					
Past smoker	47.3	46.9	47.2	45.9	43.8
Current smoker	10.0	7.4	7.1	6.7	6.6
Education (%)					
High school or post-high school	57.6	55.3	53.6	52.3	51.1
College graduation or higher	36.3	39.5	41.3	43.1	44.3
Pesticide exposure in 1982 (%)	4.9	5.0	5.2	5.4	6.6
Energy intake (kcal/day)	1,297	1,421	1,516	1,642	1,909
Vigorous physical activity (METs†/week)‡	3.9	4.3	4.6	4.9	5.0
Regular§ use of ibuprofen (%)	18.2	19.1	19.5	19.7	20.0

* Except for age, all covariates were standardized to the age distribution of the entire cohort.
† MET, metabolic equivalent task.
‡ METs were calculated by multiplying the number of hours spent per week in each activity by its typical energy expenditure requirements.
§ "Regular" was not defined in the survey.

from dairy products and risk of Parkinson's disease and to examine the potential gender difference.

MATERIALS AND METHODS

Study population

Participants in this study were drawn from the Cancer Prevention Study II Nutrition Cohort, comprising 86,404 men and 97,786 women. The cohort was established by the American Cancer Society in 1992 for a prospective study investigating risk factors for cancer incidence (8). The Nutrition Cohort is a subgroup of the 1.2 million US men and women originally recruited in 1982 for research on cancer mortality in Cancer Prevention Study II. Participants were aged 50–74 years at enrollment in 1992 or 1993, when they completed a mailed questionnaire that included questions on demographic, medical, environmental, and lifestyle factors and dietary habits. Follow-up surveys were conducted in 1997, 1999, and 2001 to update exposure information and to ascertain whether any major chronic diseases had been diagnosed. A specific question on lifetime occurrence of Parkinson's disease was asked in the 2001 survey.

The current analyses were limited to participants in the 2001 survey who did not have Parkinson's disease before they answered the baseline 1992 questionnaire. We also excluded men and women who reported extreme values for daily energy intake (<550 or >3,500 kcal/day for women and <650 or >4,000 kcal/day for men) and those who left 10 or more items blank or did not complete the beverage section of the questionnaire. Follow-up of eligible participants (n = 130,864) started on the date of return of the 1992 questionnaire and ended on the date on which the first symptoms of Parkinson's disease were noticed, for Parkinson's disease cases, or August 31, 2001, for participants without Parkinson's disease. The study was approved by the human subjects committee of the Harvard School of Public Health (Boston, Massachusetts) and the institutional review board of Emory University (Atlanta, Georgia).

Case ascertainment

The case ascertainment procedures were similar to those used in our previous studies of Parkinson's disease (9). Briefly, we wrote to all participants who reported a diagnosis of Parkinson's disease on the 2001 questionnaire and asked for permission to contact their treating neurologists. We then asked their treating neurologists (or internists, if the neurologists did not respond) to complete a diagnostic questionnaire or to send us a copy of the medical record. The questionnaire asked physicians to report the presence or absence of cardinal signs of Parkinson's disease (rest tremor, rigidity, bradykinesia, and postural instability), response to levodopa treatment, and other clinical features that may corroborate a Parkinson's disease diagnosis or suggest an alternative diagnosis. A case was confirmed if the diagnosis was considered clinically definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of Parkinson's disease made by a neurologist or evidence at a neurologic examination of at least two of the

TABLE 2. Relative risk* of Parkinson's disease according to baseline consumption of dairy products, Cancer Prevention Study II Nutrition Cohort, 1992–2001

