

# Adult nutrient intake as a risk factor for Parkinson's disease

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<b>Background</b>	This population-based case-control study evaluated nutrient intake as a risk factor for Parkinson's disease (PD) among people aged $\geq 50$ years in metropolitan Detroit.
<b>Methods</b>	Cases (n = 126) were diagnosed between 1991 and 1995 and neurologist-confirmed. Controls (n = 432) were frequency-matched for sex, age ( $\pm 5$ years) and race. Using a standardized food frequency questionnaire, subjects reported the foods they ate within the past year.
<b>Results</b>	Estimating the association between PD and risk of being in the highest versus the lowest intake quartile, there were elevated odds ratios for total fat (OR 1.94, 95% confidence interval [CI] : 1.05–3.58), cholesterol (OR 2.11, 95% CI : 1.14–3.90), lutein (OR 2.52, 95% CI : 1.32–4.84) and iron (OR 1.88, 95% CI : 1.05–3.38).
<b>Conclusions</b>	These results suggest an association of PD with high intake of total fat, saturated fats, cholesterol, lutein and iron.
<b>Keywords</b>	Carotenoids, case-control study, diet, Parkinson's disease, risk factors
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While dietary constituents have been systematically explored as risk factors in relationship to the major chronic illnesses, there have been few such studies with regard to Parkinson's disease (PD). A number of studies have focused on the consumption of selected vitamin E-rich foods or supplements as a protection against PD, with equivocal results.<sup>1–8</sup> Only four studies have used standardized food frequency questionnaires that allow the summarization of nutrient intake across foods.<sup>9–12</sup> None of the latter group found an inverse association with vitamin E, although positive associations were found between PD and increased intake of vitamin A and retinol,<sup>9</sup> calories and animal fats,<sup>10</sup> and vitamin C and carotenoids.<sup>12</sup> Protective associations were reported for vitamin C and manganese in one of these studies,<sup>9</sup> and vitamin C and beta-carotene in another.<sup>11</sup> As part of a large case-control study focusing on occupational risk factors for PD, we collected food intake data using a standardized food frequency questionnaire.<sup>13</sup> The objective of our analysis was to evaluate nutrient components and their association with PD.

## Materials and Methods

### Study population

The selection of our study subjects has also been described elsewhere.<sup>14</sup> Cases and controls were drawn from a population base consisting of all individuals residing in the urban and suburban tri-county metropolitan Detroit area who were receiving primary medical care from the Henry Ford Health System (HFHS). HFHS is a large, vertically integrated health care network that provides primary and specialty care for 15–30%, depending on geographical location, of the approximately 4 000 000 people living in southeastern Michigan. The population served by HFHS includes urban and suburban residents who are members of various age, racial and socioeconomic groups. An age-race comparison of the 1993 HFHS outpatient population with that of the 1990 Detroit metropolitan area, based on the then-current US census, showed similar percentages ( $\pm 1\%$ ) in each race-specific 10-year age stratum in the third through eighth decades of life. HFHS includes a central campus in the city of Detroit that has a major hospital and a large complex of primary and specialty care outpatient clinics. The System also comprises over 30 satellite clinics and community hospitals throughout the metropolitan area.

HFHS databases were used to select subjects 50 years of age or older who had at least one visit to a primary care physician (i.e. in internal medicine, gerontology, family practice, or gynaecology) within 5 years prior to the time of enrolment. This criterion was adopted to assure that all enrolled subjects were active members of the HFHS population base. Controls and cases were selected concurrently from this base population

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of 239 722 individuals who had one or more medical clinic visits to the HFHS between 1 January 1988 and 1 August 1992. A total of 894 individuals were identified who had been given ICD-9 code 332.0 for idiopathic PD during one or more clinic visits between 1 April 1991 and 31 July 1995 and were in the base population. Before further medical evaluation was done, 29 were determined to be ineligible because they had moved ( $n = 7$ ) or died ( $n = 22$ ). Among these potential cases, 274 did not meet eligibility criteria due to the presence of secondary causes of parkinsonism, lacked a clear diagnosis of PD, or had another neurologic disorder. Another 96 potential cases were excluded because their onset of symptoms would be more than 10 years prior to interview, raising concerns about the possible introduction of survival bias. Based on inability to provide a reliable interview (history of dementia, non-English speaker, medically unable, etc.) another 263 cases were excluded, leaving 232 eligible to recruit.

