Original Contribution

Dietary Iron Intake and Risk of Parkinson's Disease

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Dietary iron is the most important source of iron stores. Several case-control studies have described the association of high dietary iron and Parkinson's disease, but prospective data are lacking. The authors prospectively followed 47,406 men and 76,947 women from the United States who provided information through a mailed questionnaire on their diet, medical history, and lifestyle practices between 1984 and 2000. The authors documented 422 new cases of Parkinson's disease. Total iron intake was not associated with an increased risk of Parkinson's disease (relative risk (RR) = 1.10, 95% confidence interval (CI): 0.74, 1.65; $P_{\text{trend}} = 0.84$), but dietary nonheme iron intake from food was associated with a 30% increased risk of Parkinson's disease (RR = 1.27, 95% CI: 0.92, 1.76; $P_{\text{trend}} = 0.02$). A secondary analysis revealed that Parkinson's disease risk was significantly increased among individuals with high nonheme iron and low vitamin C intakes (RR = 1.92, 95% CI: 1.14, 3.32; $P_{\text{trend}} = 0.002$). Supplemental iron intake was associated with a borderline increase in Parkinson's disease risk among men. Although the authors' prospective data did not support an association between total iron intake (dietary and supplemental) and risk of Parkinson's disease, a 30% increased risk was associated with a diet rich in nonheme iron. This increase in risk was present in those who had low vitamin C intake.

ascorbic acid; diet; heme; iron; Parkinson disease; prospective studies

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; RR, relative risk.

Several different lines of evidence suggest a possible role of iron in the pathogenesis of Parkinson's disease. Both neuropathologic and imaging studies have found increased iron deposits in the substantia nigra of Parkinson's disease patients (1, 2). Free iron catalyzes the production of free radicals and is involved in lipid peroxidation and neurodegeneration (3). Iron also seems to increase *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity and to accelerate alpha-synuclein fibrillation and deposition (4, 5). Iron levels have been also shown to be elevated in the substantia nigra in autosomal recessive juvenile parkinsonism associated with mutations in the Parkin gene (6).

Chronic occupational exposure to a combination of metals, including iron, has been associated with increased risk of Parkinson's disease (7), but it is still not clear if iron overload from other environmental sources plays a role in Parkinson's disease pathogenesis. The most important source of body iron stores is dietary iron, but it has only

been inconsistently associated with increased Parkinson's disease risk (8–10). Furthermore, all of these studies used a retrospective case-control design, which in diet studies is particularly prone to recall bias, and only one used incident cases (8). The results from a study using history of blood donation as a marker of low stores of body iron were also inconclusive (11). We therefore examined the association between iron intake and Parkinson's disease in 2 large prospective cohorts of US men and women: the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS).

MATERIALS AND METHODS

Study population

The HPFS was established in 1986 when 51,529 male US health professionals (i.e., veterinarians, pharmacists,

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dentists, osteopaths, optometrists), aged 40–75 years, responded to a mailing that requested information on their disease history, lifestyle practices, and diet with a semiquantitative 131-item food frequency questionnaire. The NHS was established in 1976, when 121,700 nurses aged 30–55 years answered a similar questionnaire. We used the 1984 questionnaire as the baseline in the NHS analysis, because it was not until then that a comprehensive dietary survey had been completed.

Following the initial survey, the questionnaires have been mailed every 2 years to update information on potential risk factors for chronic disease and to ascertain medical events that have occurred in the interval. The dietary information is updated every 4 years. A specific question on lifetime occurrence of Parkinson's disease was first included in the HPFS in 1988 and in the NHS in 1994, and every subsequent questionnaire has contained a question on a diagnosis of Parkinson's disease in the previous 2 years. We excluded from our analysis participants who reported Parkinson's disease, stroke, and cancer (other than nonmelanoma skin cancer) at baseline, as well as those with extreme daily intakes of energy (≤ 800 and $\geq 4,200$ kcal) or incomplete information (≥ 70 blanks). We followed 47,406 men and 76,947 women from baseline to either the date that the first symptoms of Parkinson's disease were noticed, or death, or the end of the follow-up (January 31, 2000, in men and May 31, 2000, in women). The follow-up rates were about 90% in both cohorts. This study was approved by the human subjects committees at the Harvard School of Public Health and at the Brigham and Women's Hospital in Boston, Massachusetts.