	Quintile of dairy product intake					*p* for trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
All dairy products (g/day)	0–133.6	133.7–228.5	228.6–345.9	346.0–502.0	>502.0	
All participants						
No. of cases	53	79	79	83	94	
Person-years of follow-up†	218,219	221,412	222,398	223,874	221,502	
RR‡ (95% CI‡)	1.0§	1.4 (1.0, 2.0)	1.4 (1.0, 1.9)	1.4 (1.0, 2.0)	1.6 (1.1, 2.2)	0.05
Men						
No. of cases	33	46	49	58	64	
Person-years of follow-up	89,490	97,155	100,279	103,805	100,972	
RR (95% CI)	1.0§	1.2 (0.8, 1.9)	1.3 (0.8, 2.0)	1.4 (0.9, 2.2)	1.6 (1.0, 2.5)	0.04
Women						
No. of cases	20	33	30	25	30	
Person-years of follow-up	128,730	124,257	122,119	120,069	120,531	
RR (95% CI)	1.0§	1.6 (0.9, 2.9)	1.5 (0.9, 2.7)	1.3 (0.7, 2.3)	1.5 (0.8, 2.8)	0.5
Milk (g/day)¶	0–84.3	84.4–155.4	155.5–273.1	273.2–397.1	>397.1	
All participants						
No. of cases	49	78	87	76	98	
Person-years of follow-up	220,625	221,516	221,931	223,149	220,184	
RR (95% CI)	1.0§	1.4 (1.0, 2.1)	1.6 (1.1, 2.3)	1.4 (0.9, 1.9)	1.7 (1.2, 2.4)	0.03
Men						
No. of cases	31	50	54	45	70	
Person-years of follow-up	92,680	94,678	98,612	103,635	102,095	
RR (95% CI)	1.0§	1.4 (0.9, 2.2)	1.5 (1.0, 2.4)	1.2 (0.7, 1.9)	1.8 (1.2, 2.9)	0.02
Women						
No. of cases	18	28	33	31	28	
Person-years of follow-up	127,945	126,838	123,318	119,514	118,090	
RR (95% CI)	1.0§	1.4 (0.8, 2.6)	1.8 (1.0, 3.1)	1.7 (0.9, 3.0)	1.5 (0.8, 2.8)	0.5
Cheese (g/day)¶	0–1.7	1.8–4.9	5.0–9.4	9.7–19.6	>19.6	
All participants						
No. of cases	68	65	84	83	88	
Person-years of follow-up	216,829	223,837	213,424	233,543	219,773	
RR (95% CI)	1.0§	0.9 (0.7, 1.3)	1.3 (0.9, 1.8)	1.1 (0.8, 1.6)	1.3 (0.9, 1.8)	0.1
Men						
No. of cases	38	35	65	52	60	
Person-years of follow-up	88,678	87,742	93,008	109,826	112,446	
RR (95% CI)	1.0§	0.9 (0.6, 1.4)	1.6 (1.1, 2.4)	1.1 (0.7, 1.7)	1.2 (0.8, 1.9)	0.5

Table continues

four cardinal signs (as defined above), with one being rest tremor or bradykinesia, along with a progressive course and the absence of unresponsiveness to levodopa or other features suggesting an alternative diagnosis. The review of medical records was conducted by our movement disorder specialist (M. A. S.), who was blind to exposure status.

A total of 840 participants reported having received a diagnosis of Parkinson's disease at any time in the past, and 677 (81 percent) provided informed consent for contacting their treating neurologists. A completed diagnostic questionnaire or medical record was obtained from 648 (96 percent) patients, and 588 (91 percent) diagnoses were confirmed. After further excluding 175 cases with onset before 1992 and 25 participants with missing information on dietary intake, we finally included 388 confirmed cases of incident Parkinson's disease in the analysis. With the exception of age and educational level, these 388 cases were not significantly different from those that were not included in the