Potential controls were selected to represent a stratified, random sample of approximately three controls for each potential case based on the case distribution in 32 sex, race (white versus non-white) and 5-year age strata (50–54, 55–59...85+ years), resulting in an initial sample of 1486 individuals who also received regular primary care at HFHS. Of these, 516 were excluded due to leaving the area ( $n = 84$ ), death ( $n = 156$ ), presence of a neurologic disorder ( $n = 44$ ), complicating medical reasons ( $n = 119$ ) and inability to provide an interview ( $n = 113$ ), leaving 970 individuals eligible for recruitment as controls.

Potential subjects were sent a recruitment letter inviting them to participate in the study, followed by a phone contact within 2 weeks. Controls were screened for potential PD with a telephone administered version of a 10-item questionnaire that has been shown to have 92% specificity for correctly identifying individuals without PD in a population with a similar age distribution;<sup>15</sup> 31 potential controls failed the screen and were excluded. We were unable to contact 149 controls and 4 cases. Of those contacted and deemed eligible, 184 cases (80.7%) and 504 controls (63.8%) consented to participate in the study. A comparison of respondents and non-respondents among cases and controls showed that case respondents were significantly younger than case non-respondents by 6 years and more likely to be men (60% versus 45.5%). There were no age differences between control respondents and non-respondents, but a higher percentage of control respondents were men compared with non-responding controls (63.5% versus 56.6%).

Before subjects were interviewed, they were given a face-to-face Mini-Mental State Examination<sup>16</sup> (MMSE) to screen for cognitive impairment; the 21 cases and 40 controls who failed (score <24) were also excluded. All cases fulfilled diagnostic criteria for PD, as documented by a neurologist; 19 potential cases were excluded after neurologic examination.<sup>14</sup>

### Data collected

The reduced version of the Block food frequency questionnaire<sup>13,17</sup> was used to assess usual dietary intake. The nutrient database used to convert food frequency information into nutrients was developed using dietary data from adult respondents to the Second National Health and Nutrition Examination Survey.<sup>18</sup> The reduced version consists of 60 food items, with questions on usual use (from 'rarely/never' to a 'per day' amount) and portion size (small, medium, or large, compared to a

standard medium portion size). The final section consists of three questions inquiring about usual intake of fruits and vegetables, and use of fat in cooking, that are used to reduce measurement bias related to overreporting of total food consumption.

The questionnaires were mailed to participants for self-completion and then reviewed with an interviewer as part of subsequent face-to-face interviews. Data from each questionnaire were entered, and error conditions generated by the software (e.g. indications that a subject's caloric intake was abnormally high or low) were evaluated by a registered dietitian (KS). The 31 subjects with such errors were recontacted to obtain usable information; all questions were resolved so that their data could be included in the analyses.

### Statistical methods

The relationship of PD and exposure to individual nutrient categories was first evaluated. Continuous measures of daily intake estimates for each category were transformed into ordinal measures of daily intake based on the quartile distribution of the control group's daily intake. Data were described using the median and range, with the range summing from the 5th to the 95th percentile. Wilcoxon two-sample rank sum tests were used to compare cases to controls with respect to nutritional values.

A linear logistic model was estimated using three indicator variables for the quartile of the range in which a nutrient value fell. The first quartile, or lowest level of intake, was the reference. Odds ratios (OR) and their associated 95% confidence intervals (CI) and *P*-values were computed. This model allowed the OR to be non-linear. The models adjusted for age, gender, race and smoking status. A fifth variable, either body mass index (BMI) or total kilocalories of intake (TKcal) was used to adjust nutrient intake for overall food intake. BMI was used as well as TKcal as the latter estimate from the short version of the Block questionnaire is not considered particularly useful as an absolute measure of intake.<sup>13</sup> For selected nutrients, a logistic regression test for trend was used to evaluate the ordinal variable identifying the quartile of the data, based on the control distribution, in which a nutrient value fell. Statistical significance implied consistency with a linear trend in the OR over the quartiles. Finally, the models were re-estimated using only cases with symptom duration of a year or less prior to interview, which decreased the sample size but allowed for an evaluation of intake less influenced by disease progression. An alpha level of 0.05 was used for significance testing.

