Diet and Parkinson's disease I: A possible role for the past intake of specific foods and food groups

Results from a self-administered food-frequency questionnaire in a case-control study

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Article abstract—In a case-control study, we compared the past dietary habits of 342 Parkinson's disease (PD) patients recruited from nine German clinics with those of 342 controls from the same neighborhood or region. Data were gathered with a structured interview and a self-administered food-frequency questionnaire, and analyzed using multivariate conditional logistic regression to control for educational status and cigarette smoking. There was no significant difference between cases and controls in the consumption of fruits and vegetables, although there was a negative trend for the consumption of raw vegetables. Controls reported a higher potato consumption than patients (OR = 0.43, 95% confidence interval [CI]: 0.24–0.74, highest versus lowest quartile). Patients reported eating significantly larger quantities of sweet foods as well as having more snacks than controls. This may, however, be the result of an illness-related change in dietary habits leading to a selective recall effect, since sweet foods may enhance the transport of L-dopa across the blood-brain barrier. We also found that patients consumed less beer (OR = 0.26, 95% CI: 0.14–0.49) and spirits (OR = 0.56, 95% CI: 0.36–0.86), but not wine, and they consumed less coffee (OR = 0.27, 95% CI: 0.14–0.52, highest versus lowest quartile), but not tea, than controls. This may relate to a possible interaction between dopaminergic activity and the intake of ethanol or caffeine. Significantly more patients than controls reported ever consuming raw meat (OR = 1.78, 95% CI: 1.21–2.63). These results suggest that the intake of certain foods may be associated with the development of PD.

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There has not been adequate epidemiologic study of past dietary habits on the development of Parkinson's disease (PD). Golbe et al.[1,2] found an association between PD and the consumption of some foods rich in vitamin E early in adult life in a case-control study, but did not undertake a comprehensive assessment of dietary habits. Likewise, Vieregge et al.[3] focused on a few pertinent dietary questions, finding a difference between cases and controls in the preference for almonds and plums.

There are several lines of evidence suggesting that dietary factors could play a role in the development or pathogenesis of PD. Oxidative processes may have an important role in the progression (and thus possibly the initiation) of the nigral metabolic compromise, ultimately resulting in the clinical picture of PD.[4-11] Therefore, dietary intake of foods rich in the antioxidant vitamins C and E, as well as the carotenes, might influence the development of PD.

The large neutral amino acids (LNAAs) that act as precursors for the central neurotransmitters compete with each other for transport across the blood brain barrier.[12,13] Thus, protein intake can influence the transport of tyrosine, the precursor for dopamine, across the blood brain barrier. Furthermore, insulin causes the serum concentration of the LNAAs (with the exception of tryptophan) to decline.[14,15] Since dopamine synthesis is precursor-controlled,[12,14,15] the dietary carbohydrate-protein balance, as well as meal timing and frequency, could have an influence on the development of PD.

There are reports that alcohol consumption is inversely associated with PD.[16-19] Both ethanol[20-24] and caffeine[25,26] affect dopamine transmission and turnover in the basal ganglia and other brain regions.

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Foods rich in biogenic amines contain tetrahydroisoquinolines,[27] which have been implicated as potential causal agents for PD due to their structural similarity to *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Tetrahydroisoquinoline can produce parkinson-like symptoms in monkeys with corresponding nigrostriatal neurochemical changes.[28,29] This substance can pass the blood brain barrier[30,31] and has been found in human brain tissue.[32]

An infectious cause for PD was first suggested by the association between postencephalitic parkinsonism and the influenza pandemic of 1918.[33-35] A role for infectious agents, especially viruses, in neurodegenerative diseases, while remaining controversial, is plausible on theoretical grounds as well.[36] The consumption of raw meat and organ meats could lead to the transmission of infectious agents.