TABLE 2. Continued

	Quintile of dairy product intake					*p* for trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Women						
No. of cases	30	30	19	31	28	
Person-years of follow-up	128,150	136,094	120,417	123,717	107,327	
RR (95% CI)	1.0§	1.0 (0.6, 1.6)	0.7 (0.4, 1.3)	1.3 (0.7, 2.1)	1.3 (0.8, 2.3)	0.1
Yogurt (g/day)¶	0	4.0–14.7	14.8–35.4	35.5–92.9	>92.9	
All participants						
No. of cases	171	76	44	55	42	
Person-years of follow-up	476,919	160,036	153,863	155,688	160,900	
RR (95% CI)	1.0§	1.3 (1.0, 1.8)	0.9 (0.7, 1.3)	1.1 (0.8, 1.4)	0.9 (0.6, 1.3)	0.4
Men						
No. of cases	127	41	27	33	22	
Person-years of follow-up	261,438	63,325	55,505	62,106	49,325	
RR (95% CI)	1.0§	1.2 (0.8, 1.7)	1.0 (0.7, 1.5)	1.1 (0.7, 1.5)	0.9 (0.6, 1.4)	0.7
Women						
No. of cases	44	35	17	22	20	
Person-years of follow-up	215,481	96,711	98,358	93,581	111,575	
RR (95% CI)	1.0§	1.7 (1.1, 2.6)	0.9 (0.5, 1.6)	1.1 (0.7, 1.8)	1.0 (0.6, 1.6)	0.5
Ice cream (g/day)¶	0	1.4–6.4	6.7–12.9	15–30.9	>35	
All participants						
No. of cases	90	67	71	95	65	
Person-years of follow-up	328,560	198,273	196,897	213,427	170,248	
RR (95% CI)	1.0§	1.2 (0.9, 1.7)	1.3 (0.9, 1.7)	1.4 (1.0, 1.8)	1.1 (0.8, 1.5)	0.9
Men						
No. of cases	43	35	43	74	55	
Person-years of follow-up	120,008	69,626	70,086	125,648	106,333	
RR (95% CI)	1.0§	1.4 (0.9, 2.2)	1.7 (1.1, 2.5)	1.6 (1.1, 2.3)	1.4 (0.9, 2.1)	0.5
Women						
No. of cases	47	32	28	21	10	
Person-years of follow-up	208,552	128,647	126,811	87,779	63,916	
RR (95% CI)	1.0§	1.1 (0.7, 1.7)	0.9 (0.5, 1.4)	1.1 (0.7, 1.9)	0.7 (0.3, 1.4)	0.4

* Adjusted for baseline age, sex, smoking, energy intake, ibuprofen use, vigorous physical activity, educational level, and pesticide use reported in 1982.

† Numbers of person-years may not sum to the total number of person-years (1,107,406) because of differences in rounding.

‡ RR, relative risk; CI, confidence interval.

§ Reference category.

¶ Approximate serving sizes included 240 g/cup for milk and yogurt, 52 g for 2 ounces of cheese, and 78 g for ½ cup of ice cream.

analyses. Overall, 67.6 percent of the cases in the cohort were confirmed by the treating neurologists (55.0 percent) or movement disorder specialists (12.6 percent), 21.1 percent were confirmed by review of the medical records, and 11.4 percent were confirmed by the treating internists or family physicians.

Dietary assessment

Diet was assessed at baseline using a 68-item semiquantitative food frequency questionnaire that was modified from the brief Health Habits and History Questionnaire developed by Block et al. (10). This questionnaire asked about portion size (small, medium, or large) and frequency of consumption of individual food items, with nine possible response categories ranging from "never or less than once/month" to "2+ times/day" for foods and to "6+ times/day" for beverages. Dietary intakes of nutrients were calculated using the Diet Analysis System, version 3.8a (National Cancer Institute, Bethesda, Maryland). The questionnaire also asked about the frequencies and doses of common vitamin supplements used during the past year, including

multiple vitamins and calcium. Use of individual vitamin D supplements was rare and thus was not included in the questionnaire. Total intake of calcium was calculated from intakes of foods, multivitamins, and calcium supplements, while intake of vitamin D was calculated from foods and multivitamins.

Individual dairy foods listed on the questionnaire included whole milk, low-fat milk, skim milk, cheese, low-fat yogurt, regular yogurt, and ice cream. In addition, we estimated additional cheese intake from reported intake of pizza, assuming that cheese constituted 16 percent of the weight of the pizza. Intakes of individual dairy items, in grams, were summed to obtain total daily intake of dairy products.

The food frequency questionnaire used in the current study was validated in a subgroup of 441 participants against four random 24-hour dietary recalls completed over a 1-year period (11). After controlling for day-to-day variation in 24-hour recalls, the energy-adjusted correlations between intakes of foods/nutrients assessed by these two methods were 0.72 and 0.63 (men and women) for dairy products, 0.57 and 0.66 for calcium, 0.58 and 0.66 for fat, and 0.29 and 0.33 for protein (11). Intakes of dairy products and associated nutrients assessed in this cohort have been linked to risks of colorectal (12) and prostate (13) cancer in directions that were consistent with the biologic hypotheses.

Statistical analyses

Intakes of calcium and vitamin D were adjusted for energy intake, using the residual method (14). Intakes of protein and fat were expressed as percentage of energy. Nutrient intakes were further classified according to their sources: dairy products, other foods, or supplements. For most foods and nutrients, we categorized intake into quintiles according to the intake distribution in the overall cohort. For yogurt and ice cream, persons who never ate those foods were grouped in the lowest intake category and the rest of the participants were categorized into quartiles. We categorized supplement intakes according to their distributions, calcium into four categories (0, 1–130, 131–620, or >620 mg/day), and vitamin D into three categories (0, 1–399, or ≥400 IU/day). In each analysis, the lowest intake category was used as the reference group.