### Results

A total of 144 cases and 464 controls were enrolled. Of these, 126 cases (87.5%) and 432 controls (93.1%) completed the food frequency questionnaire. Those completing the questionnaire were similar to non-compliers in age, gender, education, cigarette smoking history, usual adult weight, Mini-Mental State score, and years since symptoms began for cases. However, African Americans were less likely to provide food intake data (83% participation versus 93% in Caucasians;  $P < 0.001$ ). Comparing subjects with nutrient data, cases were similar to controls in terms of age, gender, race, education and BMI (Table 1).

Table 2 describes the estimated intake of total energy and macronutrient categories by case-control status. There was little

**Table 1** Distribution of 126 cases of Parkinson's disease (PD) and 432 controls by age, gender, race, education, and body mass index

	PD Cases No. (%)	Controls No. (%)
<b>Age (years)</b>		
50–59	9 (7.1)	43 (10.0)
60–69	40 (31.8)	130 (30.0)
70–79	60 (47.6)	188 (43.6)
80+	17 (13.5)	71 (16.4)
<b>Gender</b>		
Male	78 (61.9)	271 (62.7)
Female	48 (38.1)	161 (37.3)
<b>Race</b>		
White and other	106 (84.1)	373 (86.3)
Black	20 (15.9)	59 (13.7)
<b>Education</b>		
<8	5 (4.0)	13 (3.0)
High school	60 (47.6)	214 (49.5)
High school +	61 (48.4)	205 (47.5)
<b>Body mass index</b>	25.7 ± 3.9	26.7 ± 4.5

difference, except for total fat consumption, although the case intake levels were generally greater than control levels. Micronutrient levels were higher across the board for cases (Table 3). There were no statistical differences between cases and controls in the intake of vitamin E, vitamin C, vitamin A or beta-carotene. There were statistically significant or borderline significant differences between the medians for saturated fat intake ( $P < 0.068$ ), cholesterol ( $P < 0.025$ ), lutein ( $P < 0.008$ ), riboflavin ( $P < 0.073$ ) and iron ( $P < 0.068$ ).

Comparing people with the highest nutrient intake (quartile 4) versus the reference category (quartile 1) and adjusting for BMI in Table 4, there were weak positive associations of PD with vitamin E (OR 1.25, 95% CI: 0.71–2.22), vitamin C (OR 1.37, 95% CI: 0.75–2.50), vitamin A (OR 1.31, 95% CI: 0.75–2.30) and beta-carotene (OR 1.24, 95% CI: 0.70–2.21). Adjusting instead for TKcal resulted in associations closer to the null. Statistically significant increased OR, adjusted for BMI, were detected for total fat (OR 1.94, 95% CI: 1.05–3.58), cholesterol

(OR 2.11, 95% CI: 1.14–3.90), lutein (OR 2.52, 95% CI: 1.32–4.84), and iron (OR 1.88, 95% CI: 1.05–3.38). Since the volume of the central nervous system is uncorrelated with body size, this analysis was repeated without an adjustment for BMI, with little change in the results. Adjusting instead for TKcal, the OR for total fat, cholesterol, lutein and iron were similar in magnitude and direction, although only lutein maintained a statistically significant increased risk estimate.

Testing for a trend of an increased risk with increased intake, statistically significant or borderline associations were found for lutein ( $P < 0.003$  and  $P < 0.009$ ) and cholesterol ( $P < 0.012$  and  $P < 0.069$ ), adjusting for BMI and TKcal, respectively. The model adjusting for BMI yielded statistically significant trends for total fat ( $P < 0.019$ ) and iron ( $P < 0.037$ ), but not when adjusting for TKcal ( $P < 0.113$  and  $P < 0.173$ , respectively).

The data were reanalysed excluding the 65 cases whose duration of symptoms was longer than a year at time of interview. The OR and  $P$ -values, adjusted for BMI and TKcal, respectively, were as follows: total fat (OR 1.71,  $P < 0.241$ ; OR 1.48,  $P < 0.554$ ), cholesterol (OR 1.58,  $P < 0.273$ ; OR 1.39,  $P < 0.507$ ), lutein (OR 4.25,  $P < 0.004$ ; OR 4.15,  $P < 0.005$ ), and iron (OR 2.0,  $P < 0.069$ ; OR 2.33,  $P < 0.089$ ). Tests for linear trend were significant for lutein at  $P < 0.001$  adjusted for BMI, and  $P < 0.002$  adjusted for TKcal.