Based on these considerations of possible diet-related etiologic influences in PD, we conducted a hospital-based case-control study using a comprehensive retrospective assessment of dietary habits. This assessment was carried out as part of a large case-control study investigating environmental influences on the development of PD.[37] In this paper, we will summarize our results mainly at the food and food groups level; detailed results at the nutrient level are described in the accompanying paper.[38]

Methods. Our methods have been described in detail elsewhere.[37] Briefly, PD patients were recruited in nine German neurologic clinics. All cases with a diagnosis of PD in 1987 or later and 65 years of age or less were identified. Four patients from three clinics up to 67 years of age were included as well. Older patients were not recruited in order to minimize memory deficits, and patients with a longer disease duration were excluded to minimize recall bias. Attending neurologists were asked to verify inclusion and exclusion criteria according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[39] Patients with secondary parkinsonian syndromes and PD patients with dementia were excluded. Of 533 eligible PD patients identified, 377 agreed to participate (71%). Five additional patients were recruited from neurologic practices affiliated with two of the centers, leading to a total of 382 participating patients.

Two controls were recruited per case on a random route basis.[40] The first control was recruited within the patient's immediate neighborhood and the second control from the same urban or rural region. Interviewers were instructed to contact every second household starting with the patient's (first control) or a predetermined "regional" (second control) address in order to find a person of the same sex and age (±3 years) as the patient. The regional address was selected randomly from a list of all addresses in the patient's voting district. In rural regions, this meant that the control person might be in a nearby small town or village. If that person was not at home at the time the contact was made, the interviewer was instructed to ask to be able to return at a mutually convenient time. On average, 21 household contacts were required to find an appropriate control willing to participate. For two cases no controls could be found, leaving 380 patients, 376 neighborhood controls, and 379 regional controls for the analysis.

Experienced interviewers were contracted with Infratest/Epidemiologische Forschung Berlin, a sociologic and health research institute. These interviewers were professionally trained in standardized interview techniques and a nondifferential approach to patients and controls. The interviewers were informed that the study dealt with environmental influences and PD, but were unaware of specific hypotheses being investigated. They were given basic information about the clinical manifestations of PD. Patients were not informed of the hypotheses. Controls were asked to participate in a "health survey"; they were unaware that the investigation dealt primarily with PD. The same person interviewed the case and the corresponding controls.

A detailed structured interview was developed in order to elicit information about a variety of environmental exposures, including some dietary habits, prior to the diagnosis of the disease. A self-administered food-frequency questionnaire (FFQ) developed and validated by the German Cancer Research Center was implemented for the documentation of dietary habits prior to disease onset. This FFQ contains 148 food items with pictures of portion sizes. Correlation coefficients comparing dietary intakes from the FFQ with those of 24-hour dietary recalls compare favorably with those documented for other FFQs in the literature.[41,42] Subjects were given detailed instructions on filling out the FFQ by the interviewer at the end of the structured interview. The interviewer also returned to pick up the questionnaire personally and to help the subjects with any problems they may have had. Responses on the FFQ were linked with the latest version of the German Federal Food Code[43] to obtain the nutrient composition of the diet.

Patients were asked to recall their dietary habits prior to the diagnosis of their disease, while controls were asked to recall their habits as they had been one year prior to the interview. This meant that, on average, controls did not have to remember backward in time as far as the patients (illness duration 3.7 ± 1.8 years). However, we thought that this would be less artificial than creating a fictitious "matched" date corresponding to the patient's diagnosis.

For financial reasons, the FFQ was only administered to the neighborhood control. If that person declined, the regional control was asked to fill out the questionnaire (53 cases). Because several subjects (mainly controls) refused to fill out the FFQ and others had a high number of missing values (>15) in conjunction with an implausibly low energy intake, only 342 case-control pairs could be evaluated. The 38 patients not evaluated for this reason did not differ from the remaining group with respect to age, sex, disease duration, smoking status, or body-mass index (BMI).

Data were compiled in a relational databank using the SIR 3.1 Database System. Basic data analysis was carried out using SPSS/PC. Continuous dietary data were converted to ranked categorical variables according to quartiles of distribution among the controls (cutpoint values not shown). Intakes were checked for plausibility. Odds ratios (OR) and 95% confidence intervals (CI) were calculated with multiple conditional logistic regression using BMDP Statistical Software. Intakes were adjusted for total energy intake by including the latter as a covariate in the

multivariate regression equations.[44] Smoking in packyears and educational status were included as covariates in the multivariate analysis to control for potential confounding. Tests for trend were calculated with the continuous variables based on logistic regression.[45] We made no adjustment for multiple comparisons. Because dietary assessment involves a large number of variables and because our hypotheses are based mainly on theoretic considerations, our study must be considered exploratory in nature.