Case ascertainment

The methods of case ascertainment for both cohorts have been previously described (12). Briefly, we asked all participants who reported a new diagnosis of Parkinson's disease for their permission to contact their treating neurologist and to have their medical records released. After obtaining permission, we asked the treating neurologist to complete a questionnaire concerning the clinical diagnosis and the certainty of diagnosis (definite, probable, or possible) and/or to send us a copy of the medical records. We also requested the date on which the first symptoms were noticed and of the first clinical diagnosis. Cases were confirmed as Parkinson's disease when the diagnosis was considered definite or probable by the treating neurologist, and/or if the medical record included either a final diagnosis made by a neurologist or evidence at the neurologic examination of at least 2 of the 4 cardinal signs of parkinsonism (rigidity, rest tremor, bradykinesia, and postural instability), with one being rest tremor or bradykinesia, along with lack of evidence of nonresponse to levodopa and of clinical features suggesting other diagnoses. The medical records were reviewed by investigators who were blind to the exposure status. We also requested the death certificates of the deceased study participants and identified Parkinson's disease diagnoses that were not reported in the regular follow-up (less than 2%). The great majority of Parkinson's disease cases were confirmed by their treating neurologist.

Exposure assessment

Intake of iron and other nutrients was assessed by using a semiquantitative food frequency questionnaire that has been extensively validated in both men and women (13). Participants were asked how often on average in the previous year they had consumed a specified portion of selected foods and beverages. Nine responses were included, ranging from never to ≥ 6 times/day. Nutrient intakes were computed by multiplying the consumption frequency of each food by the nutrient content of the specific portion and then summing these products for all food items. The food composition values were obtained from the Harvard University Composition Database derived from the US Department of Agriculture (14). Additional information was obtained from manufacturers and the nutritional literature. After adjustment for within-person variability in daily intake, the correlation coefficient between dietary iron intake from the questionnaire and multiple days of diet records for energy-adjusted total dietary iron intake was 0.50 (15, 16). Plasma levels of ferritin were also estimated in 620 healthy postmenopausal women aged 44–69 years who participated in the NHS (17). Plasma ferritin concentrations were significantly correlated to the estimated heme iron intake ($r = 0.15$, $P < 0.01$) and supplemental iron intake ($r = 0.12$, $P < 0.01$), but not to nonheme iron ($r = 0.02$, $P > 0.05$).

Statistical analyses

In the first analysis, we used the cumulative average of iron intake from all past dietary surveys as the energy-adjusted exposure of interest (18). For example, in men, iron intake in 1986 was used to predict Parkinson's disease with onset between 1986 and 1990, while the average of iron intake between 1986 and 1990 was used to predict Parkinson's disease onset between 1990 and 1994, and so forth. These cumulative averages represented the average nutrient intake from all dietary surveys in the cohort. As such, they reduced within-person variability and were the best estimate of long-term dietary intakes. In a secondary analysis, we also examined the baseline and the simple updated intake. All analyses were first conducted in each cohort (HPFS and NHS) and, hence, by gender; the data were then pooled.

To assess the association between iron intake and risk of Parkinson's disease, we used Cox proportional hazards regression to compute relative risk and 95% confidence intervals. In each analysis, iron intake was categorized into quintiles, with the lowest quintile the reference group. In the first model, we adjusted for age (months), energy, intake, and smoking. In the second model, we adjusted for other potential confounders: caffeine intake, alcohol consumption, lactose intake, vitamins C and E, and the Alternate Healthy Eating Index, a diet-quality score developed to investigate cardiovascular disease and other chronic diseases (19). The Alternate Health Eating Index score captures specific dietary patterns that have been associated with lower risk for many chronic diseases, including Parkinson's disease (20).

We calculated the P value for linear trend by using the median of each quintile category as a continuous variable in the Cox models. We calculated 95% confidence intervals

Table 1. Age-adjusted Population Characteristics According to Quintile Categories of Cumulative Intake of Total Iron in the Health Professionals Follow-up Study (1986–2000) and the Nurses' Health Study (1984–2000)