## Discussion

Initial investigations of dietary factors and PD focused on antioxidant intake, particularly vitamin E, as potentially protective. These studies utilized lists of selected food items rather than estimating summary nutrient intake. Golbe *et al.*<sup>1</sup> reported that, of a list of 17 food items, nuts, salad oil and plums, all with a high vitamin E content, were more commonly consumed by sibling controls. Tanner *et al.*<sup>2</sup> reported findings from a small study showing that controls were more likely than PD cases to have used vitamin E supplements or cod liver oil during early life, although further work by these investigators in the US and China was not supportive.<sup>3</sup> Golbe *et al.*<sup>4</sup> conducted a second study focusing on vitamin E-rich foods using a list of 31 food items administered to 106 PD subjects and spouse controls, which confirmed their earlier work. A German study<sup>5</sup> of 71 PD patients and 103 controls with other neurologic conditions examining a few selected food preferences found no difference

**Table 2** Median and range<sup>a</sup> of daily intake of energy and macronutrient categories in 126 cases of Parkinson's disease (PD) and 432 controls identified in the Henry Ford Health System from 1988–1995

Nutrient	PD Cases		Controls		P-value <sup>b</sup>
	Median	Range	Median	Range	
<b>Energy (total kcal)</b>	1491	(689–2707)	1389	(708–2611)	0.105
<b>Fibre</b>					
Bean (g)	0.76	(0–4.25)	0.88	(0.02–4.26)	0.236
Grain (g)	4.03	(1.18–8.36)	3.83	(1.19–9.32)	0.379
Vegetables and fruit (g)	6.41	(2.71–14.18)	5.89	(1.96–12.72)	0.301
<b>Total fat (g)</b>	61.3	(20.4–117.2)	55	(22.2–111.3)	0.056
<b>Protein (g)</b>	61.6	(28.7–110.2)	57.9	(29.3–109.4)	0.244
<b>Carbohydrates (g)</b>	169	(86–315)	163	(80–309)	0.285

<sup>a</sup> Range runs from 5th to 95th percentile.

<sup>b</sup>  $P$ -value from Wilcoxon test.

**Table 3** Median and range<sup>a</sup> of daily intake of selected micronutrients in 126 cases of Parkinson's disease (PD) and 432 controls identified in the Henry Ford Health System from 1988–1995

Nutrient	PD Cases		Controls		P-value <sup>b</sup>
	Median	Range	Median	Range	
Saturated fats (g)	20.1	(6.6–42.7)	18.2	(6.5–40.1)	0.068
Oleic acid (g)	21.8	(6.8–43.5)	19.3	(7.4–41.0)	0.102
Linoleic acid (g)	11.5	(3.5–24.5)	10.5	(3.6–24.3)	0.274
Cholesterol (mg)	236	(78–531)	196	(74–554)	0.025
Vitamin A (IU)	7656	(2835–22 055)	7113	(2700–17 208)	0.176
Beta-carotene (mcg)	2852	(900–9763)	2542	(774–8232)	0.24
Lutein (mcg)	1368	(402–7054)	1087	(228–6941)	0.008
Thiamin (vitamin B <sub>1</sub> ) (mg)	1.37	(0.56–2.26)	1.26	(0.54–2.42)	0.157
Riboflavin (vitamin B <sub>2</sub> ) (mg)	1.86	(0.71–3.21)	1.57	(0.66–3.46)	0.073
Niacin (vitamin B <sub>3</sub> ) (mg)	16.4	(6.4–30.0)	14.8	(6.4–31.4)	0.208
Vitamin B <sub>6</sub> (mg)	1.59	(0.60–2.64)	1.39	(0.62–2.89)	0.095
Folate (mg)	295	(126–550)	265	(111–637)	0.155
Vitamin C (mg)	137	(51–303)	126	(42–300)	0.21
Vitamin E (mg)	9	(3.4–17.6)	7.8	(3.1–19.3)	0.247
Iron (mg)	11.6	(4.4–19.2)	10.1	(4.6–20.5)	0.068
Phosphorus (mg)	1049	(429–1866)	977	(463–1840)	0.159
Sodium (mg)	2455	(1062–4190)	2285	(1137–4581)	0.092
Potassium (mg)	2370	(1161–4181)	2273	(1095–4057)	0.266
Calcium (mg)	702	(304–1376)	679	(256–1492)	0.291

<sup>a</sup> Range runs from 5th to 95th percentile.