Odds ratios shown in the text will be adjusted for energy intake, educational status, and smoking history. They will refer to the comparison between the highest and lowest quartiles and are followed by 95% confidence intervals.

Results. The mean age of patients who completed the FFQ was 56.2 ± 6.7 years, and of controls, 56.1 ± 6.9 years. Mean disease duration was 3.7 ± 1.8 years. Of the 342 patients, 224 were men and 118 were women.

Patients reported that they weighed less than controls. The bodymass index (BMI) was 25.8 ± 3.5 for patients and 26.5 ± 3.6 for controls ($p = 0.005$). The highest ever BMI was also lower in patients (26.9 ± 4.0 versus 27.3 ± 4.1, $p = 0.005$), as was the lowest ever BMI (24.3 versus 24.9, $p = 0.0005$). Adjustment for BMI by inclusion in the regression equation had a minimal effect on the results and hence is not reported. Although patients had a lower BMI than controls, they reported a significantly higher energy intake: patients 10,353 ± 3,361 kJ/day versus controls: 9,576 ± 3,361 kJ/day ($p = 0.0006$). This is discussed in detail in the accompanying paper on nutrient intake.[38]

Patients reported a significantly higher consumption of sweet foods (table 1), as is seen by elevated ORs for intake of cookies and cakes (2.87, 95% CI: 1.59–5.16, p trend = 0.0001), sweets (2.70, 95% CI: 1.49–4.92, p trend = 0.0002), sweetened beverages (1.59, 95% CI: 0.97–2.61, p trend = 0.09) and desserts (2.74, 95% CI: 1.55–4.85, p trend = 0.01). Elevated ORs were also found for ever having midmorning (OR = 1.63, 95% CI: 1.11–2.38) and bedtime snacks (OR = 1.62, 95% CI: 1.12–2.35). This may reflect intake of foods high in refined carbohydrate typically consumed as snacks.

According to our data, there were no significant differences in the consumption of fruits and vegetables between patients and controls, although a significant negative trend was found for the consumption of raw but not cooked vegetables (table 1). Patients reported a significantly lower potato consumption than controls (OR = 0.43, 95% CI: 0.24–0.74, p trend = 0.007).

In this study, controls reported a significantly higher consumption of beer (OR = 0.26, 95% CI: 0.14–0.49, p trend = 0.0006) and spirits (OR = 0.56, 95% CI: 0.36–0.86, p trend = 0.20), but not wine (OR = 1.20, 95% CI: 0.71–2.04, p trend = 0.01). The adjustment for smoking decreased the trend for spirits consumption, but the ORs themselves remain significant (table 1). When ethanol intake was analyzed at the nutrient level, an inverse relationship with PD was also seen (table 1). Controls also reported a higher intake of coffee (OR = 0.27, 95% CI: 0.14–0.52, p trend = 0.0003), but not tea (OR = 0.82, 95% CI: 0.52–1.29, p trend = 0.63). Again, adjustment for smoking did not explain this inverse relationship (table 1).

As a very rough "proxy" for foods containing isoquinolines, the intake of foods rich in biogenic amines, cheese, wine, and chocolate was looked at for patients and controls. A strongly positive association was seen between PD and chocolate intake (OR = 2.71, 95% CI: 1.55–4.79, p trend = 0.01), but no association with cheese or wine intake could be discerned.

Finally, significantly more patients than controls reported ever consuming raw meat (OR = 1.78, 95% CI: 1.21–2.63). The odds ratio for the intake of meats such as brain or thymus was also elevated, but not significantly ("ever" versus "never": 1.62, 95% CI: 0.94–2.80).

Discussion. The aim of this study was to look for possible diet-related protective factors and risk factors for Parkinson's disease. This is the most detailed assessment of past dietary habits in PD patients to date. The comparison with a control population revealed a number of differences that may be relevant to the etiology of this disease.

Case-control studies in general are open to sources of bias.[46] Although we did not have incident cases, the disease duration of our patients was relatively short, thus reducing the potential for recall bias. As this study was not population based, patient selection bias cannot be ruled out. In order to minimize such a bias, we included patients from clinics in different areas in Germany and attempted to recruit all patients under the age of 66 in each clinic. There was no difference in disease duration between patients who participated in the study and those who declined. We obtained reasons for nonparticipation from only 26 patients. Half of these stated deteriorating health as the reason for not participating. Thus, there is some evidence that patients with more severe disease declined to take part.