	Quintiles of Iron Intake				
	1	2	3	4	5
Men					
Total iron, mean, mg/day	11.0	13.3	15.5	20.1	39.0
No. of subjects	9,319	9,740	9,511	9,393	9,442
Age in 1986, mean, years	53.1	53.5	53.5	54.0	55.0
Smoking, pack-years	15.4	13.4	12.2	11.6	11.9
Dietary iron, mean, mg/day	11.1	13.3	15.1	17.2	18.8
Nonheme iron, mean, mg/day	9.9	11.9	13.7	15.9	17.5
Heme iron, mean, mg/day	1.2	1.4	1.3	1.3	1.2
Iron supplement, yes/no, %	3.0	7.4	17.1	45.4	85.0
Total energy intake, mean, kcal/day	1,842	1,986	2,061	2,050	1,914
Alcohol intake, mean, g/day	14.7	10.9	9.9	9.8	9.7
Caffeine intake, mean, mg/day	262	252	233	221	222
Vitamin C intake, mean, mg/day	306	332	366	436	693
Vitamin E intake, mean, mg/day	35.8	39.7	44.0	57.0	104
Lactose intake, mean, g/day	16.2	13.4	13.7	14.7	15.5
Body mass index, kg/m ²	25.7	25.8	25.6	25.3	25.2
Physical activity, metabolic equivalent	19.0	20.3	21.4	22.2	23.4
Alternate Healthy Eating Index	39.3	43.5	46.0	47.5	48.7
Women					
Total iron, mean, mg/day	9.5	11.4	13.7	18.1	36.3
No. of subjects	12,295	23,120	9,116	17,085	15,331
Age in 1984, mean, years	49.7	50.0	50.3	51.0	50.7
Smoking, pack-years	15.2	12.6	11.4	10.8	10.5
Dietary iron, mean, mg/day	9.5	11.2	12.6	13.8	14.3
Nonheme iron, mean, mg/day	8.5	10.1	11.5	12.7	13.2
Heme iron, mean, mg/day	1.0	1.1	1.1	1.1	1.1
Iron supplement, yes/no, %	3.0	8.6	28.1	62.8	93.4
Total energy intake, mean, kcal/day	1,654	1,765	1,813	1,814	1,701
Alcohol intake, mean, g/day	7.5	6.4	5.8	5.7	5.4
Caffeine intake, mean, mg/day	313	304	287	273	270
Vitamin C intake, mean, mg/day	239	266	299	371	512
Vitamin E intake, mean, mg/day	30.0	33.8	39.0	51.2	76.8
Lactose intake, mean, g/day	13.2	11.7	12.3	13.3	14.0
Body mass index, kg/m ²	25.0	25.3	25.2	24.9	24.7
Physical activity, metabolic equivalent	11.9	13.3	14.3	15.1	16.0
Alternate Healthy Eating Index	33.1	36.8	39.1	40.3	40.5

and 2-tailed *P* values for all relative risks. Log(relative risks) from the two cohorts were pooled by the inverse of their variances. We did not find significant heterogeneity of the associations between iron intake and Parkinson's disease risk between men and women (*P* > 0.2 for all).

Because the amount of iron that is absorbed from diet largely depends on the form in which the iron is present, we conducted separate analyses for heme iron, which originates from animal food; nonheme iron, which comes mainly from fortified cereals, vegetables, and legumes; and supplemental iron.

Table 2. Relative Risk of Parkinson's Disease According to Cumulative Iron Intake, by Sources, in the Health Professionals Follow-up Study (1986–2000) and in the Nurses' Health Study (1984–2000)^a