<sup>b</sup> P-value from Wilcoxon test.

**Table 4** Adjusted odds ratios and 95% confidence intervals (CI) of Parkinson's disease (PD) associated with the lowest quartile<sup>a</sup> daily intake of energy, macronutrients and selected micronutrients, among persons in the Henry Ford Health System from 1988–1995

Nutrient	Quartile	Model using BMI <sup>b</sup>			Model using Total Kcal <sup>c</sup>		
		Odds ratio	95% CI	P-value <sup>d</sup>	Odds ratio	95% CI	P-value <sup>d</sup>
Energy (total kcal)	Q <sub>2</sub>	0.90	0.49–1.65	0.725	–	–	–
	Q <sub>3</sub>	0.96	0.53–1.76	0.902	–	–	–
	Q <sub>4</sub>	1.62	0.90–2.92	0.111	–	–	–
Total fat (g)	Q <sub>2</sub>	1.08	0.57–2.02	0.816	1.14	0.59–2.22	0.694
	Q <sub>3</sub>	1.51	0.83–2.77	0.181	1.56	0.77–3.18	0.220
	Q <sub>4</sub>	1.94	1.05–3.58	0.034	2.02	0.79–5.18	0.143
Protein (g)	Q <sub>2</sub>	0.98	0.54–1.79	0.952	0.85	0.45–1.62	0.621
	Q <sub>3</sub>	1.18	0.64–2.16	0.599	0.91	0.45–1.87	0.805
	Q <sub>4</sub>	1.35	0.74–2.48	0.331	0.82	0.31–2.14	0.681
Carbohydrates(g)	Q <sub>2</sub>	1.07	0.59–1.93	0.837	0.94	0.50–1.77	0.854
	Q <sub>3</sub>	1.12	0.62–2.03	0.718	0.87	0.43–1.79	0.708
	Q <sub>4</sub>	1.38	0.76–2.49	0.287	0.81	0.31–2.15	0.678
Saturated fats (g)	Q <sub>2</sub>	1.16	0.63–2.12	0.636	1.16	0.62–2.17	0.651
	Q <sub>3</sub>	1.37	0.75–2.52	0.310	1.26	0.63–2.52	0.514
	Q <sub>4</sub>	1.77	0.97–3.23	0.063	1.53	0.64–3.67	0.340
Oleic acid (g)	Q <sub>2</sub>	0.66	0.35–1.26	0.208	0.69	0.35–1.36	0.282
	Q <sub>3</sub>	1.25	0.70–2.23	0.450	1.20	0.61–2.37	0.604
	Q <sub>4</sub>	1.64	0.91–2.95	0.102	1.50	0.62–3.64	0.371
Linoleic acid (g)	Q <sub>2</sub>	1.17	0.64–2.11	0.612	1.09	0.59–2.01	0.791
	Q <sub>3</sub>	1.23	0.68–2.22	0.500	1.00	0.52–1.93	0.998
	Q <sub>4</sub>	1.40	0.77–2.55	0.274	1.01	0.47–2.18	0.980
Cholesterol (mg)	Q <sub>2</sub>	1.24	0.65–2.35	0.511	1.22	0.64–2.33	0.551
	Q <sub>3</sub>	1.56	0.84–2.87	0.157	1.52	0.79–2.93	0.214
	Q <sub>4</sub>	2.11	1.14–3.90	0.017	1.93	0.92–4.07	0.082