We tried to minimize any control selection by recruiting the first matching control in the neighborhood or region according to the random walk scheme, even if this meant return visits to that household for the interviewer. Nonetheless, the employment rate of male controls at the time of the interview was lower than expected in comparison with the general population. For example, of controls aged 50 to 59 years, 53.7% of men and 38.3% of women were employed. The national average employment rate for this age group is 82.6% for men and 50.4% for women.[47] This suggests that some controls at least were easier to contact at all hours of the day. We have partly adjusted for this factor by including educational status in the regression equation. In addition, to determine if unemployment on the part of controls influenced the results, we compared controls who were still employed or older than 64 years of age (i.e., likely retired) at the time of the interview with those PD patients still employed or older than 64 years of age at the time of symptom onset, leaving 271 cases and 199 controls. This was analyzed as an unmatched data set at the nutrient level and had no substantial effect on the results beyond the occasional loss of significance that might be expected to result from a smaller study population (results not shown). As ethanol and coffee intake might be especially sensitive to a "social" selection bias, it is reas-

Table 1 *Crude and adjusted odds ratios for Parkinson's disease by quartiles* of intake of various foods*

Variable	Q	N1	N2	Crude OR†	*p* trend	Adj.‡ OR†	*p* trend	Adj.§ OR†	*p* trend
Cookies	1	45	85	1.00 —	<0.00005	1.00 —	0.0001	1.00 —	0.0001
and cakes	2	62	86	1.50 (0.88–2.50)		1.46 (0.85–2.50)		1.56 (0.88–2.78)	
	3	101	86	2.31 (1.38–3.86)		2.06 (1.21–3.50)		2.34 (1.34–4.16)	
	4	134	85	3.18 (1.94–5.21)		2.84 (1.63–4.94)		2.87 (1.59–5.16)	
Sweets	1	48	85	1.00 —	<0.00005	1.00 —	0.0006	1.00 —	0.0002
	2	71	86	1.55 (0.93–2.59)		1.34 (0.79–2.28)		1.23 (0.70–2.15)	
	3	88	86	2.05 (1.24–3.38)		1.66 (0.98–2.83)		1.57 (0.89–2.77)	
	4	135	85	3.44 (2.06–5.74)		2.81 (1.62–4.89)		2.70 (1.49–4.92)	
Sweetened	1	67	85	1.00 —	0.02	1.00 —	0.12	1.00 —	0.09
beverages	2	74	86	1.16 (0.75–1.79)		1.07 (0.69–1.67)		0.94 (0.58–1.52)	
	3	82	86	1.27 (0.80–2.04)		1.27 (0.79–2.05)		1.20 (0.72–2.00)	
	4	119	85	1.96 (1.25–3.08)		1.63 (1.02–2.59)		1.59 (0.97–2.61)	
Chocolate	1	42	84	1.00 —	0.0008	1.00 —	0.009	1.00 —	0.01
	2	73	85	1.71 (1.06–2.77)		1.63 (1.00–2.67)		1.63 (0.97–2.74)	
	3	120	96	2.58 (1.60–4.14)		2.29 (1.40–3.72)		2.26 (1.34–3.79)	