	Quintiles of Iron Intake															<i>P</i> _{trend}
	1			2			3			4			5			
	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	
<i>Total iron</i>																
Men	37			33			49			67			62			
Model 1		1			0.84	0.52, 1.36		1.11	0.71, 1.72		1.44	0.95, 2.18		1.18	0.78, 1.81	0.23
Model 2		1			0.84	0.52, 1.38		1.12	0.71, 1.77		1.49	0.97, 2.28		1.31	0.83, 2.06	0.10
Women	28			40			38			37			31			
Model 1		1			1.20	0.73, 1.96		1.11	0.68, 1.82		1.04	0.63, 1.70		0.92	0.55, 1.53	0.38
Model 2		1			1.16	0.70, 1.93		1.11	0.66, 1.86		1.06	0.63, 1.78		0.86	0.49, 1.51	0.33
Pooled		1			0.98	0.69, 1.40		1.11	0.79, 1.57		1.30	0.93, 1.80		1.10	0.74, 1.65	0.84
<i>Dietary iron</i>																
Men	44			41			35			55			73			
Model 1		1			0.85	0.55, 1.32		0.71	0.45, 1.12		1.03	0.69, 1.55		1.23	0.84, 1.81	0.05
Model 2		1			0.91	0.58, 1.43		0.77	0.48, 1.23		1.11	0.72, 1.72		1.30	0.86, 1.96	0.04
Women	27			32			29			43			43			
Model 1		1			1.10	0.66, 1.83		0.93	0.55, 1.58		1.31	0.80, 2.12		1.19	0.73, 1.93	0.36
Model 2		1			1.12	0.65, 1.94		1.03	0.59, 1.82		1.50	0.89, 2.52		1.32	0.78, 2.22	0.21
Pooled		1			0.99	0.70, 1.40		0.87	0.60, 1.24		1.26	0.90, 1.75		1.30	0.94, 1.80	0.02
<i>Nonheme iron</i>																
Men	45			36			39			55			73			
Model 1		1			0.70	0.44, 1.10		0.75	0.48, 1.16		0.96	0.64, 1.45		1.14	0.77, 1.68	0.07
Model 2		1			0.77	0.49, 1.23		0.81	0.51, 1.29		1.08	0.70, 1.67		1.24	0.82, 1.89	0.05
Women	27			30			31			41			45			
Model 1		1			1.02	0.61, 1.73		0.98	0.58, 1.64		1.17	0.71, 1.91		1.20	0.74, 1.94	0.34
Model 2		1			1.08	0.62, 1.87		1.02	0.58, 1.78		1.33	0.78, 2.25		1.31	0.78, 2.22	0.22
Pooled		1			0.89	0.62, 1.27		0.89	0.62, 1.27		1.17	0.84, 1.64		1.27	0.92, 1.76	0.02
<i>Heme iron</i>																
Men	54			56			59			41			38			
Model 1		1			1.17	0.80, 1.71		1.12	0.76, 1.65		0.97	0.64, 1.48		0.95	0.62, 1.46	0.59
Model 2		1			1.19	0.81, 1.76		1.06	0.71, 1.59		0.96	0.62, 1.50		0.85	0.52, 1.37	0.32
Women	41			36			30			34			33			
Model 1		1			0.94	0.60, 1.48		0.86	0.54, 1.39		1.07	0.68, 1.69		1.06	0.67, 1.68	0.68
Model 2		1			0.82	0.50, 1.34		0.82	0.49, 1.36		1.11	0.68, 1.80		1.11	0.67, 1.85	0.43

	Iron supplement					
	No			Yes		
	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval
Men	146			102		
Model 1		1			1.26	0.96, 1.64
Model 2		1			1.33	0.99, 1.77
Women	101			73		
Model 1		1			0.95	0.70, 1.29
Model 2		1			0.92	0.65, 1.29
Pooled		1			1.11	0.78, 1.60

^a Model 1: adjusted for age (months), smoking (packs/year), total energy (kcal/day), and caffeine (mg/day). Model 2: adjustments as in model 1 plus body mass index, vitamin C (mg/day), vitamin E (mg/day), lactose (g/day), physical activity (quintile), and Alternate Healthy Eating Index.

We also conducted stratified analyses to contrast baseline age (<60 vs. ≥60 years), smoking status (never smokers vs. ever smokers), caffeine intake (the bottom 2 quintiles of the distribution vs. the top 2 quintiles), alcohol intake (drinkers vs. nondrinkers), and intakes of vitamins C and E (the bottom 2 quintiles vs. the top 2 quintiles).

RESULTS

During the follow-up, a total of 422 incident cases of Parkinson's disease (men, $n = 248$; women, $n = 174$) were ascertained. The average age at first symptoms was 69 (standard deviation, 9) years for men and 69 (standard deviation, 7) years for women.

The average intake of iron at baseline in the HPFS was 19.2 mg (14.6 mg from food and 4.6 mg from supplements); in the NHS it was 18.0 mg (12.9 mg from food and 5.1 mg from supplements). The main sources of dietary iron in both cohorts were iron-fortified cereals/grains (approximately 35% of the total dietary intake), followed by beef and beef products (~10%). Approximately 9% of dietary iron came from heme iron, whose main sources were red meat (50%–60% of total intake) and poultry (10%–20%). The remaining 91% of dietary iron came from nonheme iron, mainly from iron-fortified cereal/grains and vegetables (including legumes).

Compared with subjects in the lowest quintile of dietary iron consumption, participants in the highest quintile smoked less and consumed less caffeine, were more physically active, and had a better Alternate Healthy Eating Index score, indicating a healthier diet (Table 1). This overall healthier behavior of subjects with a higher iron intake was associated with higher nonheme iron consumption and was consistently present in both men and women.