Table 4 Continued

Nutrient	Quartile	Model using BMI <sup>b</sup>			Model using Total Kcal <sup>c</sup>		
		Odds ratio	95% CI	P-value <sup>d</sup>	Odds ratio	95% CI	P-value <sup>d</sup>
Vitamin A (IU)	Q <sub>2</sub>	1.01	0.56–1.83	0.973	0.96	0.53–1.74	0.901
	Q <sub>3</sub>	0.97	0.54–1.76	0.931	0.87	0.47–1.62	0.662
	Q <sub>4</sub>	1.31	0.75–2.30	0.345	1.15	0.62–2.11	0.661
Beta-carotene (mcg)	Q <sub>2</sub>	1.07	0.59–1.93	0.825	1.05	0.58–1.90	0.872
	Q <sub>3</sub>	1.10	0.61–1.99	0.747	1.05	0.58–1.90	0.872
	Q <sub>4</sub>	1.24	0.70–2.21	0.458	1.16	0.64–2.12	0.629
Lutein (mcg)	Q <sub>2</sub>	1.61	0.83–3.10	0.156	1.55	0.81–2.98	0.190
	Q <sub>3</sub>	2.15	1.14–4.07	0.019	1.98	1.04–3.76	0.037
	Q <sub>4</sub>	2.52	1.32–4.84	0.005	2.34	1.20–4.54	0.012
Vitamin B <sub>1</sub> (thiamin) (mg)	Q <sub>2</sub>	0.85	0.46–1.59	0.616	0.81	0.43–1.55	0.530
	Q <sub>3</sub>	1.03	0.56–1.90	0.913	0.96	0.49–1.89	0.912
	Q <sub>4</sub>	1.50	0.84–2.69	0.174	1.22	0.55–2.68	0.625
Vitamin B <sub>2</sub> (riboflavin) (mg)	Q <sub>2</sub>	0.82	0.44–1.52	0.525	0.89	0.48–1.67	0.719
	Q <sub>3</sub>	1.04	0.57–1.89	0.894	0.97	0.51–1.86	0.938
	Q <sub>4</sub>	1.52	0.87–2.65	0.142	1.39	0.69–2.82	0.359
Niacin (mg)	Q <sub>2</sub>	0.66	0.36–1.24	0.201	0.58	0.30–1.12	0.106
	Q <sub>3</sub>	0.98	0.54–1.77	0.938	1.30	0.68–2.49	0.437
	Q <sub>4</sub>	1.34	0.76–2.36	0.308	0.82	0.38–1.78	0.617
Vitamin B <sub>6</sub> (mg)	Q <sub>2</sub>	0.69	0.36–1.30	0.246	0.70	0.36–1.33	0.274
	Q <sub>3</sub>	0.86	0.47–1.58	0.625	0.86	0.45–1.66	0.660
	Q <sub>4</sub>	1.62	0.92–2.85	0.096	1.54	0.76–3.11	0.234
Folate (mcg)	Q <sub>2</sub>	0.78	0.42–1.44	0.426	0.75	0.40–1.40	0.365
	Q <sub>3</sub>	0.92	0.51–1.69	0.793	0.85	0.45–1.59	0.610
	Q <sub>4</sub>	1.44	0.82–2.52	0.204	1.23	0.64–2.35	0.535
Vitamin C/ascorbic acid (mg)	Q <sub>2</sub>	1.21	0.65–2.23	0.548	1.20	0.65–2.22	0.554
	Q <sub>3</sub>	1.56	0.87–2.81	0.136	1.44	0.80–2.59	0.228
	Q <sub>4</sub>	1.37	0.75–2.50	0.299	1.17	0.63–2.20	0.619
Vitamin E (alpha-tocopherol)	Q <sub>2</sub>	0.87	0.48–1.58	0.649	0.79	0.42–1.46	0.445
	Q <sub>3</sub>	1.13	0.63–2.03	0.687	0.95	0.50–1.82	0.886
	Q <sub>4</sub>	1.25	0.71–2.22	0.440	0.98	0.49–1.95	0.950
Calcium (mg)	Q <sub>2</sub>	1.55	0.86–2.79	0.145	1.45	0.80–2.65	0.225
	Q <sub>3</sub>	1.16	0.62–2.18	0.643	1.01	0.52–1.97	0.976
	Q <sub>4</sub>	1.54	0.85–2.81	0.158	1.13	0.54–2.34	0.750
Iron (mg)	Q <sub>2</sub>	1.12	0.60–2.07	0.721	1.12	0.60–2.11	0.720
	Q <sub>3</sub>	1.00	0.53–1.88	0.995	1.00	0.51–1.99	0.994
	Q <sub>4</sub>	1.88	1.05–3.38	0.034	1.83	0.85–3.93	0.124
Phosphorus (mg)	Q <sub>2</sub>	1.24	0.67–2.27	0.493	1.23	0.66–2.30	0.517
	Q <sub>3</sub>	1.18	0.63–2.19	0.609	1.12	0.56–2.24	0.747
	Q <sub>4</sub>	1.77	0.98–3.21	0.060	1.57	0.68–3.65	0.291
Potassium (mg)	Q <sub>2</sub>	0.80	0.45–1.44	0.454	0.70	0.38–1.30	0.261
	Q <sub>3</sub>	0.68	0.36–1.26	0.220	0.55	0.27–1.10	0.091
	Q <sub>4</sub>	1.24	0.71–2.18	0.446	0.83	0.37–1.86	0.648
Sodium (mg)	Q <sub>2</sub>	1.46	0.78–2.75	0.241	1.41	0.72–2.75	0.320
	Q <sub>3</sub>	1.98	1.06–3.70	0.033	1.78	0.87–3.64	0.116
	Q <sub>4</sub>	1.85	0.97–3.52	0.062	1.52	0.58–4.00	0.396