	4	107	77	2.99 (1.80–4.96)		2.50 (1.48–4.23)		2.72 (1.55–4.79)	
Desserts	1	38	78	1.00 —	<0.00005	1.00 —	0.001	1.00 —	0.01
	2	74	94	1.69 (1.02–2.08)		1.65 (0.98–2.76)		1.51 (0.88–2.61)	
	3	87	84	2.23 (1.33–3.73)		2.00 (1.17–3.40)		1.70 (0.97–2.96)	
	4	143	86	3.86 (2.30–6.47)		3.33 (1.93–5.73)		2.74 (1.55–4.85)	
Raw	1	79	85	1.00 —	0.35	1.00 —	0.05	1.00 —	0.03
vegetables	2	99	86	1.24 (0.81–1.91)		1.28 (0.82–2.01)		1.35 (0.83–2.20)	
	3	83	86	1.05 (0.67–1.63)		0.94 (0.59–1.50)		0.90 (0.55–1.49)	
	4	81	85	1.03 (0.66–1.61)		0.86 (0.53–1.38)		0.76 (0.46–1.27)	
Potatoes	1	106	85	1.00 —	0.11	1.00 —	0.04	1.00 —	0.007
	2	94	86	0.81 (0.53–1.26)		0.66 (0.42–1.05)		0.68 (0.41–1.11)	
	3	74	86	0.66 (0.43–1.02)		0.56 (0.35–0.89)		0.58 (0.35–0.95)	
	4	68	85	0.58 (0.36–0.94)		0.47 (0.28–0.77)		0.43 (0.24–0.74)	
Coffee	1	147	92	1.00 —	<0.00005	1.00 —	<0.00005	1.00 —	0.0003
	2	71	81	0.51 (0.33–0.79)		0.49 (0.31–0.76)		0.49 (0.30–0.79)	
	3	97	110	0.53 (0.35–0.81)		0.49 (0.31–0.75)		0.53 (0.34–0.85)	
	4	27	59	0.25 (0.14–0.44)		0.22 (0.12–0.41)		0.27 (0.14–0.52)	
Beer	1	112	85	1.00 —	0.0001	1.00 —	<0.00005	1.00 —	0.0006
	2	97	84	0.81 (0.52–1.26)		0.77 (0.48–1.23)		0.75 (0.46–1.23)	
	3	182	81	0.54 (0.33–0.89)		0.48 (0.28–0.80)		0.49 (0.28–0.84)	
	4	51	92	0.27 (0.15–0.47)		0.21 (0.11–0.39)		0.26 (0.14–0.49)	
Wine	1	80	98	1.00 —	0.007	1.00 —	0.01	1.00 —	0.01
	2	92	83	1.42 (0.91–2.22)		1.31 (0.83–2.07)		1.20 (0.74–1.94)	
	3	87	90	1.25 (0.80–1.95)		1.27 (0.80–1.99)		1.14 (0.70–1.85)	
	4	83	71	1.53 (0.95–2.46)		1.38 (0.85–2.26)		1.20 (0.71–2.04)	
Spirits	1	193	159	1.00 —	0.10	1.00 —	0.03	1.00 —	0.19
	2	72	79	0.73 (0.49–1.07)		0.67 (0.45–1.01)		0.59 (0.38–0.91)	
	3	77	104	0.58 (0.39–0.85)		0.53 (0.35–0.79)		0.56 (0.36–0.86)	
Ethanol	1	89	85	1.00 —	0.02	1.00 —	0.002	1.00 —	0.04
	2	121	86	1.26 (0.82–1.95)		1.07 (0.68–1.69)		1.14 (0.71–1.84)	
	3	63	86	0.59 (0.35–0.98)		0.52 (0.30–0.88)		0.53 (0.30–0.93)	
	4	69	85	0.62 (0.37–1.06)		0.46 (0.46–0.81)		0.58 (0.32–1.06)	

* Occasionally, the distribution of intakes did not yield exact quartiles. The high number of probands with zero intake of spirits permitted only three categories. Exact cutpoints are filed with NAPS.

† 95% confidence intervals shown in brackets.

‡ Adjusted for energy intake.

§ Adjusted for energy intake, smoking in packyears, and education.

Q = quartile; N1 = number of cases; N2 = number of controls.

Table 2 *Stratification for disease duration: Adjusted odds ratios (highest versus lowest quartile) with 95% confidence intervals for Parkinson's disease according to intakes of various foods and food groups*