Although total iron (dietary intake and supplements) was not associated with an increased risk of Parkinson's disease (comparing the top with the bottom quintile of cumulative average intake, relative risk (RR) = 1.10, 95% confidence interval (CI): 0.74, 1.65; $P_{\text{trend}} = 0.84$), a modest increase in Parkinson's disease risk was associated with dietary intake of iron alone: After adjustment for possible confounders, the pooled relative risk comparing the highest with the lowest quintile was 1.30 (95% CI: 0.94, 1.80; $P_{\text{trend}} = 0.02$) (Table 2). A positive association was found between risk of Parkinson's disease and intake of nonheme iron (for highest vs. lowest quintile of nonheme intake, the pooled RR = 1.27, 95% CI: 0.92, 1.76; $P_{\text{trend}} = 0.02$) but not with heme iron (RR = 0.96, 95% CI: 0.68, 1.37; $P_{\text{trend}} = 0.86$) (Table 2). We did not find significant heterogeneity of the associations between iron intake and Parkinson's disease risk between men and women ($P > 0.2$ for all).

No significant associations were found when using the most recent uptake of iron or the baseline intake of iron as an exposure (data not shown).

Supplemental iron use was reported by 31.5% of men and 39.0% of women. Compared with nonusers, men who took supplemental iron showed a borderline increase in risk (RR = 1.33, 95% CI: 0.99, 1.77; $P = 0.06$), while women did not (RR = 0.92, 95% CI: 0.65, 1.29; $P = 0.61$).

We found no statistically significant interactions with baseline age, smoking, caffeine, alcohol, or vitamin E

intake. However, after stratification of participants by levels of vitamin C intake, nonheme dietary iron was associated with increased Parkinson's disease risk among participants who had a low intake of vitamin C ($P_{\text{interaction}} = 0.02$) (Table 3).

The results of the analyses restricted to cases with a diagnosis of definite Parkinson's disease were similar to all those shown above.

DISCUSSION

In this prospective study, we found that, although total iron intake (dietary iron and supplements) was not associated with increased Parkinson's disease risk, dietary iron intake alone was associated with a 30% increased risk of the disease. This association was stronger among individuals with low vitamin C intake. This was unexpectedly due to a higher risk of Parkinson's disease among participants in both cohorts who consumed large amounts of nonheme iron, whose primary source was fortified grains/cereals. No association was found with intake of the better-absorbed heme iron, but the use of supplemental iron was associated with a borderline increase in risk among men.

Three case-control studies with retrospective collection of exposure data have previously found an association between dietary iron and Parkinson's disease (7–9). Our study is based on 2 large prospective cohorts, extensive investigation of exposure at several points in time, and long follow-up periods with high response rates. Furthermore, for disease confirmation, we relied in the large majority of cases on diagnoses made by neurologists, which have been shown to be highly valid (21). Some error in dietary assessment is inevitable, but it was minimized in this study by using a food frequency questionnaire that has been standardized and validated, as well as repeated dietary assessments. We also reduced confounding by adjusting our analyses for known and suspected risk factors for Parkinson's disease, using prospectively collected and validated information. Residual confounding, however, is still possible because of the observational nature of our data. Finally, participants in the NHS and HPFS were all health professionals and mostly white; thus, generalizability may be limited. Furthermore, given the relatively small exposure variation among health professionals and nurses compared with that of the general population, the magnitude of relative risks observed in the current study is likely to be underestimated.

Several lines of biologic evidence link iron to Parkinson's disease. Free iron is a potentially neurotoxic compound, because it can catalyze the production of highly reactive oxygen species, inducing oxidative stress, which may damage proteins, membranes, and nucleic acids and eventually cause dopaminergic neuron death in the substantia nigra (22). Brain iron is responsive to peripheral iron status (23), and iron accumulation in the central nervous system can be modulated by diet through metal restriction or supplementation (24). Increased iron levels have been recently demonstrated in individual dopaminergic neurons and not only in glial cells, which strongly suggests that iron elevation in specific brain regions is due to primary changes in iron handling in Parkinson's disease (25). Iron that normally accumulates in the brain is primarily nonheme iron (26).