Relative risks and 95 percent confidence intervals were calculated from Cox proportional hazards models, with adjustment for baseline age, sex, smoking status (never, past, or current smoker (1–14, 15–24, or ≥25 cigarettes/day)), energy intake (quintiles), vigorous physical activity (quintiles), educational level (below high school, high school, post-high school, college graduation, or graduate school), and pesticide exposure (yes/no), which was reported in the 1982 Cancer Prevention Study II survey. The statistical significance of a linear trend was tested by including the median value of each category as a continuous variable in the Cox models. Stratified analyses were further conducted according to sex, baseline age (<65 years or ≥65 years), and smoking status (never smoker or ever smoker). To reduce the potential bias attributable to dietary changes caused by early and unrecognized symptoms of Parkinson's disease, we performed lag analyses by excluding the first 2 years of follow-up.

Finally, we conducted a meta-analysis by pooling the results of all three prospective studies (including the Health Professionals Follow-up Study and Nurses' Health Study cohorts, the Honolulu-Asia Aging Study cohort, and the current cohort). Statistical testing showed no heterogeneity among risk estimates from the different cohorts. We calculated overall and gender-specific summary relative risks comparing the highest dairy consumption categories with the lowest using a fixed-effects model, by averaging the natural logarithms of the relative risks from individual studies, weighted by the inverses of their variances. We performed the meta-analysis using Stata software, version 7.0 (Stata Corporation, College Station, Texas). All other analyses were conducted with SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 provides the age-adjusted baseline characteristics of the study population according to quintile of dairy product consumption. Compared with persons with low dairy consumption, those with higher intakes had proportionally more men and fewer smokers. They were also more likely to report higher education, higher energy intakes, more vigorous physical activity, and ibuprofen use at baseline and pesticide exposure in 1982.

During 1,107,406 person-years of follow-up, we identified 250 incident cases of Parkinson's disease in men and 138 cases in women. Among men and women combined, total consumption of dairy products was positively associated with Parkinson's disease risk (table 2). A linear trend was evident in men, whereas in women the risk increased between the first and second quintiles but the linear trend was not statistically significant. Of the four individual dairy items, only milk intake was significantly associated with a higher risk of Parkinson's disease (table 2). Similar findings were observed in analyses excluding the first 2 years of follow-up (71 cases were excluded): The relative risk comparing the highest intake category with the lowest was 1.5 (95 percent CI: 1.0, 2.3; p for trend = 0.07) for total dairy product consumption and 1.7 (95 percent CI: 1.2, 2.5; p for trend = 0.03) for milk consumption. No significant differences across subgroups were found in analyses stratified by baseline age and smoking status. For overall dairy products, the relative risks for the associations between extreme quintiles were 1.6 (95 percent CI: 0.9, 2.7) for participants younger than age 65 years and 1.5 (95 percent CI: 0.9, 2.5) for participants aged 65 years or older; risks were 1.6 for never smokers (95 percent CI: 0.9, 2.6) and 1.4 (95 percent CI: 0.9, 2.4) for ever smokers. The corresponding relative risks for milk consumption were 2.0 (95 percent CI: 1.2, 3.3) for younger participants, 1.5 (95 percent CI: 0.9, 2.4) for older participants, 1.6 (95 percent CI: 1.0, 2.7) for never smokers, and 1.7 (95 percent CI: 1.0, 2.8) for ever smokers.