	≤ 3 years disease duration*		> 3 years disease duration†		
Variable	Adj. OR (95% CI)‡	*p* trend	Adj. OR (95% CI)‡	*p* trend	*p* for interaction§
Raw vegetables	0.84 (0.39–1.82)	0.07	0.68 (0.33–1.41)	0.25	0.07
Cooked vegetables	1.72 (0.74–3.99)	0.43	0.67 (0.32–1.40)	0.25	0.80
Potatoes	0.65 (0.30–1.40)	0.14	0.25 (0.11–0.60)	0.03	0.90
Fruit	0.56 (0.23–1.35)	0.08	1.21 (0.53–2.60)	0.94	0.006
Cookies and cake	2.13 (0.87–5.26)	0.17	3.95 (1.75–8.92)	0.0002	0.14
Sweets	1.90 (0.84–4.32)	0.09	4.69 (1.83–12.0)	0.0007	0.10
Pop	1.63 (0.79–3.37)	0.29	1.51 (0.75–3.05)	0.22	0.74
Dessert	2.77 (1.18–6.49)	0.20	2.82 (1.26–6.34)	0.02	0.08
Beer	0.26 (0.10–0.70)	0.01	0.25 (0.10–0.61)	0.02	0.81
Wine	1.51 (0.72–3.21)	0.02	0.87 (0.40–1.91)	0.29	0.12
Spirits	0.53 (0.27–1.03)	0.15	0.57 (0.32–1.04)	0.67	0.82
Ethanol	0.46 (0.18–1.14)	0.23	0.68 (0.29–1.61)	0.08	0.46
Coffee	0.20 (0.07–0.56)	0.06	0.30 (0.12–0.73)	0.0009	0.35
Tea	0.81 (0.41–1.62)	0.37	0.85 (0.45–1.60)	0.80	0.06
Chocolate	4.90 (1.83–13.1)	0.02	2.20 (1.07–4.54)	0.12	0.93

* n = 155.
† n = 187.
‡ OR for highest versus lowest quartile (with the same cutpoints as for the other analyses), adjusted for energy intake, smoking in packyears and education.
§ *p* value for improvement of the model upon inclusion of the interaction term variable disease duration, both continuously scaled.

suring that the inverse relationships found for these variables remained unchanged in this subanalysis.

Retrospective assessment of dietary intake is relevant to many topics under epidemiologic study. Where prospective studies are not feasible, obtaining a history of dietary habits remains the only way in which to assess a possible influence of diet on the disease. Previous investigators have shown that retrospective dietary assessment correlates reasonably well with actual past intake (reviewed by Willett[44] 1990). Nonetheless, recall of past intake is influenced by present dietary habits,[44] and ill persons in particular may change their dietary habits over time.[48] In fact, subjectively, 13.5% of our patients reported marked or very marked changes in their diets since their diagnosis, 26.1% reported some change, 25.2% reported only slight change, and 35.2% reported no change. Therefore, we looked at our results after stratification for illness duration (table 2), hypothesizing that if recall were affected by current dietary habits that had changed from premorbid habits as a result of the illness, such an effect should be most marked in the group with a longer disease duration.

The positive association between the intake of foods rich in refined carbohydrates and PD was stronger and remained significant only in patients with a longer disease duration, although this did not hold for the intake of chocolate and desserts (table 2). The same pattern was observed for having frequent snacks. This could be evidence for an influence of an illness-related change in dietary habits on the recall of past habits; since raised insulin levels caused by refined carbohydrate intake enhance the transport of L-dopa into the CNS,[13] PD patients treated with this drug might have consumed larger quantities of sweet foods after the onset of their illness. This could secondarily influence their recall of past intake. Preclinically, on the other hand, raised insulin levels would lead to lowered concentrations of tyrosine, leading to less dopamine synthesis through precursor control.[12,14,15] Whether this could act as a risk factor for PD is difficult to interpret, especially as there is evidence for a plausible recall effect related to illness duration.

Overall, patients consumed less fresh (but not cooked) vegetables (trend only) as well as significantly less potatoes than controls. This has implications for the antioxidant hypothesis, which is discussed in more detail in a paper on nutrient intakes.[38] There may be evidence for an influence of disease duration on recall of intake, since there was a near-significant inverse trend for reported raw vegetable as well as fruit intake (the latter not evident before stratification) only in the group with a shorter disease duration. This could mean that PD patients started consuming more fruits and vegetables after their illness (which would be a "healthy" response), making them less likely to report a lower premorbid intake with increasing illness duration. This could falsely weaken an inverse association between PD and preclinical antioxidant intake, but such an inter-

pretation must be tentative at best, as the ORs for the intake of fruits and vegetables did not reach significance. In contrast, the strong inverse association between PD and potato consumption remained significant only in the group with a longer disease duration. This suggests decreasing potato consumption with increasing duration of illness, probably as a compensatory effect related to the parallel increase in the consumption of foods rich in refined carbohydrates.