Table 3. Relative Risk of Parkinson's Disease According to Dietary Intakes of Iron and Vitamin C in the Health Professionals Follow-up Study (1986–2000) and in the Nurses' Health Study (1984–2000)

	Quintiles of Iron Intake										P_{trend}	$P_{\text{interaction}}$
	1		2		3		4		5			
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval		
Dietary iron ^a												
Low vitamin C intake (quintiles 1 and 2)	1		1.08	0.47, 2.49	0.88	0.21, 3.66	1.42	0.55, 3.67	1.92	1.14, 3.22	0.002	0.02
High vitamin C intake (quintiles 4 and 5)	1		1.49	0.84, 2.65	1.23	0.68, 2.23	1.45	0.82, 2.57	1.27	0.72, 2.25	0.78	
Nonheme iron ^a												
Low vitamin C intake (quintiles 1 and 2)	1		0.97	0.18, 5.05	1.15	0.28, 4.80	1.42	0.50, 3.99	1.97	0.87, 4.48	0.003	0.02
High vitamin C intake (quintiles 4 and 5)	1		1.36	0.77, 2.42	1.03	0.57, 1.89	1.24	0.70, 2.19	1.17	0.66, 2.07	0.89	

^a Adjusted for age (months), smoking (packs/year), total energy (kcal/day), caffeine (mg/day), body mass index (kg/m²), vitamin E (mg/day), lactose (g/day), physical activity (quintile), and the Alternate Healthy Eating Index.

Although nonheme iron is generally unrelated to total body iron stores, the brains of subjects with Parkinson's disease have increased iron deposits of nonheme iron but lower levels of ferritin and transferrin, compared with controls (27–29). This suggests that in Parkinson's disease there is an alteration of the system that regulates the synthesis of ferritin and other proteins involved in systemic iron metabolism. These low levels of ferritin, which stores about 90% of nonheme iron in the tissues (30), may determine the inadequate response of neurons to the toxicant action of excessive iron entry in the brain. An alteration of the mechanism that transports iron through the neuron membrane may also be involved. A significant increase in lactoferrin activity, which has a much higher affinity for iron than does transferrin, has been described in the mesencephalon of Parkinson's disease patients, where dopamine loss is more severe (31). Interestingly, neuropathologic studies show that even a modest difference in iron concentration in the substantia nigra is sufficient to increase oxidative stress and cause neurodegeneration (32).

Even though these pathologic findings support a primary role of iron in Parkinson's disease, evidence that iron intake affects risk of Parkinson's disease remains inconclusive. In a case-control study, higher iron intake has been described in Parkinson's disease subjects compared with controls (33). However, these findings may reflect changes in diet due to the disease itself, as individuals with Parkinson's disease increase their total caloric intake around the time of onset of neurologic symptoms (34). Although we found a positive association between dietary iron intake and Parkinson's disease risk in the present study, it was largely explained by an increased intake of nonheme iron, which is less efficiently absorbed than heme iron (23). Intestinal absorption of dietary nonheme iron is normally strictly controlled and unlikely to result in iron overload. The positive association between nonheme iron and Parkinson's disease could possibly have resulted from a less efficient control of nonheme iron absorption or trafficking. Some of the mechanisms that regulate intestinal iron absorption may also regulate the entrance of iron into the neurons in the brain (35, 36), while others are brain specific (37). The investigation of all these possible mechanisms may increase our understanding of the role of iron in Parkinson's disease.

In the current study, the association between nonheme and Parkinson's disease risk was stronger among subjects with low intake of vitamin C. Some data suggest a protective effect of vitamin C intake on Parkinson's disease risk (38), but this was not found in either a recent meta-analysis (39) or previous work in the NHS and HPS cohorts (40). However, a protective effect of dietary intake of vitamin C has been shown in an updated analysis in the NHS and HPFS with longer follow-up and adjustment for the dietary urate index (an index reflecting the overall effects of diet on plasma uric acid, a strong antioxidant) (41). Vitamin C has important antioxidant properties, but this effect may be relevant predominantly in subjects characterized by high levels of oxidative stress because of high iron intake.

An alternative explanation of our findings is that dietary nonheme iron is a marker of a healthier lifestyle or a structure of personality that can be responsible for healthier

behavior. If this is the case, the effect of competing risks, such as cardiovascular events, on the survival of Parkinson's disease subjects may at least partially determine the observed results.

In summary, although our prospective data did not support an overall association between total iron intake (dietary iron and iron from supplement) and the risk of Parkinson's disease, a diet rich in iron was associated with a modest increase (30%) in risk of Parkinson's disease in both men and women. This effect was present in participants with a low intake of vitamin C. The Recommended Dietary Allowance of iron for men aged more than 18 years and for women aged more than 50 years is 8 mg/day, an amount considered to meet the requirements of healthy individuals (42). In our study, the change in risk was observed among those who had an intake more than twice that amount. Interestingly, the main source of nonheme dietary iron in these cohorts was fortified cereals. These findings should be considered cautiously, and they need to be replicated in other settings, possibly with biomarkers, to measure systemic iron stores and metabolism.

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