In nutrient analyses, total intakes of calcium and protein (from all sources) were associated with a higher risk of Parkinson's disease (table 3), but these associations were stronger for calcium and protein from dairy sources than from nondairy sources. In contrast, intake of calcium supplements was not associated with Parkinson's disease

TABLE 3. Relative risk* of Parkinson's disease according to baseline intakes of nutrients from dairy products or other sources, Cancer Prevention Study II Nutrition Cohort, 1992–2001

	Quintile of dairy product intake					*p* for trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Calcium (mg/day)						
Total intake	82.1–558.0	558.1–727.7	727.8–921.4	921.5–1,252.2	>1,252.2	
No. of cases	50	76	88	79	95	
RR† (95% CI†)	1.0‡	1.3 (0.9, 1.9)	1.4 (1.0, 2.0)	1.3 (0.9, 1.8)	1.6 (1.1, 2.3)	0.02
From dairy products	0–258.3	258.3–394.1	394.1–539.6	539.6–756.9	>756.9	
No. of cases	54	74	81	89	90	
RR (95% CI)	1.0‡	1.3 (0.9, 1.8)	1.3 (0.9, 1.9)	1.4 (1.0, 2.0)	1.3 (0.9, 1.9)	0.2
From other sources	37.2–203.5	203.5–252.4	252.4–316.3	316.3–465.1	>465.1	
No. of cases	64	78	101	68	77	
RR (95% CI)	1.0‡	0.9 (0.7, 1.3)	1.1 (0.8, 1.5)	0.7 (0.5, 1.0)	1.1 (0.8, 1.5)	0.6
Vitamin D (IU/day)						
Total intake	0–110.3	110.4–172.8	172.9–287.4	287.5–527.7	>527.7	
No. of cases	55	93	88	79	73	
RR (95% CI)	1.0‡	1.5 (1.0, 2.0)	1.3 (0.9, 1.9)	1.3 (0.9, 1.8)	1.1 (0.8, 1.6)	0.6
From dairy products	0–39.2	39.2–71.3	71.3–112.7	112.7–175.0	>175.0	
No. of cases	40	87	81	89	91	
RR (95% CI)	1.0‡	2.0 (1.4, 2.9)	1.8 (1.2, 2.7)	1.9 (1.3, 2.8)	1.8 (1.3, 2.7)	0.06
From other sources	0–41.2	41.2–61.2	61.2–92.8	92.8–419.8	>419.8	
No. of cases	76	68	106	68	70	
RR (95% CI)	1.0‡	0.8 (0.6, 1.1)	1.1 (0.8, 1.4)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.08
Protein (% of daily energy)						
Total intake	3.3–13.7	13.8–15.4	15.5–16.9	17.0–18.9	>18.9	
No. of cases	63	80	77	75	93	
RR (95% CI)	1.0‡	1.2 (0.9, 1.7)	1.2 (0.8, 1.6)	1.2 (0.8, 1.6)	1.6 (1.1, 2.2)	0.01
From dairy products	0–2.1	2.1–3.2	3.2–4.3	4.3–6.0	>6.0	
No. of cases	71	70	92	62	93	
RR (95% CI)	1.0‡	0.9 (0.7, 1.3)	1.3 (0.9, 1.7)	0.9 (0.6, 1.2)	1.3 (1.0, 1.8)	0.09
From other sources	1.0–9.8	9.8–11.2	11.2–12.6	12.6–14.3	>14.3	
No. of cases	70	82	84	71	81	
RR (95% CI)	1.0‡	1.1 (0.8, 1.6)	1.2 (0.8, 1.6)	1.0 (0.7, 1.4)	1.2 (0.9, 1.7)	0.5
Fat (% of daily energy)						
Total intake	4.2–26.6	26.7–32.5	32.6–37.3	37.4–42.4	>42.4	
No. of cases	77	88	95	66	62	
RR (95% CI)	1.0‡	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	0.8 (0.6, 1.2)	0.8 (0.6, 1.2)	0.1
From dairy products	0–2.0	2.0–3.5	3.5–5.4	5.4–8.6	>8.6	
No. of cases	77	70	86	82	73	
RR (95% CI)	1.0‡	0.9 (0.6, 1.2)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.0 (0.7, 1.3)	0.9
From other sources	0.3–21.9	21.9–26.7	26.7–30.9	30.9–35.8	>35.8	
No. of cases	75	89	98	74	52	
RR (95% CI)	1.0‡	1.1 (0.8, 1.6)	1.2 (0.9, 1.7)	0.9 (0.7, 1.3)	0.7 (0.5, 1.0)	0.04

* Adjusted for baseline age, sex, smoking, energy intake, ibuprofen use, vigorous physical activity, educational level, and pesticide use reported in 1982.

† RR, relative risk; CI, confidence interval.

‡ Reference category.