<sup>a</sup> Based on distribution of controls.

<sup>b</sup> Adjusted for age, gender, race, smoking and body mass index (BMI); odds ratios are in comparison to Q<sub>1</sub>.

<sup>c</sup> Adjusted for age, gender, race, smoking, and total kilocalories (Total Kcal); odds ratios are in comparison to Q<sub>1</sub>.

<sup>d</sup> Tests if individual coefficient is significant.

in intake for peanuts or oil-dressed salads, although an Oregon-based study<sup>6</sup> reported that, among numerous other factors, eating nuts and seeds was positively associated with young-onset PD. More recent studies,<sup>7,8</sup> including those based on nutrient intake,<sup>9–12</sup> as well as our study, have not shown an association between vitamin E and PD.

Considering other antioxidants, a prospective analysis using nutrient data from the Iowa Women's Health Study<sup>9</sup> and a second German study<sup>11</sup> indicated that PD was inversely associated with vitamin C consumption. However, of the other two studies using nutrient databases, one reported no association with vitamin C<sup>10</sup> and the other found a positive, although non-significant, association with PD,<sup>12</sup> similar to our findings.

The nutrient-based studies have demonstrated conflicting results for vitamin A, beta-carotene, or retinol intake, with two studies indicating increased risk,<sup>9,12</sup> one a protective effect<sup>11</sup> and the fourth,<sup>10</sup> as well as our own, no association. A small study comparing the serum levels of beta-carotene, alpha-carotene and lycopene in PD patients and spouse controls revealed no differences,<sup>19</sup> although overmatching related to dietary intake may have biased the results. A small, clinic-based case-control study from Buffalo<sup>12</sup> reported PD risk to be associated with higher intake of xanthophylls, which are oxygenated carotenoids comprising one of the two major carotenoid families.<sup>20</sup> Intake of lutein, a yellow pigmented xanthophyll, was strongly associated with PD in our study. This nutrient, which generally has no detectable provitamin A activity, possesses strong antioxidant activity<sup>21</sup> and is found predominantly in green leafy vegetables such as broccoli, Brussels sprouts, cabbage and kale. In fact, lutein has been proposed as a biomarker for dietary intake of carotenoid-rich food and vegetables in the *Cruciferae* family.<sup>22</sup>

It is interesting that lutein is found in foods shown consistently to be associated with reduced cancer risk, and that our own work<sup>23</sup> and that of others<sup>24</sup> has shown a lower prevalence of cancer among PD patients. Further, cigarette smoking has consistently been shown to afford protection against PD,<sup>25,26</sup> and it has been observed that smoking appears to lower carotenoid plasma levels,<sup>27</sup> including lutein.<sup>28,29</sup>

Little is known about the relationship of dietary intake and the metabolic fate of lutein and other non-beta-carotene carotenoids in the human body.<sup>20</sup> One small human experiment indicated that the plasma concentration of lutein was correlated with ingestion of purified lutein,<sup>21</sup> although an evaluation of the full version Block questionnaire among low income African American women showed no correlation between estimated dietary lutein intake and serum lutein levels.<sup>30</sup> Further, while carotenoids are abundant in human plasma, the few studies reported indicate substantial variability in the distribution of specific carotenoids in different organs and in different individuals.<sup>20,31</sup>