We were unable to assess the intake of tetrahydroisoquinolines accurately in this study. Using foods rich in biogenic amines (cheese, wine, chocolate) as a "proxy," only chocolate intake showed a significantly elevated odds ratio. This is difficult to interpret, as the intake of sweets in general was positively associated with the disease. However, unlike other sweets, stratification for disease duration revealed that the association was stronger in the group with a shorter disease duration, suggesting that this may indeed reflect preclinical risk. The nonsignificantly elevated odds ratio for wine is also noteworthy, as the intake of other alcoholic beverages was inversely associated with the disease. Nonetheless, further investigation of a potentially etiologic role for these substances in PD requires more background research to identify the food sources for specific isoquinolines as well as to define better their potentially neurotoxic role.

The significantly lower intake of alcoholic beverages (with the exception of wine) by PD patients, as compared with controls, is not explained by the negative association between smoking and PD, as shown by inclusion of this term in the regression equation. Other case-control studies also found an inverse association between alcohol intake and PD.[16-19,49] At least in animals, ethanol has complex and probably varying effects on dopaminergic release, synthesis, metabolism, and transmission in different brain regions, likely depending on the pattern and dosage of intake.[21-24,50,51] As the dopaminergic system is important in addictive behavior, a preclinical dopamine deficit could also influence alcohol intake. In this case, (preclinical) PD could itself be the cause of low ethanol intake, as also suggested for the low frequency of cigarette smoking among PD patients.[52-54] Similarly, Vernay et al.[55] postulate that salsolinol, a condensation product of the alcohol metabolite acetaldehyde and dopamine, plays a role in addictive behavior, in which case lower levels of this substance after ethanol intake in persons with a relative dopamine deficiency would provide less positive reinforcement. In addition, two studies[20,56] described parkinsonism provoked by alcohol abuse or by alcohol withdrawal. Alcohol withdrawal causes decreased dopamine turnover in the mouse striatum.[57] Thus, current knowledge does not permit differentiation of a possible protective effect of alcohol on the development of PD from preclinically induced neurochemical changes that could lead to less drinking among predestined PD patients.

Our data showed that PD patients consumed less coffee than controls and this also was not explained by adjustment for smoking. Caffeine readily crosses the blood-brain barrier and has complex effects on various neurotransmitter systems, including the dopaminergic system.[25,26,58]

Our patients reported more frequent consumption of raw meat and organ meats than controls. This is in contrast to findings from two other smaller studies, which found no association,[3,59] and may be attributable to recall bias. These foods could act as a vehicle for infectious agents. Although an infectious etiology for PD appeared plausible when the link between postencephalitic parkinsonism and the 1918 influenza pandemic was recognized, evidence for an infectious etiology for idiopathic PD remains inconclusive.[60-64] Attempts to transmit the disease to primates have been unsuccessful.[65] Nonetheless, a contributory causal role for infectious agents in the etiology of this and other neurodegenerative diseases cannot be ruled out.[36,66] Organ meats also contain high concentrations of heavy metals,[67] which may be implicated in the development of PD.[68]

In summary, in this retrospective dietary assessment using a case-control approach, we have found evidence that the reported past intake of certain foods or food groups, such as foods rich in refined carbohydrates, fresh vegetables (trend only), alcoholic beverages, coffee, and raw meat or organ meats, are associated with Parkinson's disease. Further analyses of our dietary data at the nutrient level through linkage with the German Federal Food Code are provided in the companion paper.[38] Ultimately, insights into mechanisms that link nutrition with PD risk may give rise to new treatment approaches and preventive recommendations.

Note. *Readers can obtain 6 pages of supplementary material from* the National Auxiliary Publications Service, c/o Microfiche Publications, PO Box 3513, Grand Central Station, New York, NY 10163-3513. Request document no. 05333. Remit with your order (not under separate cover), in US funds only, $7.75 for photocopies or $4.00 for microfiche. Outside the United States and Canada, add postage of $4.50 for the first 20 pages and $1.00 for each 10 pages of material thereafter, or $1.75 for the first microfiche and $.50 for each fiche thereafter. *There is a $15.00 invoicing charge on all orders filled before payment.*

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Diet and Parkinson's disease I: A possible role for the past intake of specific foods and food groups: Results from a self-administered food-frequency questionnaire in a case-control study

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