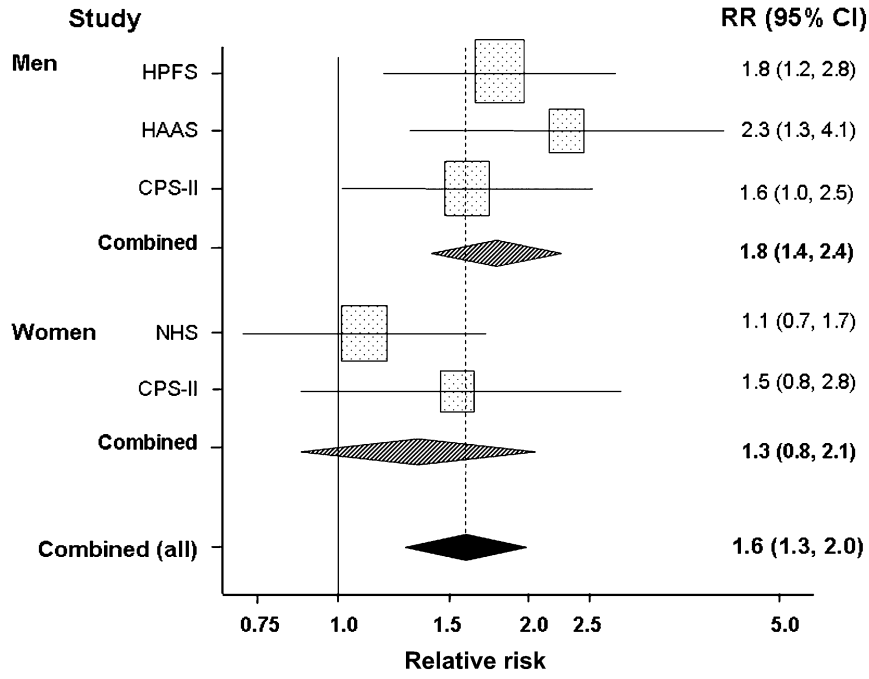

FIGURE 1. Results of a meta-analysis of data from all prospective studies on dairy product/milk consumption and risk of Parkinson's disease in men and women. Relative risks (RRs) and 95% confidence intervals (CIs) compare the highest intake category with the lowest. Squares indicate the individual RR in each study. The size of each square is proportional to the percent weight of that individual study in the meta-analysis, and the horizontal line represents the 95 percent CI. Pooled RRs and 95 percent CIs are indicated by the shaded diamonds. The pooled RRs were statistically significant ($p < 0.001$) for men and for the combined analysis. HPFS, Health Professionals Follow-up Study (men only); HAAS, Honolulu-Asia Aging Study (men only); CPS-II, Cancer Prevention Study II Nutrition Cohort; NHS, Nurses' Health Study (women only).

risk: Compared with persons who did not take supplemental calcium, the multivariate relative risks were 0.7 for users of 1–130 mg/day, 1.0 for users of 131–620 mg/day, and 1.2 (95 percent CI: 0.9, 1.7; p for trend = 0.2) for users of more than 620 mg/day. Furthermore, supplemental intake of vitamin D was associated with a lower risk of Parkinson's disease; the corresponding relative risks for persons with intakes of 1–399 IU/day and ≥400 IU/day as compared with nonusers were 0.7 and 0.8 (95 percent CI: 0.6, 1.0; p for trend = 0.03), respectively. Further analyses with the same nutrients from different sources simultaneously adjusted in the same analytic model confirmed that only nutrients from dairy products, except for dairy fat, tended to be positively associated with Parkinson's disease risk (data not shown). Energy intake was not related to Parkinson's disease risk in this study population (data not shown).

To date, three prospective studies have evaluated consumption of dairy products or milk in relation to Parkinson's disease. These studies varied in sample size, population composition, length of follow-up, and methods of dietary assessment and case identification. Despite these differences, a meta-analysis of the results of these studies clearly demonstrated that higher dairy/milk consumption was associated with a moderately increased risk of Parkinson's disease, particularly in men. The combined relative risks for extreme intake categories were 1.6 (95 percent CI: 1.3, 2.0; $p < 0.001$) for men and women combined, 1.8 (95 percent CI: 1.4, 2.4; $p < 0.001$) for men, and 1.3 (95 percent CI: 0.8, 2.1; $p = 0.3$) for women (figure 1).