Logroscino *et al.*<sup>10</sup> the first to use a standardized food frequency questionnaire<sup>32</sup> and report data beyond antioxidant intake, found, similar to our study, that intake of calories and animal fats was significantly higher among cases. They suggested that this association is biologically consistent with the hypothesis that oxidative stress and lipid peroxidation, associated with diets high in lipid content, are positively related to PD.<sup>10</sup> However, contrary to our findings, they had no evidence of an association with iron intake.<sup>33</sup>

Iron has been demonstrated to be involved in free-radical formation and lipid peroxidation induction.<sup>34</sup> Analyses of iron in the brains of Parkinson's patients have shown a selective and increased level of iron in the substantia nigra pars compacta, the area bearing the brunt of damage in the disease.<sup>35</sup> If iron is freed from binding to neuromelanin or ferritin, hydroxyl radicals produced by the Fenton reaction might induce neuronal and other local cellular death.<sup>36</sup> However, the mechanism by which iron accumulates in the PD nigra is unknown. Moreover, although dietary intake of iron is related to total body iron store,<sup>37</sup> it is unknown how such stores are related to the level of iron in the brain.

Our study results must be considered in light of design strengths and limitations. The population-based nature of this study<sup>38</sup> and the use of a standardized food frequency questionnaire strengthens confidence in these results. The food frequency questionnaire was self-administered, which may be less optimal than the use of a personal interview, although the longer version of this instrument has been shown to give comparably valid results with either method.<sup>39</sup> Interviewers were available by phone for questions or coaching, and they followed-up with subjects for clarification when the forms or specific items appeared to be completed incorrectly. To reduce subject burden, we used the shorter version of the questionnaire, which does not produce as valid a measure of absolute total caloric intake,<sup>13</sup> which would have been useful analytically for adjustment purposes.

Since there were no *a priori* hypotheses regarding nutrient factors and PD, and little if any information about this issue in the popular literature, it is unlikely that the participants' responses were subject to recall bias. Further, most respondents would be unaware of the relative nutrient content of the various foods on the questionnaire.

One concern is the poorer response for dietary data among African Americans. However, we reanalysed the data to include only Caucasians, with no material change in the results. The amount of many nutrients, such as the carotenoids, present in an ingested food varies by many factors related to agricultural practices. Therefore, these analyses assume that such variation did not differ systematically between cases and controls.

A curious, and to us, unexpected finding in this study, but also apparent in the work of others,<sup>10,11</sup> is the higher overall dietary intake among PD cases, despite, as reported by Hellenbrand<sup>11</sup> and found by ourselves, a lower BMI among cases. In fact, small clinical studies indicate that PD patients have high caloric intake but undergo weight loss, which is not explained by poor nutrition or muscle loss,<sup>40–42</sup> and is hypothesized by Davies to be the result of an increased metabolic rate.<sup>42</sup> Under these circumstances, the challenges which impede nutritional epidemiology are even more profound. Both BMI and total calorie intake probably change with disease progression. Therefore these variables may confound the association between individual nutrients and PD, presumably to a greater extent the further in time a case is from diagnosis. The degree to which confounding variables are misclassified, particularly a concern with total caloric intake due to the data collection instrument as well as the timing of the interview, the greater the potential for biased results due to a reduction in the control of confounding.<sup>43</sup> In order to partially address this issue, we restricted the analyses to subjects with recent symptom

onset, which decreased our sample size. However, while the results for total fat and cholesterol were weakened, the OR for lutein and iron intake increased in magnitude.

Finally, it is not known whether the nutrient intake data accurately reflect the diet during the 'critical' time period when individuals were at risk for PD development. Though this time frame is unknown, and is the subject of much controversy,<sup>44,45</sup> it is likely to be many years prior to the appearance of clinical signs and symptoms. Thus the assumption has been made that the relative food intake patterns of cases and controls have remained fairly stable over time.

In summary, four categories of nutrients were suggested, using several analytical approaches, to be associated with PD: total fat, cholesterol, iron and in particular, lutein. PD, particularly among those over 50 years of age, is considered to have a strong non-inherited component, and the pattern of nutrient intake may play a role in the development or promotion of this disease.

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