DISCUSSION

In this large observational study, we found that higher consumption of dairy products was associated with increased risk of Parkinson's disease. The association was stronger in men and was mostly explained by milk consumption. Because this investigation was based on a prospective cohort study with a long follow-up period and validated dietary assessment, recall and selection biases are unlikely to be the explanation for our findings. Reverse causality or confounding by known Parkinson's disease risk factors such as age and smoking is also not very likely, because the association remained after exclusion of the first 2 years of follow-up or adjustment for relevant covariates. However, potential confounding by unmeasured factors, such as a lack of a novelty-seeking personality (15), could not be excluded. Another potential limitation of the current study is that we were unable to physically examine individual Parkinson's disease patients and had to rely on the diagnoses made by treating neurologists for case confirmation. Although a few misdiagnoses are likely, recent clinicopathologic studies revealed that 90 percent of neurologist-diagnosed Parkinson's disease cases could be confirmed at autopsy (16). Furthermore, any diagnostic error would probably have attenuated

the association between dairy food intake and Parkinson's disease, because case identification was most likely independent of the dietary assessment.

The findings of the present study are consistent with those from two previous prospective investigations. In the first study (5), men in the highest category of dairy consumption had an 80 percent higher risk than men in the lowest category; among women, the results showed a slightly inverse U-shaped association, with higher risk among women with moderate dairy consumption. In the second study (7), a study of Japanese-American men in Honolulu, Hawaii, men who consumed more than 16 ounces (0.5 liters) of milk per day had a 130 percent higher risk of Parkinson's disease than men who did not drink milk.

In all studies, the results could not be attributed to measured levels of dairy-associated nutrients such as calcium. A pooled analysis of data from the current study with data from the previous ones confirmed a moderate positive association between dairy food consumption and risk of Parkinson's disease, particularly in men. In both the current study and previous investigations, the relation was less clear in women than in men. Among women in the Nurses' Health Study, the relative risks for dairy intake quartiles were 1.0 (referent), 1.3, 1.3, and 1.1, with a p value for linear trend of 0.9. In the current study, on the other hand, Parkinson's disease risk among women increased approximately 60 percent at the second dairy consumption quintile and tended to remain at that level for higher consumption categories. However, both analyses were based on a relatively small number of cases; a prospective study with more female cases is needed to better evaluate this relation in women.

So far, the epidemiologic evidence suggests that the association between dairy products and Parkinson's disease is unlikely to be due to calcium, vitamin D, or fat. All three studies generally found that calcium and vitamin D were positively associated with Parkinson's disease risk only when they were derived from dairy foods, and fat from either dairy foods or other sources was not related to increased Parkinson's disease risk. Furthermore, neither calcium nor vitamin D from supplements was significantly related to increased risk of Parkinson's disease.

The observation of similar findings on dairy products and Parkinson's disease risk in all three of these well-established prospective studies suggests that the association is unlikely to be fortuitous. One possibility is that dairy products in the United States are contaminated with neurotoxic chemicals. Substantial epidemiologic and experimental evidence suggests that exposure to pesticides may increase Parkinson's disease risk (17), and postmortem studies have found higher levels of organochlorines, polychlorinated biphenyls, and dieldrin in the brains of Parkinson's disease patients than in control brains (18, 19); some of these compounds are present at low levels in dairy products. Furthermore, chemicals that induce parkinsonism in rodents and primates (20, 21), such as tetrahydroisoquinolines (22) and precursors of β-carbolines, are present in a variety of dairy foods (23, 24). However, the overall contribution of dairy food consumption to exposure to pesticides and other neurotoxins is probably only modest. Another potential explanation for the positive association between dairy products and Parkinson's disease may involve the potential effects of dairy products on circulating levels of uric acid. Higher dairy food consumption has been related to lower circulating levels of uric acid and lower risk of gout (25–27). Uric acid has been hypothesized to be neuroprotective by preventing oxidative damage caused by reactive nitrogen and oxygen species, and higher plasma levels of uric acid have been prospectively linked to a lower risk of incident Parkinson's disease in two cohorts (28, 29). Because of the lack of experimental data, any potential explanation is speculative.

In summary, accumulating evidence from this study and previous prospective studies supports the hypothesis of a positive association between dairy food consumption and risk of Parkinson's disease, particularly in men. Future epidemiologic and experimental investigations are needed to further evaluate this association and to ascertain the underlying mechanisms.

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